MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

October 15, 2009

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Subject: Clinical Review of Biologics License Application for Human Papillomavirus 16, 18 L1 Virus Like Particle Vaccine, AS04 Adjuvant-Adsorbed (Cervarix)

To: BLA STN# 125259

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1. Title and General Information

1.1 Title: Medical Officer's Review

1.1.1 STN BLA 125259

1.1.2 Related INDs: ---(b)(4)---

1.1.3 Reviewer's Name: Nancy B. Miller, M.D., DVRPA, HFM-475

1.1.4 Submission Date: 3/29/07; Resubmission Date: 3/24/09

1.1.5 Review Completed: 10/15/09

1.2 Product

1.2.1 Proper Name: Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant

1.2.2 Trade Name: Cervarix

1.2.3 Product Formulation: Each 0.5 mL dose of the vaccine contains:
20 mcg of human papillomavirus (HPV) 16 L1 protein
20 mcg of HPV 18 L1 protein
500 mcg aluminum hydroxide
50 mcg 3-O-desacyl-4'-monophosphoryl lipid A (MPL)
0.624 mg sodium dihydrogen phosphate dihydrate as buffer

1.3 Applicant: GlaxoSmithKline Biologics (GSK)

1.4 Pharmacologic Category: Vaccine

1.5 Proposed Indications from the sponsor: Prevention of cervical cancer (squamous cell carcinoma and adenocarcinoma) by protecting against the following precancerous or dysplastic lesions and infections caused by oncogenic human papillomaviruses (including types 16 and 18 and some non-vaccine HPV types:

- cervical intraepithelial neoplasia (CIN) grade 2 and grade 3 and adenocarcinoma *in situ* (AIS)
- cervical intraepithelial neoplasia (CIN) grade 1
- abnormal cytology (i.e., atypical squamous cells of undetermined significance [ASC-US], low and high grade squamous intraepithelial lesions [LSIL and HSIL]
- persistent infection
- incident Infection

Indications proposed by CBER: CERVARIX is a vaccine indicated in girls and women 10-25 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types 16 and 18:

- cervical cancer
- cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ (AIS)
- cervical intraepithelial neoplasia (CIN) grade 1

1.6 Proposed Population: Females 10-25 years of age

1.7 Dosage Form and Routes of Administration: The vaccine is administered by intramuscular injection as a three dose series at 0, 1, and 6 months. It will be supplied in 0.5 mL single dose vials and prefilled TIP-LOK syringes; and packages of ten 0.5 mL single dose prefilled disposable TIP-LOK syringes (packaged without needles).

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3. **Executive Summary**

Cervarix™ is a non-infectious, recombinant vaccine which contains Virus Like Particles (VLPs) of the L1 capsid proteins of HPV 16 and 18. It is adjuvanted with aluminum hydroxide and monophosphoryl lipid A (MPL).

Under Biologics License Application (BLA) #125259, the sponsor, GlaxoSmithKline Biologicals (GSK), agreed to the following indication:

CERVARIX is a vaccine indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18:

- *cervical cancer,*
- *cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ, and*
- *cervical intraepithelial neoplasia (CIN) grade 1.*

CERVARIX is approved for use in females 10 through 25 years of age.

In addition to *in vitro* and animal studies, data from 13 clinical studies involving ~30,000 females 10-55 years of age were submitted to the BLA in support of licensure. After review of the data, and in consultation with the Vaccines and Related Product Applications Advisory Committee (VRPBAC), CBER has concluded that the safety and efficacy data support the licensure of Cervarix for the stated indication.

EFFICACY

Prophylactic Efficacy

The pivotal efficacy study, HPV-008, was a randomized (1:1), controlled, double blind trial which recruited 18,000+ women, regardless of cytology status or evidence of HPV exposure, to compare Cervarix to active control (Havrix) for the prevention of CIN2+, defined as a composite endpoint of CIN 2,3, AIS and invasive cervical cancer. In the According to Protocol (ATP)[1] population, efficacy against HPV 16 and 18 associated CIN2+ was 92.9%, with 96.1%CI (79.9, 98.3). No subjects in either Cervarix or the control group developed invasive cervical cancer during the study.

In HPV-008, several intent-to-treat analyses were performed to evaluate efficacy in pre-specified analysis populations. The Total Vaccinated Cohort (TVC)[2], in which 26% of subjects were seropositive and/or PCR positive to HPV 16 and/or 18, provides an estimate of efficacy among 16-25 year old females, regardless of HPV status. In this population, the point estimates for efficacy against HPV 16/18-associated CIN2+ and any HPV type associated CIN2+, were 52.8% (96.1% CI: 43.2, 65.3) and 30.4%, (96.1%CI : 16.4, 42.1), respectively. Because a definitive efficacy trial using cervical disease as an endpoint would not be practical in pre-adolescents, efficacy of the vaccine in such a population was estimated using the TVC naïve cohort, in which subjects were PCR negative to 14 oncogenic HPV types, seronegative to HPV 16 and 18, and cytology normal at baseline. In this analysis, the point estimates for efficacy against HPV 16/18-associated CIN2+ and any HPV type associated CIN2+, were 98.4% (96.1% CI: 90.4, 100) and

[1] According to Protocol (ATP) cohort included all subjects who had received all three doses of vaccine, did not have major deviations from the study protocol, had normal or low-grade cytology at baseline (cytological abnormalities including atypical squamous cells of undetermined significance [ASC-US] or low-grade squamous intraepithelial lesions [LSIL] at baseline, and were naïve[1] (PCR and serology negative) for assessed HPV serotype and remained PCR negative through Month 6. Cases counted beginning 1 day after administration of third dose.

[2] Total Vaccinated Cohort (TVC) included subjects for whom data was available, with cases counted starting 1 day after dose 1.

70.2% (96.1%CI: 54.7, 80.9), respectively. In a secondary analysis, efficacy against HPV 16 and/or 18 related CIN1+ in the ATP cohort was 91.7%(96.1% CI 82.4, 96.7).

The sponsor also conducted virological analyses to demonstrate prevention of persistent infection in study HPV-008 (secondary endpoint). In the ATP cohort, Cervarix reduced the incidence of 12-month persistent infection with HPV 16 and/or 18 by 91.2% (96.1% CI: 85.9, 94.8). CBER considered this and other analyses of incident and persistent infection to be supportive of, but not pivotal to, the evaluation of the vaccine for the sought after indication. This approach is consistent with recommendations from the November 2001 VRBPAC meeting, in which CIN2+ was established as the optimal surrogate endpoint for efficacy studies in the prevention of cervical cancer.

Prophylactic efficacy in an HPV naïve population (defined as PCR negative for 14 oncogenic HPV types, seronegative for HPV 16/18, and cytology normal at baseline) was also evaluated in the phase IIB study, HPV 001/007. In this study, 1,113 females 15-25 years of age were randomized to Cervarix or aluminum hydroxide control. The estimate of efficacy for the primary endpoint of incident infection with HPV 16/18 in the ATP cohort was 92.6% (95% CI: 64.5, 98%). An extension of HPV 001/007, in which 776 subjects were followed for up to 6.4 years, was designed to evaluate long term efficacy for the pre-specified endpoints. In this analysis, efficacy against 12 month persistent infection with HPV 16/18 was 100% (98.67% CI: 74.4, 100). In addition, although the study was not powered for CIN2+, secondary analysis for this endpoint generated a point estimate of efficacy of 100% (98.67% CI: 28.4, 100). Among the subset of subjects followed for 6 years, 0 cases of HPV 16/18 persistent infection and 0 cases of HPV 16/18 associated CIN2+ occurred in the Cervarix group. The 98.67% confidence interval reflected in this final analysis results from statistical adjustment for analyses previously conducted.

Prevention of Non-Vaccine HPV Type Infection and Disease

In HPV-008, the estimate of efficacy in the TVC naïve cohort demonstrated that there was a reduction of CIN2+ irrespective of HPV type by 70.2% (54.7, 80.9%). The major contribution appears to be due to prevention of CIN2+ lesions related to HPV-16 and/or HPV-18. However, since approximately 56% of CIN2+ lesions were related to HPV 16 and/or HPV-18 in the control group, the 70.2% point estimate of efficacy in prevention of CIN2+ lesions irrespective of HPV DNA detected indicates that there may be some additional impact in reduction of CIN2+ lesions related to prevention of non-vaccine HPV types.

To further explore the effect on non-vaccine HPV types, study HPV-008 included a secondary objective which was a composite endpoint of prevention of CIN2+ associated with the following oncogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. In this analysis the efficacy estimate in the ATP cohort was 54.0% (96.1% CI: 34.0, 68.4). Because HPV 16 and/or 18 were detected in many of the lesions in the control group but not in the vaccine group, it was clear that these two types had a substantial impact on the composite endpoint analysis. Therefore, perhaps the best estimate of the impact on non-vaccine types comes from a *post hoc* analysis in which HPV 16 and 18 were excluded. Here, the point estimate for efficacy in the prevention of CIN2+ associated with the remaining 12 oncogenic HPV types in the ATP cohort was 37.4% (96.1% CI: 7.4, 58.2).

Determining the contribution of individual non-vaccine HPV types to prevention of histopathologically confirmed disease is complex. CBER's approach was to exclude co-infections with HPV 16 and/or 18, adjust for multiplicity, and estimate efficacy in the prevention of CIN2+ for each non-vaccine type individually. In this analysis, prevention of CIN2+

associated with HPV 31 was statistically significant in both the ATP and TVC naïve cohorts, with estimates of efficacy of 89.4% (99.7%CI: 29.0, 99.7%) and 100% (99.7%%CI: 36.3, 100%), respectively. In the case of most of the other 11 oncogenic non-vaccine HPV types tested when HPV 16 and/or 18 containing lesions were excluded from the anlaysis, none of the estimates of efficacy reached statistical significance.

Therapeutic Efficacy
In HPV-008, there was no apparent reduction in CIN2+ lesions associated with HPV 16 and/or 18 in women who were PCR positive for the relevant HPV type at baseline, regardless of serostatus (and with normal or low-grade cytology). In this analysis, vaccine efficacy was 0.5% (96.1% CI: -47.7, 32.9%).

Efficacy Bridge to Female 10-14 years of age
Efficacy analyses of non-naïve subjects (seropositive and/or PCR positive at baseline) as compared to naïve subjects for HPV 16 and/or 18 related CIN2+ for HPV 16/18 related CIN2+ suggest that Cervarix has limited efficacy in non-naïve subjects. Thus, females who have not been exposed to HPV serotypes in the vaccine, among them pre-adolescent females who have not yet been exposed to HPV infection through sexual exposure, may benefit most from being vaccinated prior to HPV exposure.

Because the incidence of HPV-related genital lesions is very low before the onset of sexual activity, a placebo-controlled efficacy trial based on histopathological endpoints in subjects <16 years of age would be impractical. CBER therefore accepted immunogenicity bridging studies as a reasonable approach to inferring protection in this age group. A serology bridging study, HPV-012, was conducted to compare the immune response to Cervarix of females 10-14 years of age to that of females 15-25 years of age. In this study, the geometric mean titers (GMTs) and seropositivity rate of females 10-14 years of age was non-inferior to those of females 15-25 years of age. The seropositivity rate was 100% in both age groups, and the GMTs of anti-HPV-16 and anti-HPV-18 were more than twice as high in the 10-14 year old females compared with the 15-25 year old females.

In addition, the sponsor compared the immune response of females 10-14 years of age (participating in study HPV-013) following three doses of Cervarix to the response of females 15-25 years of age who participated in the HPV-001 efficacy study. The sponsor demonstrated that one month following the third dose of Cervarix, the HPV 16 and 18 GMTs of girls 10-14 years of age were higher than those of females 15-25 years of age who participated in the efficacy study HPV-001.

Duration of Efficacy
The longest period of follow-up with efficacy endpoints comes from study HPV 001/007, in which 6- and 12-month persistent infection and CIN2+ were assessed in subjects for up to 6.4 years. Analyses of efficacy related to HPV 16/18 from this study, in which subjects were HPV naïve at baseline, are as follows: prevention of 6-month persistent infection, 100% (98.7%CI 86.2, 100); prevention of 12-month persistent infection, 100% (98.7%CI 74.4, 100); prevention of CIN2+, 100% (98.7%CI 28.4, 100).

The full duration of efficacy has not yet been determined. It is also not yet clear whether booster doses will be necessary. The sponsor is conducting several long-term follow-up studies (one a further extension of study HPV-001/007) to provide additional data regarding the duration of efficacy of the vaccine.)

IMMUNOGENICITY
Cervarix is adjuvanted with ASO4, a combination of aluminum hydroxide ($AlOH_3$) and monophosphoryl lipid A (MPL). If approved, Cervarix would be the first vaccine licensed in the U.S. which contains MPL as a component of the adjuvant. In preclinical studies and phase IIa trials, the sponsor demonstrated higher initial titers with the addition of MPL over $AlOH_3$ alone. In subjects followed to 4 years, the difference persisted with statistically significantly higher GMT's (by most measures) in the ASO4 group. No correlate of protection has yet been established for prevention of HPV infection and disease, primarily because the low number of cases among vaccinees (with either Cervarix or Gardasil® vaccine) prevents meaningful analysis of a possible correlation between vaccine failure and vaccine-induced anti-HPV titers. Therefore, the clinical significance of higher titers demonstrated with ASO4 is not yet clear.

Immunogenicity was measured by ELISA titers, which were shown to correlate well with pseudovirion-based neutralization assay titers (PBNA). In each study, GMT's in the Cervarix group were considerably higher than those in subjects with serological evidence of a history of natural infection. Seroconversion rates (SCR) in study HPV-008 were 99.5% at 1 month post-dose 3. Additionally seroconversion rates remained high (~98%) in the subset of subjects followed to 76 months in HPV-001/007.

Additional Indications requested by sponsor

- ***Prevention of HPV 16 and 18 infection (incident and persistent infection, 6- and 12-month definition):*** In general, CBER has indicated infectious disease vaccines for the prevention not simply of infection, but for prevention of the disease caused by the infectious agent. Considering also that the recommendations of the November 2001 VRBPAC that CIN2+ is the optimal surrogate for prevention of cervical cancer, CBER did not concur with the indication of prevention of HPV 16 and/or 18 infection.
- ***Prevention of abnormal cytology associated with HPV 16 and/or HPV-18:*** CBER did not concur with the indication for prevention of HPV 16 and/or HPV-18 related abnormal cytology, because of error inherent to the test itself, particularly its low sensitivity, and because mildly abnormal cytology does not always lead to definitive cervical therapy.

SAFETY:
In the BLA submission, 12,785 females 10 through 25 years of age received at least 1 dose of Cervarix and 10,928 females 10 through 25 years of age received at least one dose of control vaccine (either Havrix formulation or aluminum hydroxide) in 9 studies. Controlled studies included HPV-001/HPV-007, HPV-008, and HPV-013. Subjects 18-25 years of age participating in an ongoing study (HPV-009) were included in the overall reports of deaths and serious adverse events. In addition, subjects 26-55 years of age participating in a separate ongoing study (study HPV-015) in which subjects received Cervarix or aluminum hydroxide were included in the overall totals for deaths, serious adverse events, and pregnancy outcomes for complete reporting of the safety experience with Cervarix.

Injection Site Reactions: In three controlled trials (HPV-001/007, HPV-008 [subset completed vaccine report card], and HPV-013) and three uncontrolled studies (HPV-012, HPV-014, and HPV-016) in which solicited local adverse reactions and general adverse events were monitored using Vaccine Report Cards, a higher proportion of Cervarix recipients experienced pain at the injection site (~91.8%) within the 7 days after any dose, as compared to control formulations (78.0% for HAV 720 in 15-25 year old females and 64.2% for HAV 360 control in 10-14 year old females; and 87.2% for aluminum hydroxide control in 15-25 year old subjects). In addition, a higher proportion of Cervarix recipients reported redness and swelling at the injection site as compared to any of the control groups.

General Adverse Events: In the same studies as noted above, the proportions of subjects with a systemic adverse event within 7 days after any dose were generally similar to subjects in the control groups, although the rates varied by ages of subjects.

Unsolicited Adverse Events: These events were collected for 30 days after vaccination in the same studies for which local adverse events and general adverse events were recorded on vaccine report cards. The rates for these events were generally comparable across treatment groups for the combined controlled (study HPV-001/007, HPV-008, and study HPV-013) and uncontrolled trials (study HPV-012, HPV-014, and study HPV-016). In females 15-25 years of age in study HPV-008, the incidences of unsolicited AEs in the 30 days after vaccination were similar in both groups (42.5% HPV, 43.6% HAV). Grade 3 unsolicited AEs were reported in similar proportions of subjects in each treatment group (7.6% HPV and 6.9% HAV). The most common unsolicited AEs were headache, influenza, gynecological chlamydia infection, nasopharyngitis, pharyngolaryngeal pain, and dizziness. In females 10-14 years of age in study 013, the proportions of subjects with at least one unsolicited AE were similar in the two groups (37.3% HPV, 41.4% HAV). Infections were most frequently reported unsolicited AE in the 30 days after vaccination (21.8% HPV, 23.3% HAV), followed by respiratory illnesses (6.5% HPV, 5.2% HAV).

Adverse Events/Serious Adverse Events leading to discontinuation from studies: In the Complete Response letter of 12/14/07, CBER requested a summary of adverse events which led to discontinuation across studies by treatment groups. In studies submitted to the BLA, from a total of 29,953 subjects included in the pooled safety analysis, 72 subjects were withdrawn due to an AE or SAE (43 subjects received Cervarix [0.27%] and 29 subjects received control [0.21%]). A total of 31 subjects withdrew due to an SAE (14 subjects received Cervarix [0.09%] and 17 subjects received control vaccine [0.12%]). Of these, sixteen events were fatal events and the other 15 subjects withdrew due to other SAEs, none of which were assessed as causally related to vaccination by the study investigator.

The 15 non-fatal SAEs resulting in withdrawal include the following:

- 7 subjects who received Cervarix: the withdrawals were due to multiple sclerosis, a prolapsed vertebral disc, moderate dermatological infection, invasive ductal carcinoma stage I (left breast), cervical adenocarcinoma, and spontaneous abortion (2 subjects);
- 8 subjects who received Havrix (360 EL.U. HAV antigen and 250μg Al(OH)3 per 0.5 mL dose): the withdrawals were due to enteritis, abdominal pain, renal abscess, anorexia nervosa, cervical carcinoma stage 0, malignant neoplasm, uterine prolapse, and multiple trauma following an automobile crash.

There were in total 41 other subjects who experienced non-serious adverse events that led to study withdrawal, of which 29 subjects received Cervarix (0.18%) and 12 subjects received control vaccine (0.09%).

Serious Adverse Events: In the Complete Response letter of 12/14/07, CBER requested a summary of serious adverse events across studies by treatment groups. In the pooled safety database, inclusive of controlled and uncontrolled studies which enrolled females 10 through 72 years of age, 5.3% (862/16,142) of subjects who received Cervarix and 5.9% (814/13,811) of subjects who received control vaccine reported at least one serious adverse event, without regard to causality, during the entire follow-up period (up to 7.4 years). In the vaccination period (Month 0 to Month 6), 1.3% of subjects in each group (206/16,142 Cervarix recipients and 180/13,811 control subjects) reported a serious adverse event. Among females 10 through 25

years of age enrolled in these clinical studies 6.4% of subjects who received Cervarix and 7.2% of subjects who received the control vaccine reported at least one SAE during the entire study period (up to 7.4 years). There was no imbalance in the proportions of subjects who experienced a serious adverse event across studies. In review of serious adverse events by System Organ Classification, there was no apparent imbalance between the Cervarix and control groups.

Deaths: In the Complete Response letter of 12/14/07, CBER requested a summary of deaths across studies by treatment group. During 7.4 years of follow-up across all studies in which 57,323 females 10-72 years of age were enrolled, a total of 37 deaths were reported: 20 in subjects which had received Cervarix (0.06%, 20/33,623) and 17 in subjects who received control vaccine (0.07%, 17/23,700). The most common causes of death were motor vehicle accident and suicide. Among females 10 through 25 years of age enrolled in clinical studies, 17 deaths were reported (0.06%, 10/16,142 of subjects who received Cervarix and 0.05%, 7/13,811 of subjects who received control vaccine).

Other Issues identified during the clinical review
At the time of the original BLA submission, several issues were identified for which CBER required additional information prior approving the application. A complete response letter was sent to the sponsor on 12/14/07. The clinical issues are discussed below.

- CBER requested that GSK provide evidence that there are no safety issues related to inclusion of the adjuvant (AS04). The sponsor provided additional analyses related to assessment of neuroinflammatory events and autoimmune events.
  - ***New Onset Chronic Diseases (NOCDs):*** During the vaccination period through Month 7, the proportions of subjects with such events were comparable at 1.2% in the Cervarix group (163/13,591) and 1.0% in the pooled control group (119/11,341). In the entire observation period, the proportions of subjects with such events were comparable at 2.4% in the Cervarix group (342/13984) and 2.6% in the pooled control group (309/11,724). The most commonly reported NOCDs were asthma, hypersensitivity and urticaria, as seen in the initial pooled safety analysis of NOCDs. The percentage of subjects reporting these events was low and similar among the treatment groups.
  - ***New Onset Autoimmune Diseases (NOADs):*** In subjects available for this analysis, there were 0.2% in each treatment group during the vaccination period (25/13,591 for Cervarix group and 19/11,314 for control group). In the entire study period, 0.7% Cervarix recipients (96/13,984) and 0.8% pooled control (88/11,724) reported a new onset autoimmune disease. In subjects 10 through 25 years of age, the incidence of potential NOADs in the Cervarix and control groups was 0.8% (96/12,533 subjects) and 0.8%, 87/10,730 subjects, respectively, during the 4.3 years of follow-up (mean 3.0 years). The most common events reported were hypothyroidism (0.2% Cervarix group and 0.3% pooled control), hyperthyroidism (0.1% in each group), psoriasis (0.1% in each group) and inflammatory bowel disease (0.06% Cervarix and 0.04% pooled control).
  - ***Neuroinflammatory Events:*** At the time of the original BLA submission, a nominal imbalance in events of potential neuroinflammatory etiology was noted: six in the HPV-AS04 group and three in the pooled control group. The 6 events in the HPV-AS04 group included optic neuritis [clinically isolated syndrome] 9 days postdose 1; multiple sclerosis [clinically isolated syndrome] 25 days postdose 2; myelitis (uncertain diagnosis) 47 days postdose 2; demyelinating disease [clinically isolated syndrome] (129 days postdose 2; optic neuritis [clinically isolated syndrome] 15 months postdose 3; optic neuritis and multiple sclerosis [clinically isolated syndrome] 17 months postdose 3. The 3 events in the pooled control group included multiple sclerosis 60 days postdose 1 (possibly not new case); optic neuritis [clinically isolated syndrome] 134 days postdose 3; optic neuritis

[clinically isolated syndrome] 23 months postdose 3. In additional follow-up provided in March 2009, 4 additional cases were diagnosed in the HPV group. Two of these subjects developed multiple sclerosis, 1 optic neuritis, and 1 myelitis. Because of the interval from vaccination to event (2-6 yrs), these additional 4 cases were not thought to be temporally related to vaccination (events which occurred within 12 weeks of vaccination were considered to be plausibly related to receipt of vaccination). In GSK's meta-analysis for HPV-AS04 products in controlled studies, the overall relative risk was increased at 2.33, but not statistically significant (95% CI: 0.53, 13.97). (Specific events had relative risks as follows: multiple sclerosis relative risk = 1.50 [95% CI: 0.17, 17.97]; optic neuritis relative risk = 3.00 [95% CI: 0.24, 157.50]). GSK's expert panel concluded that there was not an increased risk of developing neuroinflammatory disorders following vaccination with MPL-containing vaccines. CBER consulted an outside expert neurologist who concluded that the data were insufficient to establish a link, although they were sufficient to raise concern, and further monitoring was recommended (post-marketing reports).

- ***Events of Potential Autoimmune Disease in Musculoskeletal System Organ Class:*** In response to request from CBER, GSK performed an analysis of musculoskeletal events potentially related to immune mediated etiology, e.g., arthritis, fibromyalgia. In the resulting meta-analysis for MPL containing products, cases were reviewed in blinded manner by a panel of rheumatologists. The overall relative risk for HPV-AS04 containing products in controlled studies over entire study period was 1.31 (95% CI: 0.79, 2.20). The most frequently reported musculoskeletal events were arthritis, fibromyalgia, rheumatoid arthritis, systemic lupus erythematosus and arthropathy. In an extended analysis recommended by the expert panel using additional MedDRA terms, the relative risk for entire study period for HPV-AS04 vaccines in controlled trials was 1.08 (95% CI: 0.68, 1.72). GSK also submitted a Time to Onset analysis with review by one additional blinded expert in 8/09. In that assessment, further calculations were made of relative risks of immune-mediated rheumatologic events with a confirmed diagnosis adjudicated by the expert panel for subjects reporting at least one event (Levels 1 controlled studies, Total vaccinated cohort). During the time at risk (1 to 6 months after last vaccination), 4 events occurred (3 HPV-AS04, 1 control) with a relative risk = 3.00 (95% CI: 0.24, 157.41). For the anytime at risk period, there were 14 events, 7 in each group, relative risk = 1.00, (95% CI: 0.30, 3.34).
- ***Grave's disease:*** CBER also requested that GSK re-evaluate Grave's disease in their meta-analysis of subjects who received MPL versus non-MPL containing vaccines. In the update provided by GSK, there were no imbalances statistically when comparing the rates of disease between the MPL group and the non-MPL group.

At time of licensure, CBER and GSK were discussing a study in a US Managed Care Organization (MCO) to assess neuroinflammatory events and autoimmune diseases (as a composite and individually). This study will be conducted as a post-marketing commitment (see overview section).

- **Pregnancy Outcomes:**
  Overall, pregnancy outcomes were similar among subjects receiving Cervarix, Havrix and aluminum hydroxide. In a *post-hoc* subgroup analysis there was an imbalance in the rate of spontaneous abortions between the Cervarix and the Havrix group among vaccine recipients with pregnancies around the time of vaccination. CBER requested additional analyses to include the pregnancy outcomes in study HPV-009 as well as for all studies. In addition, the comparisons of congenital anomalies and stillbirths were also requested.

Spontaneous Abortions

While women were advised not to become pregnant during Cervarix studies, nonetheless 18.6% (3696/19,871) in the Cervarix group and 20% (3580/17,548) of the pooled control subjects did become pregnant. Of the pregnancies that occurred, 2.0% (396/19,871) and 2.1% (365/17,548) in the Cervarix and control groups, respectively, had an estimated date of conception within -30 to +45 days of vaccination. In this risk window in the 15-25 year old subjects, 13.51% for Cervarix, 8.33% for aluminum hydroxide, and 8.92% for Havrix 720 control of documented pregnancies ended in spontaneous abortions. In females > 25 years of age, the proportions were similar for Cervarix (19.05%) and aluminum hydroxide control (20.0%). The following limitations to assessing spontaneous abortion rates in this situation were noted: (1) the studies were not designed to assess the possible effects on pregnancy; (2) spontaneous abortion was not a pre-specified outcome the clinical trials were not designed to study spontaneous abortion; (3) the choice of risk window was not pre-specified; (4) the imbalance at issue was largely among subjects who became pregnant *after they were vaccinated;* very few subjects with established pregnancies were actually vaccinated because each subject received a urine HCG (pregnancy test) the day of vaccination and if positive, vaccination was deferred; (5) the rate of spontaneous abortion in each group, including the Cervarix group, was consistent with background rates reported in the literature (9-21%); (6) in pregnancies which occurred around the time of vaccination, there was no difference in the mean time to spontaneous abortion in each group; and (7) pre-clinical reproductive toxicology studies did not identify any increase in risk. However, the result of a National Cancer Institute (NCI) analysis was that the statistician could neither refute nor confirm an increased rate in spontaneous abortion among vaccine recipients. (In that analysis, the 1-sided P-value for the primary permutation test was 0.16 using the nearest vaccination as the reference date. Among pregnancies with estimated conception date between day 0 and 89 from nearest vaccination, the miscarriage rate was 15.4% (58) miscarriages in the treatment arm and 9.6% (34) in the control arm (1-sided P-value of 0.036 did not meet the standard threshold for significance.) In addition, the Independent Data Monitoring Committee found no evidence for causal association between HPV and spontaneous abortion, but could not exclude a possible association between HPV vaccine and spontaneous abortions in the first 90 days after vaccination and onset of pregnancy. CBER concluded that the imbalance in rates of spontaneous abortions met regulatory criteria for a safety signal. Therefore, GSK will be required to conduct a post-marketing study to evaluate pregnancy outcomes, particularly spontaneous abortions.

A US pregnancy registry is to begin immediately following licensure. Discussions are ongoing as to final study to be conducted, and the sponsor has agreed to conduct such a study. The US pregnancy registry would be augmented by 3 additional data sources: the ongoing pregnancy registry in the United Kingdom; the ongoing clinical studies HPV-040 (Finnish community trial), HPV-024 (long-term follow-up study of HPV-001 and HPV-007) and HPV-055 and HPV-057 (cross-over vaccination of subjects in HPV-008); electronic capture of pregnancy outcomes in the phase IV US based Managed Care Organization safety study.

- **Congenital anomalies:** CBER requested a full accounting of congenital anomalies which occurred in clinical studies with Cervarix, including explanation of an occurrence of ventricular septal defect (VSD). CBER noted that there was a neonate with a ventricular septal defect (VSD) whose mother participated in Study HPV-009 and received dose 2 of Cervarix approximately 5 weeks prior to her last menstrual period (LMP). A second neonate whose mother received aluminum hydroxide also developed a VSD, but the time interval between vaccination and estimated date of conception was 714 days, and temporal association in this second case is not apparent. From the full results provided to the BLA for VSDs and congenital anomalies, the events appear unrelated to HPV vaccine. Furthermore, a group of external experts consulted by GSK concluded that there is **no evidence** that the risk of birth

defects in children of women who were immunized with Cervarix prior to pregnancy is measurably increased or that any particular birth defect occurs in excess among these children. However, the experts further expressed the opinion that the data available to assess the potential reproductive toxicity of Cervarix was limited.

- **Stillbirths:** CBER also requested that GSK present these events across studies. The number of subjects who became became pregnant and in which the child was stillborn was approximately the same in each group across studies. There were 19 such events in the pooled control group and 20 such events in the Cervarix group.
- **Analysis of child cases (serious adverse events) and abnormal infant outcomes:** A total of 92 child case reports including abnormal infant outcomes (other than congenital anomalies) were reported from 87 study subjects (including 5 twin pregnancies) in GSK sponsored studies up to the data lock point of August 31, 2008. These reports were from 37 subjects in the Cervarix group, 12 subjects in the aluminum hydroxide (control) group and 38 subjects in the Hepatitis A vaccine (HAV 720 control) group; one subject did not receive any study vaccination. The most commonly reported events were associated with prematurity: 46 study subjects delivered 50 premature infants (including 4 twin pregnancies).The most commonly reported events were as follows:
  - Respiratory disorders related to hypoxia (perinatal): fetal or neonatal respiratory distress syndrome or asphyxia (56 infants), neonatal aspiration (10 infants) and respiratory failure (12 infants).
  - Prematurity reported in 44 infants (6 twins) from 38 study subjects, and
  - Jaundice, reported in 39 infants (1 twin).

The Vaccines and Related Biological Products Advisory Committeee (VRBPAC) meeting: On September 9, 2009 following presentations by the manufacturer and by FDA, the VRBPAC voted 12/13 that the data supported the efficacy of Cervarix to prevent HPV 16/18 related cervical cancer and precancerous lesions CIN and AIS in females 15-25 years of age. The committee voted 12/13 that immunogenicity bridging data support effectiveness for prevention of HPV 16/18 related cervical cancer and precancerous lesions CIN and AIS in adolescent females 10-14 years of age. CIN1+ was not considered to be as predictive of development of high-grade dysplasias and there was discussion about its inclusion in the indication. The committee was also asked to comment on the strength of the data supporting efficacy in prevention of non-vaccine HPV types. The chairperson summarized the discussions by indicating that there was good basis fo concluding that this bivalent vaccine does protect against some non-vaccine serotypes, most likely those to which there has been demonstrated cross protection in animal models or cross neutralization, but that they were uncomfortable with the term "any non-vaccine HPV type". There was some difference of opinion as to whether there was need to be any more specific than that with regard to specific types, particularly HPV-31. Caution was also advised in regards to assays used and their ability to differentiate between non-vaccine HPV types. Safety issues of concern were also discussed, namely neuro-inflammatory and autoimmune events, as well as the issue of spontaneous abortion. Strong post-marketing studies were advised to follow these events. Two committee members advised caution for use in females with pre-existing autoimmune disease.

Pediatric Research Equity Act Requirements

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this Biologics License Application is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric age groups. Effective upon approval of the supplement, the product will be lableled for use in children 10 years of age and older. A deferral for children 9 years of age was granted because the product was ready for approval before studies in this age group were complete. The applicant has committed to completion of Study 048, which will

generate safety and immunogenicity data adequate to evaluate the vaccine for use in children 9 years of age.

The applicant requested a partial waiver from the requirements of PREA for children 0-8 years of age. The review team agreed to grant the waiver request because necessary studies are impossible or highly impractical and there are too few children with the disease/condition to study. The Pediatric Review Committee (PeRC) concurred with this decision.

Post-marketing commitments and requirements (See FDA approval letter for final wording of Post-Marketing commitments):

Post-marketing Requirement: FDA has determined that GSK is required to conduct a postmarketing study pursuant to section 505(o)(3)(B)(iii) of the Act based upon a subgroup analysis of clinical trial data demonstrating a numerical imbalance in spontaneous abortions among Cervarix recipients whose pregnancies occurred around the time of vaccination (defined as the last menstrual period occurring 30 days before until 45 days after vaccination), compared to control subjects. These findings were evaluated in an exploratory analyses conducted by the National Cancer Institute (NCI) which identified higher rates of spontaneous abortion among those 15 to 25 years of age who received Cervarix around the time of conception (estimated date of conception between day 0 to 89 from nearest vaccination). GSK is required to conduct the following study:

Analytic Epidemiologic Study to Assess the Risk of Spontaneous Abortion Following Cervarix Administration: GSK has committed to a post-licensure analytic epidemiologic study to assess the risk of spontaneous abortion following Cervarix vaccination. The primary study population will be comprised of women whose estimated date of conception lies between –30 days and +90 days from nearest Cervarix vaccination, relative to a comparison group. The study will include karyotype analysis in a subset of women in order to address the issue of background spontaneous abortions due to chromosomal abnormalities. While the study design is still under discussion, all aspects of the final study protocol are subject to FDA review and ultimate approval pursuant to Section 505(o)(3) of FDAAA. GSK has committed to providing the draft protocol within two months after vaccine licensure followed by the final study protocol within 6 months after vaccine licensure. Study initiation will preferably occur within six months but no later than 12 months after protocol finalization. Interim reports will be submitted to the FDA every 6 months for the duration of the study.

CBER acknowledges the timetable GSK submitted on September 21, 2009, which states that GSK will conduct this trial according to the following schedule:

- Final Protocol Submission: April 2010

Study Completion Date: The study completion date will be subject to the final study design (case control versus cohort study) which is still under discussion. Additionally, the study completion date will be to subject to other factors impacting patient accrual, including overall vaccine uptake, date of study initiation, pregnancy avoidance behaviors among vaccine recipients, and size of the surveillance population. The anticipated study completion date will be when subject enrollment is sufficient to detect an increased relative risk of approximately 2.0 for spontaneous abortions.

Final Report Submission: 6 months after study completion

GSK is required to report periodically ti FDA on the status of this study. GSK also will be required to periodically report to FDA on the status of any study or trial otherwise undertaken to investigate a safety issue associated with Cervarix.

Postmarketing commitments include the following:

- GSK has committed to conduct a US-based Phase IV, observational, cohort study in a managed care organization. The overall objective is to evaluate the incidence of new onset autoimmune disease among Cervarix recipients 10 through 25 years of age 12 months after each vaccination. The study population will consist of at least 50,000 Cervarix recipients, compared to approximately 50,000 control subjects not vaccinated with Cervarix, but who potentially have received other recommended vaccines, including other HPV vaccines. At least 135,000 administered doses of Cervarix will be evaluated in this study. Given the low background rates for autoimmune conditions, composite endpoints will be used to enhance signal detection. In the primary analysis, neuroinflammatory events (comprising all demyelinating conditions) will be evaluated separately from all other non-demyelinating autoimmune conditions. In secondary analyses, autoimmune diseases will be assessed using an alternative classification system consisting of: (a) systemic diseases, (b) organ-specific T-cell mediated diseases, (c) organ-specific antibody-mediated conditions, and (d) fibromyalgia and psoriasis, which will be separately analyzed due to substantially higher background rates. Exploratory analyses of confirmed cases of individual autoimmune conditions will also be conducted. Propensity score matching methods will be used to address unequal distribution of risk factors. Annual interim reports will be submitted within 3 months after the yearly cut-off date. GSK has committed to the following study timeline:

Final Protocol Submission Date:	March 2010
Projected Completion Date for Subject Accrual:	March 2013 (subject to vaccine uptake)
Projected Study Completion Date:	September 2014 (subject to vaccine uptake)
Projected Final Report Submission Date:	March 2015 (or 6 months after study completion)

- GSK has committed to establish a US-based pregnancy registry. This prospective observational pregnancy exposure study will actively collect data on Cervarix exposures occurring immediately before or during pregnancy, in addition to the associated pregnancy outcomes, and potential confounding factors, such as other medication exposures. The objective will be to provide clinically relevant human data to assist medical providers in treating and counseling patients who are pregnant or are anticipating pregnancy, and to support any necessary changes to the product label. The pregnancy-related outcomes to be evaluated include live births, still births, congenital anomalies, intrauterine fetal demise, and induced and spontaneous abortions. Pregnant women will be enrolled before the outcome of the pregnancy is known and questionnaires collecting data on outcomes and confounding factors will be sent to reporters within 3 and 6 months after the estimated date of delivery. The total number of patients enrolled will be contingent on vaccine uptake. Risk estimates will be performed on only medically confirmed, prospectively collected, pregnancy outcomes; incidence rates for all events will be compared to existing national population-based surveillance programs. Retrospectively collected data will be analyzed separately. Reporting of vaccine-exposed pregnancies to the registry will be voluntary, but patients and their healthcare providers will be encouraged to enroll. Public awareness will be stimulated by the sponsor's pregnancy registry website and through telephone contact information provided in the product label. The study will be initiated immediately after vaccine licensure and continue for at least 5 years. Annual interim reports will be submitted to FDA within 3 months after the yearly cut-off date. Supplemental data from an ongoing pregnancy registry in the United Kingdom, operated by the Health Protection Agency, will be included in all GSK analyses submitted to FDA.

- GSK has committed to provide the final clinical study report of study HPV-008 (A Phase II, double-blind, randomized, controlled, multi-center study to evaluate the efficacy of GlaxoSmithKline Biologicals' HPV-16/18 VLP/AS04 vaccine compared to hepatitis A vaccine as control in prevention of persistent HPV-16 or HPV-18 cervical infection and cervical neoplasia, administered intramuscularly according to a 0, 1, 6 month schedule in healthy females 15-25 years of age). The estimated date of study completion is 10/30/09, and the projected submission of this clinical report will be December 2010.

- GSK has committed to provide the final clinical study report for HPV-009 (A double blind, controlled, randomized, phase III study of the efficacy of an HPV16/18 VLP vaccine in the prevention of advanced cervical intraepithelial neoplasia (CIN2, CIN3, adenocarcinoma *in situ* [AIS] and invasive cervical cancer) associated with HPV16 or HPV18 cervical infection in healthy young adult women in Costa Rica (study under supervision of National Cancer Institute). The estimated dates of completion and projected date of submission of final clinical study reports are pending confirmation from the National Cancer Institute.

- GSK has committed to provide the final clinical study report for HPV-015 (A phase III, double-blind, randomized, controlled study to evaluate the safety, immunogenicity and efficacy of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a three-dose schedule (0, 1, 6 month) in healthy adult female subjects aged 26 years and above.) The estimated date of study completion is 10/30/10, and the projected submission date of the final clinical study report is 12/11.

- GSK has committed to provide the final clinical study report for HPV-023 (A blinded long-term follow-up study of the efficacy of candidate HPV-16/18 L1 VLP AS04 vaccine in young adult women in Brazil vaccinated in the phase IIb, double-blind, multi-center primary study HPV-001 and having participated in the follow-up study HPV-007). The estimated date of study completion is 9/30/10 and the projected date of final clinical study report is 9/11.

- GSK has committed to provide the final clinical study report for HPV-024 (An open, phase II, multicenter study to assess the safety and immune response to a HPV-16/18 L1 VLP AS04 vaccine fourth dose in healthy, young, adult women in North America previously vaccinated with 3 doses of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine). The study was completed 12/22/08 and the projected date of the final clinical study report is 9/09.

- GSK has committed to provide the final clinical study report for HPV-040 (A phase III/IV, community-randomized, controlled study to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule in healthy female –(b)(4)--- study participants aged 12 – 15 years.) The estomated date of study completion is 6/30/14, and the projected date of submission of the final clinical study report is 12/15.

4. Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls – See review by Dr. Robin Levis. Cervarix is unique in that it contains a novel adjuvant, AS04, which contains aluminum hydroxide and monophosphoryl lipid A. In addition, the vaccine was produced using insect cells. The HPV-16/18 L1 VLP AS04 vaccine is manufactured through recombinant DNA technology using the baculovirus expression system. AS04, which contains aluminum hydroxide ($Al(OH)_3$) and 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), was included as an adjuvant

in Cervarix to enhance the immune response to the VLPs for HPV-16 and HPV-18. MPL is derived from cell wall lipopolysaccharide (LPS) of the Gram-negative *Salmonella minnesota* R595 strain, but demonstrates greatly reduced toxicity and pyrogenicity compared to the parent LPS molecule. GSK and many research groups are currently studying the mechanisms of action of MPL and $Al(OH)_3$. MPL is a stimulator of the innate immune system, thought to act primarily as a Type 4 Toll-like Receptor (TLR4) agonist. GSK has data to suggest that like $Al(OH)_3$, MPL acts locally at the site of injection to target antigen presenting cells (APCs). AS04 appears to enhance activation of APCs and migration into the local draining lymph node. Other data suggest that as compared to LPS, MPL results in a lower induction of proinflammatory cytokines at the injection site.

4.2 Animal Pharmacology/Toxicology – See reviews by Dr. Steve Kunder, Ph.D., Dr. Ching-Long Sun, Ph.D. and Dr. Marion Gruber, Ph.D.

4.3 Neurology Consult – See review by Dr. Patricia Coyle, M.D.

4.4 Statistical Review – See review by Dr. Martha Lee, Ph.D, OBE.

4.5 Office of Biostatistics and Epidemiology – See review by Dr. Michael Ngyuen, M.D.

CLINICAL REVIEW

5. Clinical and Regulatory Background

5.1 Disease Studied and Available Interventions: Genital HPV infection is the most common sexually transmitted disease in the United States. The Centers for Disease Control and Prevention (CDC) estimates that more than 6 million people are infected each year.[3] More that > 100 HPV types have been identified, and approximately 40 HPV types infect the human genital tract. Most of these infections are self-limited, although certain high-risk HPV types are known to be carcinogenic. HPV-16 (alpha-9) and HPV-18 (alpha-7) were classified as cervical carcinogens by the World Health Organization International Agency for Research and Cancer in 1995, and HPV 31 and HPV 33 (alpha-9) were categorized as probably carcinogenic.[4,5] HPV 16 is considered a very efficient carcinogen, and is associated with approximately 55% of cervical cancers globally. HPV 18 is another important oncogenic HPV type and is associated with adenocarcinoma and another approximately 16% of other cervical cancers. Other oncogenic HPV types include HPV-31, 33, 39, 45, 51, 52, 56, 58, and 59, and account for a lower proportion of cervical cancers. The American Cancer Society estimates that approximately 11,270 cases of invasive cervical cancer will be diagnosed in the United States in 2009, and that approximately 4070 women will die from the disease. In the United States and other developed countries, the number of cases of cervical cancer and number of deaths from cervical cancer has decreased significantly, and is largely the result of women getting regular Pap tests.[6] Worldwide, the World Health Organization (WHO) indicates that cervical cancer is the second most common cause of female cancer mortality, with 288,000 deaths yearly. The WHO estimates that approximately 510,000 cases of cervical cancer are reported each year, with 80% of cases in developing countries.[7]

Cervical cancer has been associated with HPV infection. The applicant, GlaxoSmithKline (GSK), in conjunction with MedImmune, began a clinical development program in 1999

[3] CDC. Quadrivalent Human Papillomavirus Vaccine, Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007; 56 (RR02):1-24.
[4] Schiffman M et al. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. Infectious Agents and Cancer 2009; 4:8
[5] Schiffman M et al. Human papillomavirus and cervical cancer, The Lancet 2007; 370 (9590): 890-907
[6] http://www.cdc.gov/cancer/cervical/statistics/
[7] http://www.who.int/vaccine_research/diseases/hpv/en/

with a recombinant HPV virus-like particle (VLP) vaccine for the prevention of cervical cancer. The applicant's clinical development program proceeded using a bivalent VLP vaccine, Cervarix, that contains the major capsid protein (L1 protein) from HPV-16 and HPV-18, which together are thought to be responsible for more than 70% of cervical cancers. Cervical intraepithelial neopalsia grade 2+ (CIN 2+) is considered to be a precursor to cervical cancer. A vaccine that is efficacious in providing protection against HPV types 16 and 18, based on available epidemiological data, might be capable of having an impact in preventing cervical cancer, and other HPV associated diseases related to the vaccine HPV types.

Endpoint for demonstrating efficacy
In November 2001, the Vaccines and Related Biological Products Advisory Committee considered appropriate endpoints for licensure of HPV vaccines and determined that given standard of care in developed countries, CIN 2/3 and AIS or worse associated with vaccine HPV types could be considered a valid surrogate endpoint for cervical cancer. Thus, the primary efficacy endpoint for study HPV-008 was the prevention of CIN 2+ associated with the relevant vaccine HPV type for which the subject was naïve at baseline. Persistent infection with an oncogenic HPV type is also known to be associated with development of cervical cancer, although the specific duration of infection associated with oncogenesis has not been defined for the different oncogenic HPV types.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

Gardasil is a licensed vaccine which contains 4 HPV types, HPV types 6, 11, 16, and 18 and an aluminum adjuvant. This product was licensed in June, 2006 for use in females 9 to 26 years of age in the United States, and has been demonstrated to have efficacy in the prevention of vaccine HPV type related genital disease in women without evidence of infection related to the relevant HPV type at the time of vaccination. The present indications for Gardasil include the following: prevention of cervical cancer, vaginal and vulvar cancer related to HPV 16 and 18; genital warts related to HPV 6 and 11; and cervical intraepithelial neoplasia grades 2/3 (CIN 2/3) or worse, adenocarcinoma in situ, cervical intraepithelial neoplasia grade 1 (CIN 1), vulvar intraepithelial neoplasia grades 2 and 3 (VIN 2/3), and vaginal intraepithelial neoplasia grades 2 and 3 (VaIN 2/3) related to HPV types 6, 11, 16, and 18. There is no clear evidence of protection against vaccine HPV type-related genital disease present at the time of vaccination, nor against non-vaccine HPV type-related genital disease.

5.3 Previous human experience with the product or related products as well as foreign experience

There is experience with Phase I, II, and III trials conducted during the development of Cervarix. Cervarix has been licensed for use in 77 other countries since 2007. The vaccine was first licensed for use in Australia in women 10-45 years of age (5/21/07), and received marketing approval in the European Union (9/24/07). In addition to safety information available from the clinical trials which supported licensure, passive reports of post-marketing adverse events have been submitted to the BLA submission to provide additional safety data.

5.4 Regulatory Background Information: The initial IND was submitted by MedImmune, and GSK continued development of the product to license application. Cervarix has been investigated under a U.S. Investigational New Drug (IND) application to CBER beginning in September 1998. Studies have been conducted both under IND as well as in non-IND studies outside the U.S. These study reports were submitted to the

Biologics License Application (BLA) in support of licensing the product. GSK submitted a BLA for Cervarix on March 29, 2007. In review of this original submission, CBER assessed that additional efficacy and safety data were required in order for CBER to satisfactorily complete their review. A Complete Response letter was sent to GSK on 12/14/09. GSK provided satisfactory responses to the comments, and all requests had been completed as of the re-submission date of 3/27/09.

Table 1- Regulatory Background Information [CBER generated]

Date	Action
7/98	Pre-IND meeting
9/98	Original IND Submission
11/01	VRBPAC meeting to discuss Endpoints for Phase 3 trials
2/04	End of Phase 2 meeting
5/06	Pre-BLA Meeting
3/07	Submission of final part of rolling BLA
7/10/07	Request for safety meta-analysis for all MPL products
12/14/07	CR Letter sent
6/26/08	Meeting with CBER and GSK re:discussion of safety and proposal for final efficacy 008
10/4/08	Meeting with CBER and GSK re: discussion re: AS04 and MPL
3/30/09	Completion of responses to CR letter
6/22/09	Request for NCI analysis of spontaneous abortions in HPV-008 and HPV-009
7/13/09	First labeling comments sent to GSK
7/20/09	Second labeling comments sent to GSK
9/9/09	VRBPAC meeting to discuss Cervarix
10/15/09	Approval of BLA

Phase I/IIa clinical studies were conducted under IND and included the following studies: HPV-002, HPV-003, HPV-004 and HPV-005. Phase IIb/III clinical studies submitted to the BLA conducted under IND included protocols HPV-001, HPV-007, HPV-008, HPV-009, HPV-010, HPV-015, and HPV-016. Phase III clinical studies not conducted under IND included HPV-012, HPV-013, and HPV-014. Study HPV-008 is ongoing (although a final analysis has been submitted to the BLA in support of licensure). The final analysis of and study HPV-009 is ongoing. Studies that enrolled pediatric subjects included Parent/Guardian consent as well as subject assent.

6 Clinical Data Sources, Review Strategy, and Data Integrity

6.1 Material Reviewed

BLA 125259 contained the sponsor's clinical study reports.

6.2 Tables of Clinical Studies

Table 2 - Clinical Studies Reviewed in Cervarix BLA

Study Number	Vaccine HPV Type	Phase	Endpoint	Total sample size: Cervarix™ [C]/Control	Geographic Distribution of Study Populations	Dates conducted
002	16, 18 & 16/18	I	S and I for monovalent and bivalent vaccine in naïve females 18-30 years of age	N=49	United States	2/99-7/99
003*	16/18 (includes non-naïve)	I/IIa	S and I for bivalent vaccine in non-naïve females 18-30 years of age	N=61 (31 C/30 AlOH3)	United States	11/99-6/01
004*	16/18 (no adjuvant, AlOH3, AS04)	I/IIa	S and I for adjuvanted and unadjuvanted products in naïve females 18-30 year s of age	N=60	United States	10/00-12/01 + 4 year extension for subgroup
005*	16/18 (dose ranging)	IIa	S and I for different VLP doses adjuvanted with AS04 or Al(OH)3 in naïve females 18-30 years of age	N=209	United States	10/99-5/01 + 4 year extension for subgroup
001*	16/18	IIb	E (incident infection), I, S - RCT in naïve* females 15-25 years of age (Cervarix™ compared to Al(OH)3 [18 months initial with extension to 27 months]	N=1113 (560 C/553 AlOH3)	Brazil, Canada and United States	1/01-4/03
007*	16/18	IIb	Extension study of HPV-001 in subgroup to follow E, I and S [follow-up up for additional 3 years]	N=776 (extension of study HPV-001: 393C/383 AlOH3)	Brazil, Canada and United States	11/03-7/05
008*	16/18	III	E, I, and S RCT study (CIN2+ related to HPV 16/18) in females 15-25 years of age (naïve and non-naïve) compared to Havrix	N=18644 (9319C/9325 Havrix)	Asia, Europe, North Americas, South America	5/04-ongoing (final analysis event driven with continued follow-up of subjects to 4 years]
009*†	16/18	III	E, I and S RCT study (CIN2+ related to HPV 16/18) in females 15-25 years of age (naïve and non-naïve)	N=7466	Costa Rica	Approximately 7/04 - ongoing
012	16/18	III	I and S uncontrolled study to compare immune responses in different age groups and lot consistency for vaccine produced by different methods	N=770 (lot consistency) (158 in 10-14 yo ♀ and 612 in 15-25 yo ♀)	Europe	9/04-7/05 (+12 months additional data provided to date)
013*	16/18 (10-14 year old girls)	III	I and S RCT in females 10-14 years of age (Cervarix™ compared to Havrix)	N=2067 (1035C/1032 Havrix)	Asia, Australia, Europe	6/04-8/05 (+ 12 months additional data provided to date)
014	16/18 (15-55 year old ♀)	III	I and S uncontrolled study to compare immune responses in females 25-55 years of age to those 15-25 years of age	N=666 (229 in 15-25 yo♀, 226 in 26-45 yo ♀, and 211 in 45-55 yo ♀)	Europe	10/04-7/05 (+12 months additional data provided to date)
015*†	16/18 (26-55 year old ♀)	III	E, I, and S RCT study (Persisent infection and CIN1+) in women >25 years of age as compared to Al(OH)3	N=5751 (2880C/2871 AlOH3)	Asia, Australia, Europe, North and South America	2/06-ongoing
016	16/18	III	I and S study for lot consistency in 18-25 year old females	N=798 (lot consistency)	Europe	10/05-9/06

S=Safety; I=Immunogenicity; E=Efficacy; RCT= Randomized Controlled Trial; Naïve = no evidence of exposure to relevant HPV type; Naïve*=in study HPV-001, subjects had no evidence of exposure to oncogenic HPV types and had normal Pap test at baseline
Non-naïve = evidence of exposure to relevant HPV type
* Double-blind, randomized, placebo-controlled studies
† Ongoing

Clinical study reports from 13 clinical trials were provided in the BLA. In addition to the study reports for studies HPV-002, -003, -004, -005, -001/007-008, 012, 013, 014, and 016, a report for the ----------(b)(4)----------, along with a report for sero-HPV-106, an epidemiology study conducted in Brazil were submitted. Study HPV-015 included an interim safety analysis of women 25-55 years of age, and SAEs and deaths were included in totals from the safety analysis; no efficacy data were available in this population for this BLA. A copy of a safety data report for AS04 was also included (prepared 2/06), although more detailed information was requested regarding the safety database for GSK products either licensed or in development which included MPL as an adjuvant (see review of safety). The study report for HPV-009 included tables of serious adverse events with case narratives, and pregnancy case narratives, although since this is an ongoing study, most of the cases were still blinded since this is an ongoing study. Narratives for subjects with serious adverse events, deaths, or pregnancies were included as well, although in this document, most of the cases were listed as having blinded vaccine. Subject treatment allocations were found within the JMP datasets, which were closely reviewed. Reviewer generated tables were constructed from review of the unsolicited datasets to more closely review SAEs, unsolicited adverse events throughout the studies, as well as diseases with potentially autoimmune causes.

In addition, multiple additional (annex) reports for several studies were also submitted. These included additional reports for study HPV-002; study HPV-003; study HPV-004; study HPV-005; pooled study report for study HPV-004 and HPV-005; study HPV-013 (through Month 24); study HPV-001; study HPV-007 through Month 36); study HPV-012; and study HPV-014 (through Month 24). In addition, study HPV-008 was submitted with data from interim analysis at the time of the original BLA (3/07); and at the time of the final analysis (3/09). In addition, there were pooled safety data meta-nalyses for all studies, with unblinded tables provided for overall unsolicited events Days 0-29, SAEs throughout the studies, New Onset Chronic Diseases (NOCDs) throughout the studies, and safety updates.

In response to the Complete Response letter, GSK submitted additional documents to address CBER comments and these were reviewed. Additionally, GSK submitted summary reports of safety and efficacy, an updated summary of safety, and an overview of the Cervarix development program, which were also reviewed.

6.3 Review Strategy

The individual clinical study reports, summary reports, and overviews were initially reviewed (Phase I, II, and III), followed by review of SAS datasets with JMP software. As noted above, the safety datasets for the unsolicited adverse events were carefully reviewed, and reviewer generated tables were constructed. Many requests for additional clinical narratives for subjects identified in the review of the unsolicited datasets (wunsol) were made in many communications (see licensing package for all telecons and dates), and the responses from the sponsor were reviewed as well. The data submitted in response to the complete response letter was also reviewed. The final submission to the complete response letter included the final analysis of the clinical study report for study HPV-008.

6.4 Good Clinical Practice (GCP) and Data Integrity – See BIMO review by Mr. Solomon Yimam. There were several issues identified within review of the BLA as related to GCP. Please see separate review by Mr. Yimam. Data from one study site in study HPV-008 were not included in analyses because of concerns of data integrity. In addition, when problems were identified with sites in Brazil, GSK undertook action to investigate these issues and correct them. GSK indicated that they had not and will not utilize the services of any disbarred personnel as defined by Section 306 of the Food, Drug and Cosmetic Act.

6.5 Financial Disclosures – From data provided by the sponsor, the sponsor had not entered into any disclosable financial arrangements with investigators involved in studies HPV-001/007 and HPV-008 except as follows:

Study HPV-008: 3 investigators and 1 sub-investigator at 3 sites which enrolled a total of 0.93% of subjects (support of clinical research and honoraria).

Study HPV-001/007: 1 investigator and 1 sub-investigator at 1 site which enrolled a total of 3.2% of subjects (honoraria).

7. Human Immunogenicity – As there were so few cases of breakthrough infections or vaccine related dysplasias in subjects who were not yet exposed to these vaccine HPV types, an immune correlate of protection could not be identified. Up to 76 months following first vaccination in study HPV-001 (up to 70 months following completion of the full vaccination course), 98.6% or more of the vaccinees in the According to Protocol (ATP) population for Immunogenicity remained seropositive for both HPV-16 and HPV-18 IgG antibodies as measured by enzyme-linked immunosorbent assay (ELISA). Geometric mean titer (GMT) levels for both HPV-16 and HPV-18 reached a plateau during study HPV-007 at approximately one log below the peak response level observed at Month 7 (in study HPV-001) without evidence of apparent further decline between Month 18 and the last time intervals evaluated (Months 69-74 and 75-76). Seropositivity rates and GMTs were very similar in the Total Vaccinated Cohort as compared to the ATP cohort for immunogenicity out to Months 69-74 and Months 76-76. GMTs in the vaccine group were much higher than subjects in the control group and persisted through Month 76. Immune responses will also be presented in each study.

No breakthrough cases of **persistent HPV-16/18 infection** (6-month and 12-month definition) were observed in the vaccine group during studies HPV-001 and HPV-007. However, three cases of breakthrough HPV-**16/18 incident infection** were reported in the vaccine group. The ELISA titers obtained for these subjects with breakthrough infection were provided. In two subjects, when compared to subjects in the ATP cohort for immunogenicity, the GMTs for anti-HPV-16 and-18 were lower throughout the study period as compared to subjects who did not develop an infection with either HPV-16 or HPV-18. The third subject's GMTs were somewhat lower for HPV 16 initially, but were higher than GMTs in the ATP cohort at the later time points, so there was no consistent pattern noted in these subjects with "breakthrough" cases. Because of the low number of subjects with breakthrough cases, and the lack of a consistent pattern of ELISA titers in subjects with a breakthrough case, an immune correlate of protection was not possible to identify.

The seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 pseudovirion (PSV) neutralizing antibodies in a subset of subjects were presented. GMT levels for both HPV-16 and HPV-18 assessed by assays for PSV neutralizing antibodies showed a plateau that began approximately at Month 18 post vaccination and was sustained for up to 76 months of follow-up. Seropositivity rates for both HPV-16 and HPV-18 ($\geq$ 98.0%) were similar to those observed with ELISA ($\geq$ 98.6%).

Immune responses to two non-vaccine HPV types also were reported in study HPV-007 involving the bivalent HPV vaccine. Although the anti-HPV 31 IgG seropositivity rates were 69.2% and HPV-45 IgG seropositivity rates in a subset of vaccine recipients were 92.3% at Months 51-56, the seropositivity rate for PSV neutralizing antibodies for HPV-31 was 47.6% seropositivity at Month 7 and had fallen to 0% by Month 45-50. For HPV-45, the seropositivity rate for PSV neutralizing antibodies was 9.5% at Month 7 and 0% at Month 45-50 in a subset of subjects who were followed from study HPV-001 to study HPV-007.

This observation may indicate that the immune response to non-vaccine HPV types HPV-31 and HPV-45 may be less robust and shorter in duration as compared to the immune response elicited for HPV 16 and HPV 18.

8.Clinical Studies: The Phase I/II trials will be reviewed, followed by the Phase IIb/III trials (controlled, then uncontrolled studies).

Phase I/II studies include the following:

- **HPV-002:** Safety and immunogenicity of HPV 16/18 and components (N=49, 18-30 yrs)
- **HPV-003:** Safety and immunogenicity in previously infected women (N=31 C, 30 AlOH3; 18-30 yrs)
- **HPV-004:** Safety and immunogenicity of HPV 16/18 with AS04, alum, or non-adjuvanted (N=60, 18-30 yrs)
- **HPV-005:** Safety and immunogenicity of HPV 16/18 at 3 doses of VLPs with either alum or AS04 (6/6+AS04, 20/20+AS04, 60/60+AS04, 20/20+AlOH3) (N=209, 18-30 yrs)

These 4 studies were conducted by ----------(b)(4)----------.)

Completed Phase IIb/III studies include the following:

- **HPV-001:** Proof of concept that Cervarix prevents incident infection with HPV 16 and/or 18 in naïve women (secondary persistent infection, abnormal cytology, immunogenicity, safety) compared to ALOH3 (N=560 C, N=553; 15-25 yrs)
- **HPV-007:** Long term efficacy study of HPV-001 in prevention of HPV 16 and/or 18 incident infection (secondary persistent infection – 6 & 12 months, abnormal cytology, immunogenicity, safety) (N=393 C, 383 AlOH3; females from HPV-001)
- **HPV-008:** Pivotal efficacy trial in prevention of HPV 16 and/or18-related CIN 2+ (secondary safety and immunogenicity) compared to active control Havrix (N=9319 C, 9325 HAV; 15-25 yrs)
- **HPV-013:** Safety and immunogenicity of Cervarix in young females compared to active control Havrix (N=1035 C, 1032 HAV; 10-14 yrs)

Uncontrolled Studies include the following:

- **HPV-012:** Lot consistency (immunogenicity) between 3 industrial production lots --b(4)----------; and then NI of those ----b(4)---------- lot (secondary safety, NI of --b(4)-- in 10-14 yrs as compared to 15-25 yrs; NI of ----b(4)---------- produced HPV vaccine in terms of immunogenicity of HPV vaccine used in HPV-001) (N=770C, 10-25 yrs)
- **HPV-012** Ext: Long term immunogenicity (secondary safety) in 012 subjects
- **HPV-014:** NI of immune response in women 26-45 yrs as compared to women 15-25 yrs (secondary NI in women 46-55 yrs and safety in all age groups) (N=666C, 15-55 yrs)
- **HPV-014 Ext:** Long term immunogenicity (secondary safety, immune response in genital samples) in 014 subjects (N=524)
- **HPV-016:** Lot consistency study vaccine manufactured in different quantities. (N=798C)

Other Studies (contributed subjects to pooled safety data, not individually reviewed)

- **----—----------b(4)----------**
- **HPV-015:** Efficacy in prevention of persistent infection (6-mo) and 16-18 related CIN1+ (secondary persistent infection 12 mo, 16/18 CIN 1+ or CIN 2+, abnormal cytology, immunogenicity, safety) (N=2280 C, 2871 AlOH3; **26 yrs +)**

8.1: Trial #1: HPV-002 [MI-CP044]: A Phase I Study of the Safety and Immunogenicity of HPV 16/18 VLP Vaccine (formerly MEDI-517), a Vaccine Against Human Papillomavirus Types 16 and 18, in Healthy Adult Female Subjects.

Study Dates: 2/8/99 to 7/8/99.

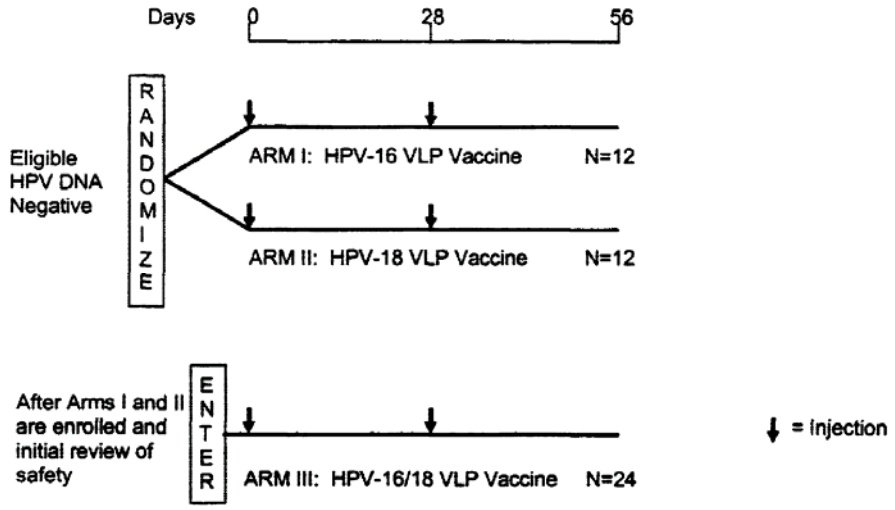
Study Site: The study was conducted at one site in Austin, Texas.

Study Objectives:

- **Primary objective:** assess the safety of HPV-16/18 VLP vaccine and its components HPV-16 VLP vaccine and HPV-18 VLP vaccine in healthy young adult women. All vaccines were formulated with AS04 adjuvant (formerly called SBAS4).
- **Secondary objectives:** determine the immune response to HPV-16 VLP vaccine, HPV-18 VLP vaccine; HPV-16/18 vaccine after two monthly injections; and to HPV-16 VLP vaccine after a 3rd vaccination given 12 weeks after the 2nd vaccination.

Study Design: This was a Phase I, randomized, open label study. A schematic of the study is provided below. A 3rd dose of HPV-16 VLP vaccine was administered at Day 112 and safety and immunogenicity further analyzed at Day 140.

Figure 1 – Study HPV-002 Flowchart



Source: STN 125259/0, CSR HPV-002, p. 21

Table 3 – Study HPV-002: Treatment Plan

Dosage Level (Vaccine)	Sample Size	Dosage Schedule	Time of Analysis
HPV 16 L1 VLP 20 mcg+AS04*/0.5 mL	12	0, 28; 8 subjects @ 112 days	56 and 140 days
HPV 18 L1 VLP 20 mcg+AS04*/0.5 mL	12	0, 28 days	56 days
HPV 16 L1 VLP 20 mcg +18 L1 VLP 20 mcg+AS04*/0.5 mL	25	0, 28 days	56 days
Total	49		

*AS04 formerly called SBAS4 = aluminum hydroxide 500 mcg + monophosphoryl lipid A (some lots with thimersol)

Summary Results for HPV-002: The HPV-16, HPV-18 and HPV-16/18 VLP vaccines used in this study were tolerated and no limiting toxicities were observed. Serologica1 and cell mediated immune responses to both HPV-16 Ll VLPs and HPV-18 Ll VLPs, separately and in combination, were detected after two injections of study vaccine. There was no evidence of interference between the HPV-16 and HPV-18 components of the HPV-16/18 VLP vaccine with respect to stimulation of an immune response to each of these components. Further increases in serological immune response to HPV-16 L1 VLP vaccine was observed in all subjects after dose 3 of this vaccine. (Details of Study HPV-002 can be found in Appendix A-Phase I/IIa studies).

HPV-002, Annex 1: The dates of this study were 2/8/99 – 8/5/03. This supplemental report summarizes the results of the longer-term follow-up that includes the results of the binding ELISA and inhibitory ELISA assays conducted by GlaxoSmithKline (GSK) to evaluate serological responses after vaccination with 3 injections of the HPV-16 vaccine. These analyses were conducted under an amendment to the protocol. Subjects who returned for their visit at the 4.5 year time point, had all samples tested using the binding ELISA (new assay), including those from the parent study (Study Days 7, 28, 35, 56, 112, 119, and 140) as well as the extension study (Study Year 1.5, 2, 2.5, 3, 3.5, 4 and 4.5). Seven of the eight subjects who received dose 3 of the vaccine enrolled in this extension study.

During the primary study, all results for testing antigen against HPV-18 were negative (since these subjects did not receive HPV-18 vaccine). Therefore, ELISA binding and inhibiting evaluations against HPV-18 were not performed for the long term specimens.
Due to the small number of subjects enrolled in the extension study, the variability in the length of the follow-up, and the non-uniformity in the antigen concentrations eliciting a Cell Mediated Response (CMI), the CMI assay results were only presented as a subject listing.

Summary of HPV-002, Annex 1: At 4.5 years after the first injection, ELISA binding and serum antibody responses to HPV-16 persisted in all subjects, and inhibitory ELISA responses to HPV-16 were detectable in 1/3 (33.3%) subject. Overall, HPV-16 and HPV-18 lymphoproliferative responses and specific IFN-γ and IFN-gamma responses remained elevated in the 7 subjects from 2 to up to 4.5 years. The sponsor concluded that these data suggest that the VLP-like vaccine adjuvanted by ASO4 induced a sustained immunogenicity and supported its continued clinical evaluation. (Details of Study HPV-002, Annex 1 can be found in Appendix A).

8.2: Trial #2: HPV-003 [MI-CP058]: A Phase I/II Study of the Safety and Immunogenicity of HPV 16/18 VLP Vaccine, a Virus-Like Particle Vaccine Against Human Papillomavirus Types 16 and 18, in Healthy Adult Female Subjects who are HPV-16 or HPV-18 DNA positive.
Study Dates: 11/22/99 to 6/19/01.
Study Site: The study was conducted at 27 sites in the US.

Study Objectives

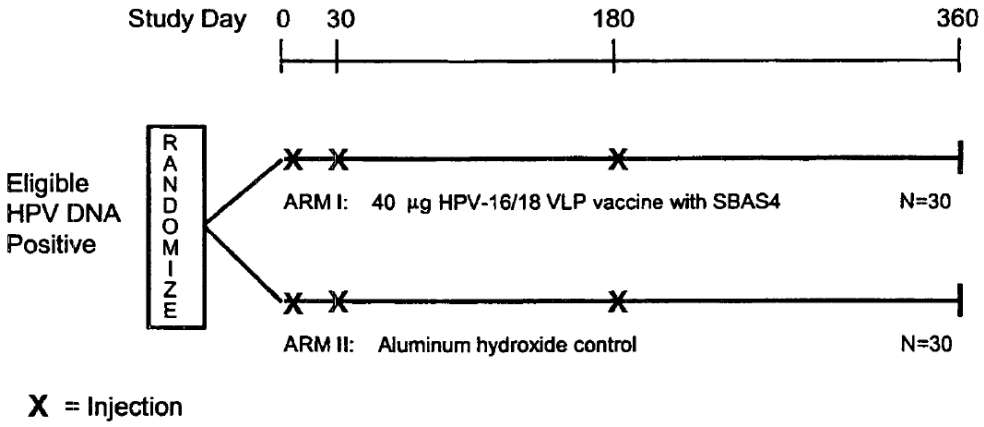
- **Primary objective:** describe the safety of 40μg HPV 16/18 VLP vaccine with a control of 0.5 mg aluminum hydroxide, when given to healthy adult women who had evidence of HPV-16 and/or HPV-18 DNA detected in cervical brushings.
- **Secondary objectives:**
  - Determine the effect of HPV16/18 VLP vaccine compared with aluminum hydroxide control on the proportion of subjects who were positive for HPV DNA (of the same type present at study entry) in cervical swab (brushing) specimens taken on Study Day 60 (30 days after the second injection of study vaccine). The proportion of subjects who were

positive for HPV DNA (of the same type present at study entry) was also to be evaluated at Study Day 210 and at Study Day 360.

- Describe the antibody response (by ELISA) to HPV 16/18 VLP vaccine through 360 days after the first injection.

Study Design: This was a Phase I/II, double-blind, randomized, comparative trial of HPV-16/18 VLP vaccine or an aluminum hydroxide control (alum) given at 0, 30, and 180 days by intramuscular injection, in healthy adult female subjects aged 18 to 30 years of age. A flowchart of the study is shown below.

Figure 2 – Study HPV-003 Flowchart



SBAS4 = AS04
Source: STN 125259/0, CSR 003, p. 18

Duration: Each subject was to be followed for 1 year.

Vaccine Products Used:
HPV 16/18 L1 VLP vaccine: 20 mcg HPV 16 VLP + 20 mcg HPV 18 VLP + AS04 (formerly SBAS4) (0.5 mg aluminum hydroxide + 50pg 3'-deacylated monophosphoryl lipid A) Lot number L099AH04A or Lot 099AH04AW) was supplied in single use vials (0.75 mL).
Aluminum Hydroxide (0.5 mg per 0.5 mL dose): Aluminum hydroxide (Lot 0 99AH01A or Lot #99AH01AW) was supplied in single use vials containing 0.75 mL of aluminum hydroxide at a concentration of 0.5 mg of aluminum in the form of aluminum hydroxide per 0.5 mL.

Reason for dose selected: This dose was selected on the basis of safety and immunogenicity results obtained in HPV-002 and was one of the doses which were studied in two Phase II companion studies, HPV-004 and HPV-005 (also known as MI-CP055 and MI-CP057, respectively).

Population: Healthy female adults (18-30 years) who were using acceptable contraception beginning 30 days before dose 1 through 60 days after dose 3, whose cervical specimen was positive for HPV-16 and/or HPV-18 DNA using the Digene Hybrid Capture II HPV test within 21 days of study entry, with cervical cytology by Pap smear that was either normal or no greater than ASCUS or AGCUS (using the Cytyc ThinPrep Pap Test) within 21 days of study entry, and no evidence of anogenital HPV disease or evidence of other gynecologic pathogens on pelvic exam within 21 days of study entry. Those subjects with ASCUS or AGCUS must have had a

clinical evaluation by colposcopy within the previous month that showed no evidence of CIN or SIL. Women were excluded for acute illness, pregnancy, history of cancer or other specified illnesses (e.g., Hepatitis C, Hepatitis B, HIV) or prior receipt of study material including monophosphoryl lipid A or prior receipt of a vaccine for HPV.

Vaccination Schedule: Each volunteer's dose of study vaccine was selected by random assignment. Each volunteer was to receive an injection of study vaccine on Study Days 0, 30, and 180 by intramuscular injection in the deltoid muscle. Subjects and investigators were blinded as to treatment assignment.

Summary Study HPV-003: In subjects with evidence of prior HPV 16 and/or 18 infection, the HPV 16/18 vaccine and the aluminum hydroxide control were generally well tolerated. Immunization was not associated with enhanced rates of clearance of HPV-16 or HPV-18 viral DNA as detected by the Hybrid Capture II test (Digene). Antigen- specific antibody responses to both HPV-16 and HPV-18 were demonstrated after two injections of study vaccine and were boosted after a third injection. (Details of Study HPV-003 can be found in Appendix A).

Study HPV-003, Annex 1: This annex report provided an analysis of clearance rates of HPV-16 and HPV-18 DNA in subjects who participated in study HPV-003 (also known as MI-CP058), using Delft Diagnostic Laboratories (DDL) HPV PCR Assay. In the DDL assay, ---b(4)------- PCR -----b(4)---------- DDL ----------b(4)---------- Any specimen testing positive using this "generic" PCR assay was then tested by type specific PCR for HPV-16 and HPV-18 for confirmation. Using the DDL assay, 35 women were found to be viral DNA positive for types HPV-16 and/or -18 at baseline. Four of these 35 women did not receive the full three-dose regimen and of the remaining 31 women, 11 subjects in the HPV 16/18 group and 12 in the alum control group had only HPV-16 identified at baseline; 3 subjects in each group had only HPV-18 identified at baseline. There was only 1 volunteer in each group who was HPV-16 *and* HPV-18 DNA positive at baseline.

In women who had DNA from a single HPV type identified at baseline, the rate of HPV-16 or HPV-18 viral DNA recovery by DDL PCR declined through Study Day 360 in both the HPV 16/18 and the alum control groups. The 1 volunteer in each of the HPV 16/18 or control groups with both HPV-16 and HPV-18 DNA at baseline did not clear at Study Day 360. Using the DDL assay, no enhanced rates of clearance of HPV-16 or HPV-18 DNA were detected in women receiving three injections of HPV 16/18 vaccine compared to alum controls. However, subject numbers were insufficient to definitively demonstrate differences in HPV DNA clearance between groups.
Summary Results, Study HPV-003, Annex 1: The PCR results were in agreement with those generated previously with the Digene assay in the original HPV DNA analyses in study HPV-003.

8.3: HPV-004 Trial #3 [MI-CP055]: A Phase II Double-Blind, Randomized Study to Evaluate the Safety and Immunogenicity of HPV 16/18 vaccine (formerly MEDI-517), a Virus-Like Particle Vaccine Against Human Papillomavirus Types 16 and 18, When Formulated With Aluminum Hydroxide, AS04 (formerly known as SBAS4), or Without Adjuvant, in Healthy Adult Female
Study Dates: 10/3/00-12/6/01
Study Site: The study was conducted at 6 clinical sites in the US.

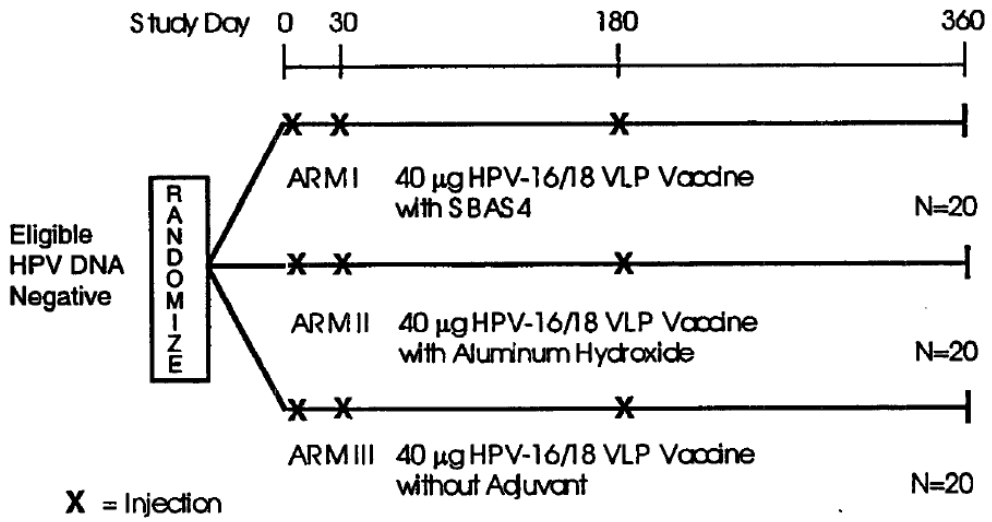
Study Objectives:

- **Primary objectives:**
  - Evaluate safety of three formulations of HPV 16/18 vaccine, two with adjuvant and one without adjuvant, when given by intramuscular injection at 0, 30, and 180 days to healthy adult female subjects who are HPV-16/18 seronegative and negative for DNA by PCR from high-risk HPV types.
  - Evaluate the immune response (by ELISA) 30 days after the third injection.

- **Secondary objectives**:
  - Evaluate the kinetics of the antibody response (by ELISA and neutralizing antibody) to HPV 16/18 vaccine through 1 year after the initial injection.
  - Evaluate the cell-mediated immune response to HPV 16/18 vaccine by lymphoproliferation assay and by interferon-γ (IFN-γ) and interleukin-5 (IL-5) release through 24 months after the initial injection.
  - Evaluate HPV-16 and HPV-18 immune responses by ELISA and inhibitory ELISA from 18 months through 48 months after the initial injection.

Study Design: This was a Phase II, double-blind, randomized, comparative trial of three formulations of HPV-16/18 vaccine, given at 0, 30, and 180 days by intramuscular injection to healthy adult female subjects aged 18 to 30 years. Subjects were randomized in a 1:1:1 ratio into Arms I, II, and III, respectively, with approximately 20 subjects per arm. A schematic of the initial part of the study is provided below.

Figure 3 - Study HPV-004 Flowchart



SBAS4=AS04
Source: STN 125259/0, CSR HPV-004, p. 23

Duration: Subjects were ultimately followed through 48 months after vaccination.

Vaccine Products Used:
HPV 16/18 VLP vaccine (40 mcg) with AS04 (formerly SBAS4) (0.5 mg aluminum hydroxide and 50 mcg 3'-deacyl monophosphoryl lipid A per 0.5 mL dose): HPV 16/18 vaccine was

supplied in single use glass syringes containing 0.6 mL of HPV 16/18 vaccine at a concentration of 40mcg/0.5 mL forrnulated with AS04 adjuvant. A 0.5 mL dose contained 20 mcg of HPV-16 VLPs plus 20 mcg of HPV-18 VLPs.

HPV 16/18 VLP vaccine (40 mcg) with aluminum hydroxide (0.5 mg per 0.5 mL dose): HPV 16/18 vaccine was supplied in single use glass syringes containing 0.6 mL of HPV 16/18 VLPs at a concentration of 40 mcg/0.5 mL formulated with aluminum hydroxide adjuvant. A 0.5 mL dose contained 20 mcg of HPV-16 VLPs plus 20 mcg of HPV-18 VLPs).

HPV 16/18 VLP vaccine (40 mcg) without adjuvant: HPV 16/18 vaccine was supplied in single use glass syringes containing 0.6 mL of HPV 16/18 VLPs at a concentration of 40 mcg/0.5 mL formulated with no adjuvant. A 0.5 mL dose contained 20 mcg of HPV-16 VLPs plus 20 mcg of HPV-18 VLPs and ----b(4)---------.

Population: Healthy female adults (18-30 years) who, within 3 weeks of study entry, were seronegative for HPV-16 and HPV-18 antibodies, had a normal Pap smear, had a pelvic examination showing no evidence of anogenita1 HPV lesions or other gynecologic pathogens, and had a cervica1 specimen negative for HPV. Women were excluded for acute illness, pregnancy, history of cancer or other specified illnesses (e.g., Hepatitis C, Hepatitis B, HIV), prior receipt of specified immunosuppressive therapy, prior receipt of study material including monophosphoryl lipid A or prior receipt of a vaccine for HPV.

Vaccination Schedule: Each volunteer's dose of study vaccine was selected by random assignment. Each volunteer was to receive an injection of study vaccine on Study Days 0, 30, and 180 by intramuscular injection in the deltoid muscle. Subjects and investigators were blinded as to treatment assignment.

Summary Study HPV-004: 40 mcg HPV 16/18 vaccine formulated with AS04, aluminum hydroxide or no adjuvant did not elicit a specific safety signal. Antigen-specific HPV 16 and 18 humoral and cellular immune responses to both HPV-16 and HPV-18 were demonstrated after two injections of study vaccine, were boosted after a third injection, and remained elevated above baseline at Study Day 360. ELISA titers were nominally higher in the AS04 group than in the aluminum hydroxide or no-adjuvant groups at Study Day 210. The kinetic profile of antibody to HPV-16 and HPV-18 was similar to the profile of neutralizing antibody, including a trend to highest responses to HPV-16 in the AS04. Although the AS04 formulation may be slightly more reactogenic, it appeared to induce the greatest humoral responses.
Reviewer's Comment: As noted, the anti-HPV 16 and anti-HPV 18 antibody levels as measured by ELISA were higher in the AS04 adjuvanted group > aluminum hydroxide group > no-adjuvant group. A higher immune response might be expected to result in prolonged duration of prevention of HPV 16 and/or 18 related disease, although this would not be able to be proven unless there is evidence of actual prolonged prevention. Regarding the parameters for cell-mediated immunity (lymphproliferative response, and IFN-γ and IL-5 release), the responses to HPV 16/18 vaccine were similar in the AS04 and alum-adjuvanted product. It is noted that both adjuvanted products elicited higher immune responses (humoral and cell mediated immune responses) as compared to the non-adjuvanted product. The sponsor used these data to support going further in development of the candidate vaccine using the AS04 adjuvant. Although no specific safety signal was identified (except for more local reactogenicity such as pain with the AS04 adjuvanted product, a much larger safety database would be needed to assess for more rare adverse events.) (Details of Study HPV-004 can be found in Appendix A).

Study HPV-004, Annex 1: Additional details of the cell-mediated immune response parameters (at 3 different doses of VLPs) were provided. The sponsor concluded the following:

- Specific proliferative responses were substantially induced after two vaccinations, and the third vaccination boosted slightly this specific response. The specific cellular immune response was persisting at Month 12 (Day 360)- 6 months after the third vaccination.
- Cytokine (IFN-γ and IL- 5) secretion levels were near background value at pre-vaccination for all groups. Significant increase in cytokine secretion were induced after two vaccinations and boosted by the third dose and was still present 6 months post 3. No significant difference could be observed between adjuvanted groups. Specific secretion of IFN-γ and IL- 5 were lower in the non- adjuvanted group.
- IFN-γ secretions were produced at a rather high level, revealing a Th1 profile of the cellular immune response induced. IL- 5 was also secreted in response to antigens, but at a lower level.

Study HPV-004, Annex 2 and 3: Annex 2 report contains data for results of immune responses at Year 1.5 and 2 for some subjects who participated in study HPV-004 (MI-CP055) as well as HPV-005 (MI-CP057). Annex 3 report contains data for study HPV-004 through Year 4. Safety was not followed in the extension study.
Study End Dates: 12/11/02 (last volunteer completed Year 2); 1/19/05 (last long-tern follow-up visit)

Subjects: 38 subjects from HPV-004 enrolled in the extension study. 20/38 subjects completed year 4 of the study (9 in the AS04 group; 2 in the aluminum hydroxide group; and 9 in the non-adjuvant group). 18 subjects did not complete the full follow-up: 13 were lost to follow-up; 3 withdrew consent; and 2 did not complete the study due to relocation. All subjects (except for subject except 1 received all 3 study vaccine injections # 431620 in the no- adjuvant group received only 2 injections.

The sponsor concluded that after 3 injections of HPV 16/18 formulated with AS04, aluminum hydroxide, or no adjuvant, ELISA binding and serum antibody responses to both HPV- 16 and HPV- 18 persisted through 3 and 4 years after the first injection. Inhibitory ELISA responses to both HPV- 16 and HPV- 18 were detectable at 3 and 4 years after first injection in more subjects in the AS04 adjuvant group, compared with those who received aluminum hydroxide adjuvanted formulation or unadjuvanted formulation. The magnitude of the antibody responses to both HPV-16 and HPV- 18 was most robust in the AS04 adjuvanted treatment group. Subjects who received HPV 16/18 with no adjuvant had ELISA binding and inhibitory responses that were lower in magnitude than subjects who had received HPV 16/18 with AS04 or aluminum hydroxide adjuvant. The sponsor indicated that the data support the continued clinical evaluation of HPV 16/18 formulated with AS04. (Details of Study HPV-004 Annex 2 and 3 can be found in Appendix A).

8.4 HPV-005 Trial #4 [MI-CP057]: A Phase II Double-Blind, Randomized, Dose Comparison Study to Evaluate the Safety and Immunogenicity of HPV 16/18 VLP Vaccine (with AS04) in Healthy, Adult Women
Study Dates: 10/29/99-5/24/01

Study Objectives
Primary Objective: Evaluate safety and antibody response (by ELISA at 30 days postdose 3) of three different doses of HPV 16/18 VLP vaccine with AS04 when administered IM at 0, 30 and 180 days to healthy adult females who were HPV 16/18 seronegative and high-risk DNA negative.

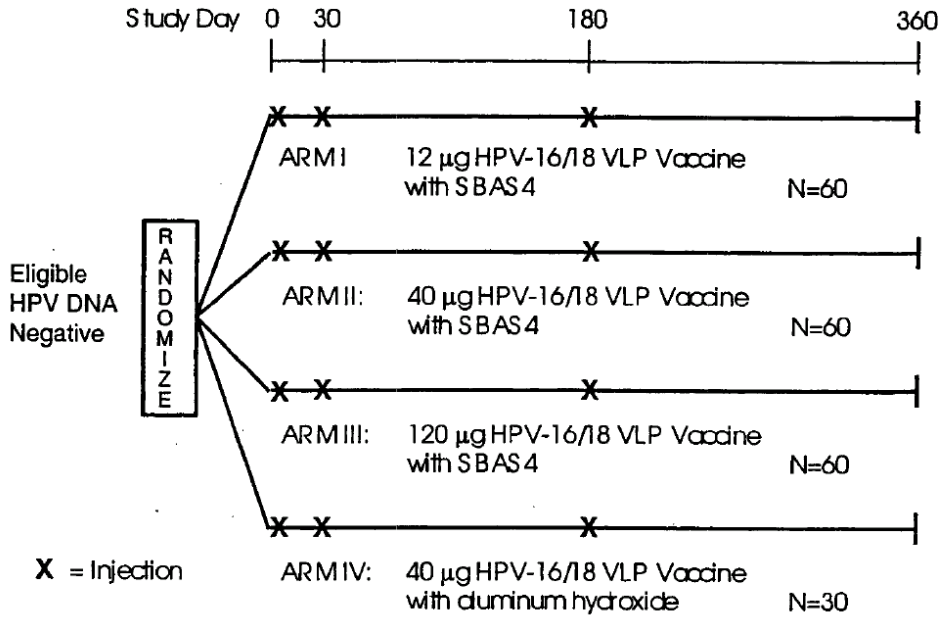
Secondary Objectives:

- Evaluate antibody response (by ELISA) to HPV 16/18 VLP vaccine with AS04 through 30 days after dose 3.
- Evaluate the neutralizing antibody response to candidate HPV 16/18 vaccine.
- Evaluated the cell mediated immune response to candidate HPV 16/18 vaccine by lymphoproliferation assay and by interferon gamma (IFN-γ) and interleukin-5 (IL-5) release.
- Evaluate the duration of immune response to candidate HPV 16/18 vaccine through 360 days (using assays listed.)
- Evaluate the antibody response to candidate HPV 16/18 vaccine in cervical and vaginal secretions.
- Evaluate the safety profile and immune response (using assays listed) of candidate vaccine with either AS04 or alum.

Study Design: This was a Phase II, double-blind, randomized, dose-comparison, multicenter study in healthy adult females 18-30 years of age. Subjects received one of three doses: 12, 40, and 120 µg formulated with AS04 on study days 0, 30, and 180. The subjects in the fourth study group received 40 mcg HPV 16/18 VLPs formulated with alum on study days 0, 30, and 180.

Subjects were to be randomized 2:2:2:1 ratio into the first three and fourth study groups, respectively. There were to be 60 subjects in each of the AS04 groups and 30 subjects in the alum group. Safety was assessed by clinical evaluation of adverse events for 30 days after each injection, evaluation of serious adverse events through 30 days after dose 3, and evaluation of laboratory variables at study days 0, 30, and 210. Data for specific, solicited, injection site and general adverse events were to be collected on diary cards provided at the time of each injection for 7 days after each injection. Immune response was evaluated by determination of serum antibody titers (ELISA) to HPV-16 and HPV-18 at study days 0, 7, 30, 60, 180, 210, and 360; by determination of an anti-HPV 16 and 18 neutralizing antibody titers at study days 0, 61, 210, and 360; and by cell mediated immunity to HPV 16 and 18 (lymphoproliferation and IFN-γ and IL-5 release) at study days 0, 60, 210, and 360. Cervical secretions were collected at screening and at study days 210 and 360 for evaluation of anti-HPV-16 and anti-HPV-18 antibody titers. Antibodies in cervical secretions and CMI were evaluated in a subset of subjects. All subjects at selected sites (app. 20% of the subjects) were to have this evaluation.

Figure 4 - Study HPV-005 Flowchart



SBAS4=AS04
Source: STN 125259/0, CSR 005, p. 24

Duration: Subjects were to be followed for 360 days.

Vaccine Products Used:
Vaccines Formulated with AS04 (0.5 mg aluminum hydroxide and 50µg 3-deacyl monophosphoryl lipid A per 0.5 mL dose):

- **HPV 16/18 12 mcg formulation:** Lot #99AH03A was supplied in single use vials containing 0.75 mL of HPV 16/18 vaccine at a concentration of 12µg/0.5 mL formulated with AS04. A 0.5 mL dose contained 6 mcg HPV 16 VLPs and 6 mcg HPV 18 VLPs.
- **HPV 16/18 40 mcg formulation:** Lot #99AH04A was supplied in single use vials containing 0.75 mL of HPV 16/18 vaccine at a concentration of 40µg/0.5 mL formulated with AS04. A 0.5 mL dose contained 20 mcg HPV 16 VLPs and 20 mcg HPV 18 VLPs.
- **HPV 16/18 120 mcg formulation:** Lot #99AH05A was supplied in single use vials containing 0.75 mL of HPV 16/18 vaccine at a concentration of 120µg/0.5 mL formulated with AS04. A 0.5 mL dose contained 60 mcg HPV 16 VLPs and 60 mcg HPV 18 VLPs.

Vaccine Formulated with Aluminum Hydroxide (0.5 mg aluminum in the form of aluminum hydroxide per 0.5 mL): HPV 16/18 40 mcg formulation: Lot #99AH02A was supplied in single use vials containing 0.75 mL of HPV 16/18 vaccine at a concentration of 40µg/0.5 mL formulated with aluminum hydroxide adjuvant. A 0.5 mL dose contained 20 mcg HPV 16 VLPs and 20 mcg HPV 18 VLPs.

Reason for Dose Selected: In a previous study, 40 mcg HPV 16/18 VLPs with AS04 was shown to be generally well tolerated and to induce an immune response. A range of doses was included in this study to provide additional safety and immunogenicity data for selecting a dose to be used for the further clinical development of the vaccine.

Population: The subjects were healthy females 18-30 years of age. They were screened by serum antibody testing, testing for HPV DNA, Pap smear, and physical examination to exclude those with evidence of current or prior HPV 16 and/or 18 infection.

Study HPV-005 Summary: HPV 16/18 formulations, 12 mcg with AS04, 40 mcg with AS04, 120 mcg with AS04, and 40 mcg with aluminum hydroxide, were generally tolerated. There were no apparent dosage effects seen in the frequency, duration, or intensity of solicited AEs or the frequency of unsolicited AEs in the AS04 groups except for injection site swelling which was seen more frequently in the 120 mcg dose group. Local reactions at the injection site were more frequent for all AS04 formulations compared to the aluminum hydroxide formulation, but there was no apparent difference in systemic AEs. Serological and CMI responses to both HPV 16 and HPV 18 were demonstrated after 2 injections of study vaccine (one each on study days 0 and 30), were boosted by dose 3 administered at study day 180, and remained elevated at study day 360. Although there was no consistent or clear evidence of a dosage effect on cellular responses demonstrated for the AS04 formulations, there was a trend towards higher ELISA titers with increasing dose level that suggested that the 12 mcg AS04 formulation was less immunogenic than the other AS04 doses tested. The sponsor used the higher ELISA titers as support for selection of HPV 16/18 40 mcg with AS04 formulation for subsequent clinical development. (Details of Study HPV-005 can be found in Appendix A).

Study HPV-005, Annex 1: In this report, the HPV vaccine specific antibody responses were described and compared the anti-HPV-16 and anti- HPV-18 antibody levels found in cervicovaginal secretions (CVS) with those found in serum.

A subset of subjects (approximately 20% planned of the total number of subjects) was evaluated for anti-HPV-16 and anti-HPV-18 antibody levels in CVS on Study Days 0, 210, and 360. Eligible subjects were those who received all three doses of AS04 or aluminum hydroxide formulations in study 005.

Subjects: 34 subjects enrolled in the study and 33/34 (97%) completed the study through study day 360. One subject was lost to follow-up. Mean age, mean weight, and race were similar across study groups. The mean age of the subjects was 24.3 years, with a range of 18-30 years. The majority of the subjects were white/non-Hispanic (79.4%).

Summary Study HPV-005, Annex 1: After immunization of subjects with 3 doses of the AS04 and aluminum hydroxide adjuvanted HPV-16/18 vaccines, HPV-16/18 IgG-specific responses in CVS were found in the majority of immunized subjects. At Study Day 210, IgG HPV-16/18-specific responses in the serum and CVS were detected in 80%-90% of subjects who received the candidate 40-µg dose of the AS04-adjuvanted HPV-16/18 vaccine. There appeared to be a dose effect on the magnitude of the responses found in the CVS and serum in the AS04 12-µg, 40-µg, and 120-µg treatment groups. There was a positive correlation between serum anti-HPV 16 and HPV-18 antibodies with antibodies in cervical secretions. This finding and the fact that there were no instances of detection of HPV-specific activity in the CVS in the absence of detection in the serum would suggest that the HPV VLP-specific antibody found in the CVS transudated from the serum. (Further details of Study HPV-005, Annex 1, can be found in Appendix A).

Study HPV-005, Annex 2: This report is identical to study 004, annex 2 report.

Study HPV-005, Annex 3: This report provided immunogenicity follow-up through 4 years of subjects who received study vaccine at the 40 µg dose level, formulated with AS04 or aluminum hydroxide, administered at 0, 30, and 180 days to healthy adult female subjects who were

seronegative for HPV-16 and HPV-18, negative for high-risk HPV DNA, with normal Pap smears.

The initial binding ELISA assay used for the first 3 years of the study was re-validated by GSK when supplies of reagents were exhausted. The new binding ELISA was used only on blood samples of subjects who completed years 3 and 4 of the extension study. All of those subjects' samples, including those from the parent study as well as the extension study, were re-tested using this new assay, the results of which are presented in this report.

Subjects: Of the 91 subjects randomized in the parent study (64 and 27 subjects in the AS04 40-µg HPV 16/18 group and the aluminum hydroxide 40-µg HPV 16/18 group, respectively), 69 subjects (48 and 21 subjects, respectively) received all 3 injections of study vaccine and were eligible to participate in the extension study. Of these 69 eligible subjects, 35 subjects (25 and 10 in the AS04 and aluminum hydroxide groups, respectively) were enrolled in the extension study and followed up at Year 2. Of these 35 subjects, 30 (85.7%) were followed through Year 3 and 27 (77.1%) were followed through Year 4. The reasons for not completing the extension study through Year 4 included lost to follow-up (4 subjects), withdrawal of consent (3 subjects), and other (1 volunteer, unable to return for follow-up visits due to relocation).

Results

Binding ELISA: The present analysis using the new ELISA binding assay includes only those subjects that returned for either a Study Year 3 (N=30) or a Study Year 4 (N=27) visit. When the serological status at entry was evaluated using the ELISA assay version 1, all subjects were seronegative. In the subset of subjects evaluated in this report, 9 and 5 subjects had ELISA binding activity higher than the limit of quantitation for HPV 16 and HPV 18, respectively, using the assay ELISA version 2; ELISA binding levels were <58 units/ml in all subjects. These subjects were included in the analysis.

In both the AS04 and aluminum hydroxide groups, antibody levels increased through Study Day 60, peaked at Study Day 210, and had declined less than one log10 through Study Year 2. Further less pronounced decline in antibody levels, up to 3-fold, occurred from Study Year 2 through Study Year 4, except for HPV-16 in the aluminum hydroxide group for which antibody levels remained steady. These values were above the pre-vaccination titers. For all 4 years of the study, log10 mean HPV-16 and HPV-18 binding ELISA antibody levels were higher in the AS04 group than in the aluminum hydroxide group. At Study Year 3, the AS04 treatment group had log10 mean HPV-16 and HPV-18 antibody levels of 3.0 and 2.7, respectively, vs. 2.6 and 2.3 for the aluminum hydroxide group. At Study Year 4, the AS04 treatment group had log10 mean HPV-16 and HPV-18 antibody levels of 2.8 and 2.5, respectively, vs. 2.7 and 2.2 for the aluminum hydroxide group.

Inhibitory ELISA Antibody Levels: Serum samples collected from immunized subjects during the extension study were serially diluted and assayed by inhibitory ELISA for the presence of HPV-16 and HPV-18 VLP-specific antibodies. No subject had detectable inhibitory ELISA activity at Study Day 0. In the AS04 treatment group, 14/18 subjects who continued through Study Year 4 had detectable HPV-16 and HPV-18 antibodies at Study Year 4, 3/18 subjects had detectable HPV-16 antibodies but no detectable HPV-18 antibodies at Study Year 4, and 1/18 did not have either HPV-16 or HPV-18 antibodies detected at Study Year 4. In the aluminum hydroxide treatment group, 5/9 subjects had detectable HPV-16 and HPV-18 antibodies at Study Year 4; 2/9 subjects had only detectable HPV-16 antibodies, and 2/9 subjects did not have either HPV-16 or HPV-18 antibodies at Study Year 4.

For all 4 years of the study, log10 mean HPV-16 and HPV-18 ELISA inhibitory antibody levels were nominally higher in the AS04 group than in the alum group. At Study Year 3, the AS04 treatment group had log10 mean HPV-16 and HPV-18 inhibitory antibody levels of 2.2 and 2.0, respectively, vs. 1.8 and 1.7 for the aluminum hydroxide group. At Study Year 4, the AS04 treatment group had log10 mean HPV-16 and HPV-18 inhibitory antibody levels of 2.1 and 2.1, respectively, vs. 1.8 and 1.7 for the aluminum hydroxide group.

The sponsor concluded that the higher biding ELISA antibody levels, as well as the higher inhibitory ELISA levels for HPV 16 and HPV 18 measured in subjects who received the 40 mcg AS04 formulation supported further development of this vaccine.
Reviewer's Comment: At this time, an immune correlate of protection has not been identified for prevention of HPV 16 and HPV 18 infection and/or disease. Higher antibody levels could potentially translate into a longer duration of protection, but this has not been definitively demonstrated at this time,

The sponsor has also prepared 2 reports of pooled antibody results from studies 004 and 005.

Studies HPV-004 and HPV-005: Pooled Evaluation of the Immune Responses in Healthy Adult Female Subjects from Two Double-Blind, Randomized Phase II Studies, HPV-004 (MI-CP055) and HPV-005 (MI-CP057), of HPV-16/18 Vaccine against Human Papillomavirus (HPV) Types 16 and 18, when formulated With Aluminum Hydroxide or AS04
Subjects were followed for long-term immunogenicity and cellular responses, and in this report, antibody levels by ELISA and CMI were pooled for subjects who received 40 mcg AS04 formulation and 40 mcg alum formulation from studies 004 and 005 up to Year 4.

Study Objective: To evaluate the persistence of specific antibody and cellular immune responses following three doses of HPV-16/18 vaccine formulated with Al(OH)3 adjuvant or AS04 adjuvant, from Study Day 0 through Study Year 4.

Patient Populations: The primary population for immunogenicity summaries consists of subjects receiving at least one dose of study vaccine.

Endpoint(s)
The following specific antibody and cellular immune evaluations were performed:
Immunogenicity
- Determination of the antibody response to HPV-16 and HPV-18 using ELISA Assay version 1 for all subjects at Pre, Days 7, 30 and 60, Months 6, 7, 12 and 18, and Years 2 and 3.
- Determination of the antibody response to HPV-16 and HPV-18 using ELISA Assay version 2 for subjects who came back at Year 3 and/or Year 4, at all available time points (Pre, Days 7, 30 and 60, Months 6, 7, 12 and 18, and Years 2, 3 and 4).
- Determination of the antibody response to the major neutralizing epitopes of HPV-16 and HPV-18 (V5 or J4 epitopes, respectively) using an inhibitory ELISA, for a subset of subjects at (Pre, Days 7, 30 and 60, Months 6, 7, 12 and 18, and Years 2, 3 and 4).
- Neutralizing antibodies to HPV-16 and HPV-18 for a subset of subjects at Pre and Months 7 and 12.

Cell Mediated Immune Response (CMI)

- Determination of the in vitro lymphoproliferative responses to HPV-16 and HPV-18 and the productions of interferon-γ (IFN-γ) and interleukin-5 (IL-5) in the culture supernatant at Pre, Day 60, Months 7, 12 and 18, and Year 2.
- Determination of the frequency of CD4 and CD8 T-cell responses specific to HPV-16 and HPV-18 on a subset of subjects from HPV-004 (MI-CP055) at Pre, Day 60, Months 7, 12 and 18 and Year 2.
- Determination of the frequency of memory B-cell specific to HPV-16 and HPV-18 on a subset of subjects from HPV-004 (MI-CP055) and HPV-005 (MI-CP057) at Pre, Day 60, Months 7, 12 and 18, and Year 2.

Summary Pooled Evaluation of the Immune Responses in Healthy Adult Females Subjects from Studies HPV-004 and HPV-005: Immunogenicity analyses were performed on the Total Vaccinated Cohort and on the Kinetic Cohort. Both AS04- adjuvanted and aluminum hydroxide formulations were immunogenic and induced antigen-specific humoral responses, including antibodies that neutralized HPV-16 and HPV-18 in vitro. ELISA antibody titers to HPV-16 and HPV-18 were significantly higher in the AS04 group for up to 4 years after initiating the 3 doses vaccination series. Although the numbers of subjects analyzed for cell mediated immunity is limited, both formulations were immunogenic and induced specific CD4+ T-cell response. The functional characterization of the HPV specific CD4+ T-cells revealed that high frequency of IL-2 producing T cells with high lymphoproliferative capacity were induced and persisted for months following HPV vaccination. IFN producing CD4 cells and high levels of IFN-γ produced in culture supernatants were detected. No specific CD8 were detected after vaccination. (Details of the Pooled Evaluation of the Immune Responses in Healthy Adult Female Subjects from studies HPV-004 and HPV-005 can be found in Appendix A).

Studies HPV-004 and HPV-005, Annex 1: This annex report presents the pooled neutralization data from Month 7 to Year 4 of the HPV-16/18 vaccine. Subjects in 004 completed this extension on 1/9/05 and the subjects in 005 completed the extension on 9/9/04.

Summary Studies HPV-004 & HPV-5, Annex 1: This annex report presents analyses of the neutralizing antibodies to HPV-16 and HPV-18 from Month 0 through Year 4 in women vaccinated in studies HPV-004 and HPV-005. Results from these analyses indicate that both formulations induced antibodies that neutralized HPV-16 and HPV-18 in vitro. Observed GMTs (point estimate) on neutralizing antibody titers to HPV-16 and HPV-18 were higher in the AS04 group for up to 4 years after initiating the 3 dose vaccination series, with significant difference observed at most time-points up to Year 4 for HPV-16 and up to Year 2 for HPV-18, respectively. (Further details of Pooled Studies HPV-004 and HPV-005, Annex 1, can be found in Appendix A).

Summary of Phase I/II Studies: Studies HPV-002, -003, -004 and -005 demonstrated that the HPV 16/18 vaccine adjuvanted with AS04 was generally tolerated (except for a higher proportion of subjects with local reactogenicity) and that the candidate vaccine at the chosen formulation was immunogenic in eliciting anti-HPV 16 and ant-HPV 18 antibodies (when measured by ELISA and by neutralizing antibodies). The studies provided data to demonstrate nominally higher humoral antibody levels through Year 4, and when data was pooled from 2 of these studies and samples run using the same assays, demonstrated statistically higher antibody levels (IgG by ELISA and neutralizing antibodies) through Year 4 for the Total Vaccinated Cohort. It is not clear that higher antibody levels will ultimately translate into longer duration of prevention of HPV 16 and/or 18 related genital dysplasias and cervical cancer.

CONTROLLED STUDIES SUPPORTING LICENSURE IN FEMALES 10-25 YEARS OF AGE

Phase IIb/III studies – Controlled Studies
8.5 HPV-001 (Trial #5): A randomized, double-blind, control-controlled pilot phase IIB study of the efficacy of an human papillomavirus (HPV) HPV-16/18 L1/AS04 vaccine in the prevention of HPV-16 and/or HPV-18 cervical infection in healthy adolescent and young adult women in North America and Brazil.
Study Dates: 1/3/01-4/30/03
Study Sites: The study was conducted at 32 sites in the US, Canada, and Brazil.

Objectives
Primary Objective: Evaluate vaccine efficacy in the prevention of infection with HPV-16 and/or HPV-18 between months 6 and 18 in adolescent and young adult women who were initially HPV-16/18 seronegative (by ELISA) and HPV-16/18 DNA negative (by PCR).
(Adolescent and young adult women that were included for the evaluation of the primary objective were seronegative for HPV-16 or HPV-18 at month 0 and were DNA negative for high risk HPV types (i.e. HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) at month 0.)

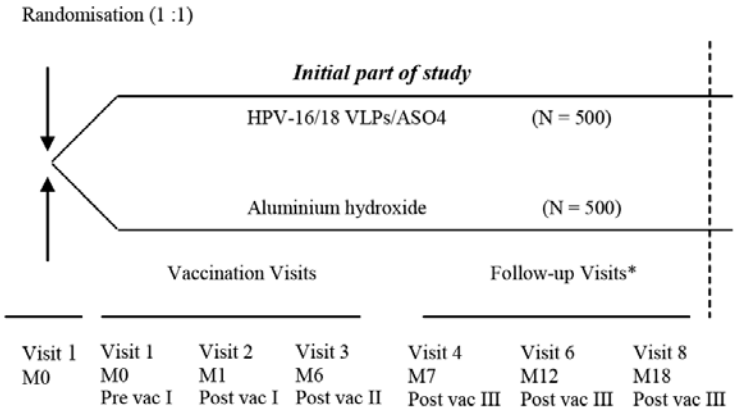
Secondary Objectives
- Evaluate vaccine efficacy in the prevention of persistent infection with HPV-16 and/or HPV-18 between months 6 and 18, and months 6 and 27, in adolescent and young adult women who were initially HPV-16/18 seronegative and HPV-16/18 DNA negative. (Adolescent and young adult women that were included for the evaluation of this secondary objective were seronegative for HPV-16 or HPV-18 at month 0 and were DNA negative for high risk HPV types (i.e. HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) at month 0.
- Evaluate vaccine efficacy in the prevention of LSIL (Low grade squamous intraepithelial lesions), HSIL (High grade squamous intraepithelial lesions), squamous cell cancer, or adenocarcinoma associated with HPV-16 and/or HPV-18 infection between months 6 and 18, and months 6 and 27, in adolescent and young adult women.
- Evaluate vaccine efficacy in the prevention of infection with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic types between months 6 and 18, and months 6 and 27, in adolescent and young adult women.
- Evaluate vaccine efficacy in the prevention of persistent infection with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic types between months 6 and 18, and months 6 and 27, in adolescent and young adult women.
- Evaluate vaccine efficacy in the prevention of LSIL, HSIL, squamous cell cancer, or adenocarcinoma associated with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic type infection between months 6 and 18, and months 6 and 27, in adolescent and young adult women.
- Evaluate viral load for HPV-16 and HPV-18 (positive samples to be tested by type-specific PCR to quantify the level of DNA in the sample).

Other objectives
- Evaluate the safety of the candidate vaccine.
- Evaluate vaccine immunogenicity (by ELISA, neutralizing assays and V5/J4 monoclonal antibody inhibition tests).

Study Design: This was a multicenter, double blind, control-controlled, randomized clinical trial. Subjects were originally to be followed for 18 months postdose 3; an extension was added

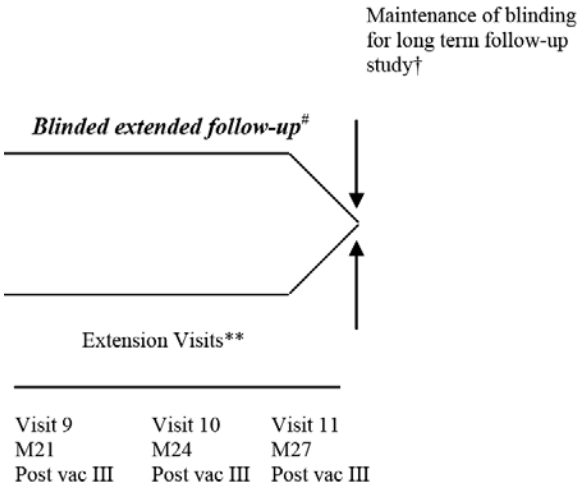
to provide long-term follow-up of safety out to Month 27 postdose 3. Blinding of subjects and staff were maintained during the extension phase.

Figure 5 - Study HPV-001: Overview of study design (initial part of study)



Source: STN 125259/0, CSR 001, Figure 1, p. 43

Figure 6 - Study HPV-001: Overview of study design (Blinded extended follow-up)



Source: STN 125259/0, CSR 001, Figure 1, p. 43

Duration: Subjects were originally to be followed for 18 months after dose 3; an extension phase was added to provide long term follow-up for 27 months after dose 3.

Screening: During the screening, cervical specimens and blood samples were obtained. Women with normal cervical cytologies who were high-risk HPV DNA negative (including HPV-16 and HPV-18 DNA negative) by PCR and HPV-16 and HPV-18 seronegative by ELISA, were invited to participate in the vaccination part of the study. Subjects who had previously participated in an epidemiology study (999910/106) evaluating the prevalence of HPV-16, HPV-18 and other high-risk HPV types and who met the criteria were also invited to participate in this present study. These subjects did not have to undergo a separate screening for this present study unless they had completed study 999910/106 more than 90 days prior to enrolment.

Blinded extension phase: Subjects who completed their month 18 visit before 2/1/03 were invited to participate in a blinded extension phase lasting up to 9 months (maximum of 27 months

total study participation). The number of study visits made by participants in this extension depended upon the date of their month 18 visit (visit 8).

Discussion regarding study design: The study was a double blind, control-controlled efficacy trial based on virological endpoints (HPV infection detected by PCR analysis of cervical samples) as recommended by CBER (at a meeting held with GSK and MedImmune, Inc on 3/24/00 and further discussed at a teleconference held on 7/31/00). The primary endpoint was based on incident infection rather than persistent infection as it was expected that persistent infection would occur infrequently, rendering the trial insufficiently powered to evaluate persistent infection. However, persistent infection was evaluated as a secondary endpoint.

Six amendments were made to the protocol. A major change impacting the study design was made with the 4th protocol amendment (5/6/02), which described the addition of optional extended follow-up visits to ensure sufficient statistical power in case of a lower than estimated attack rate for the virological endpoints. All subjects completing the initial follow up (at month 18) before 2/1/03, were asked to return for visits (or participate in telephone contacts and return self-obtained cervicovaginal specimens by mail) at approximately 3 month intervals until the last subject enrolled completed the initial study period (4/03). Subjects completing their month 18 visit (visit 8) on or after 2/1/03 were not eligible to participate in the blinded extension phase. This blinded extension phase is different from the long-term follow-up study 580299/007, which is a long-term follow-up study and will provide additional data for the original study cohort.

Table 4- Study HPV-001: Outline of Study Procedures

	Subjects not enrolled in HPV-106		Subjects enrolled in HPV-106								Blinded Extended Follow-up		
	D-90 to 0	V1 M0	V1 M0	V 2 M1	V3 M6	V4 M7	V5* M9	V6 M12	V7* M15	V8 M18	V9 M21	V10 M24	V11 M27
Informed consent	X		X										
Addendu, to IC										X			
Inclusion criteria	X	X	X										
Exclusion criteria	X	X	X							X	X		
Elimination criteria		X	X	X	X	X							
Contraindications		X	X	X	X								
Medical history	X		X										
Interim medical history		X	X	X	X	X		X		X	X	X	X
Interim medication		X	X	X	X	X							
Demographic data	X		X										
Urine for pregnancy	X	X	X	X	X								
Directed physical exam	X		X										
Pelvic exam (Pap & HPV DNA)	X				X			X		X			
Return self-obtained HPV DNA		X	X		X		X	X	X	X	X	X	X
Questionnaire	X									X			
Randomization (IB)		X	X										
Serology HPV 16 & HPV 18	X	X	X	X	X	X		X		X			
Chem/heme labs		X	X	X	X	X							
Vaccination		X	X	X	X								
Distribution diary cards		X	X	X	X								
Return diary cards				X	X	X							
Record NSAEs up to 1 Month after vaccination				X	X	X							
Reporting of SAEs				X	X	X	X	X	X	X	X	X	X
Study Conclusion										X	X	X	X

Women who participated in the GSK epidemiology study, 999910/106, within 90 days of entry into study 580299/001 did not need to undergo a separate screening and were to have the procedures shown in this column performed at visit 1. Women who had completed the epidemiology study, 999910/106 more than 90 days prior to enrolment in the present study or women not participating in 999910/106 were to undergo the screening and visit 1 procedure in the 2 previous columns.

Women with abnormal cervical cytologies indicating the presence of LSIL, AGUS (Atypical Glandular Cells of Undetermined Significance) or HSIL were to be immediately referred
for colposcopy and appropriate medical follow-up.

Subjects were to use two Dacron swabs to obtain cervical samples ('self-samples') for HPV DNA PCR testing.

Biochemical and haematology analyses was performed in subjects enrolled in centers 10, 17, 18, 23, 40, 70, 100 and 130.

Visits at months 9, 15, 21, 24 and 27 at study centers for the return of self-samples were optional. However, collection of self samples and reporting of SAEs etc was to continue throughout the study period

All subjects were to complete the initial part of the study at visit 8 after which time some subjects, depending upon their consent and the date of their month 18 visit, participated in a blinded extension phase. The number of visits in the extension phase depended upon the date of the subject's month 18 visit (visit 8).

Source: STN 125259/0, CSR 001, Table 1, p. 47-49

Dosage and Administration: Doses were selected based on an interim analysis of post dose 2 data from a previous phase II study (HPV-004). The vaccine schedule used (0, 1, 6 months) was based on a standard schedule used for other subunit vaccines and clinical experience in Phase I/IIa studies. The vaccine was administered intramuscularly in the non-dominant deltoid muscle. Vaccinees were observed closely for at least 30 minutes.

Intervals between study visits: Study-specified time intervals between visits were provided.

Vaccine Products Used: HPV 16/18 L1/AS04 vaccine and control vaccine (aluminum hydroxide) were supplied as liquids in single use glass vials containing 0.7 ml as a standard nominal fill volume. See Table 5.

Table 5- Study HPV-001: Vaccines, formulation, lot numbers and allocation

Vaccine	Formulation	Lot number	Group
Vaccine (CPMS number 580299)	40 µg HPV-16/18 L1/AS04 vaccine: • 20 µg HPV-16 L1, • 20 µg HPV-18 L1, • 50 µg MPL, • 500 µg aluminium hydroxide	DVLP017A2	Vaccine
Control (placebo)	500 µg aluminium hydroxide	DVLP018A2PL	Placebo

Source: STN 125259/0, CSR 001, Table 3, p. 55

Study population: The target population for enrolment included healthy adolescent and adult female subjects between 15 and 25 years of age. The recruitment areas were located in two geographical regions, North America (USA and Canada) and Brazil.

Inclusion Criteria:

- Healthy female 15-25 years of age
- written informed consent of subjects or parent or legal guardian of the subject
- ≤ 6 lifetime sexual partners prior to enrolment
- intact uterus
- non-childbearing potential (surgical or on appropriate contraception for 30 days prior to vaccination, had a negative urine pregnancy test and to have agreed to continue such precautions for two months after completion of the vaccination series.)
- for subjects not enrolled in the HPV epidemiology study (999910/106) and for subjects who completed the study (999910/106) >90 days prior to enrolment in the present study: agreement to complete both entrance and exit study questionnaires concerning general personal information, and sexual, contraceptive, reproductive and other gynaecological medical history
- for subjects previously enrolled in the HPV epidemiology study and who had completed the study and an entrance questionnaire ≤ 90 days prior to enrolment in the present study: agreement to complete the exit questionnaire only
- normal cervical cytology (Pap smear) at screening, using the Cytyc ThinPrep® Pap Test
- seronegative for HPV-16 and HPV-18 antibody by ELISA at screening
- HPV DNA PCR negative for high-risk HPV types by PCR at screening and genotyping was to be specified using a reverse line probe assay specific for the detection of 14 high risk HPV types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 and 11 low risk HPV types (HPV-6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74).

Exclusion Criteria:

- pregnant or lactating female; Female who planned to become pregnant during the first eight months of the study (months 0-8)
- abnormal vaginal discharge at the time of entry (could participate after appropriate treatment)
- previous administration of monophosphoryl lipid A (MPL) or ASO4 adjuvant
- chronic administration (defined > than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose
- administration of immunoglobulin and/or any blood products within the three months (90 days) preceding the first dose of study vaccine or planned administration during the study period

- planned administration or administration of a vaccine not foreseen by the study protocol within 30 days of the first dose of study vaccine. Guidelines regarding commonly administered vaccines was provided.
- receiving or expecting therapy for external or internal condylomata. Subjects with external condylomata not requiring therapy were eligible to participate in the study
- genital herpes disease involving the cervix or characterized (on examination or by history) by extensive external lesions. Subjects with a history of recurrent genital herpes disease characterized by limited external lesions were eligible to participate in the study
- history of an abnormal cervical cytology (Pap smear) test (other than a single prior report of ASCUS with a subsequent normal report)
- treatment for cervical disease by ablative therapy (cryotherapy or laser ablation) or excisional therapy (laser cone biopsy, loop excision, cold-knife conization)
- any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection
- family history of congenital or hereditary immunodeficiency
- major congenital defects or serious chronic illness
- history of any neurological disorders or seizures, with the exception of a single febrile seizure during childhood
- acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests
- acute disease at the time of enrolment. [95% CI:Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines could be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness; Oral temperature ≥99.5°F (≥37.5°C) / axillary temperature ≥99.5°F (37.5°C) / rectal temperature ≥100.4°F (≥38.0°C) / tympanic temperature on oral setting ≥99.5°F (37.5°C) / tympanic temperature on rectal setting ≥100.4°F (≥38.0°C)]
- history of chronic alcohol consumption and/or intravenous drug abuse within the past 2 years
- known or suspected allergy to any vaccine component, e.g., MPL, AS04
- hepatomegaly, right upper quadrant abdominal pain or tenderness.

Exclusion criteria for subjects electing to participate in the blinded extension phase: Ablative or excisional therapy of the cervix, or hysterectomy; Visit 8 occurring after 31 January 2003.

Treatment Allocation and Randomization: The target sample size was 1000 subjects, stratified equally between North America (USA and Canada) and Brazil with the following distribution: 425 subjects in US; 75 subjects in Canada; 500 subjects in Brazil. Approximately 1000 subjects (500 subjects per treatment group) were to be enrolled to obtain a total of approximately 770 evaluable subjects for the final primary efficacy analysis. Randomization was performed using an Internet-based central randomization system.

Blinding: This was a double blind study. The investigator and associated study personnel were blinded to treatment assignments for the subjects.

HPV PCR results: A clinical management sub-committee, consisting of selected study investigators was established prior to study initiation to obtain a consensus among investigators for the management of women with abnormal cytologies. The consensus of the sub-committee was that available data did not support the use of HPV PCR test results in the triage algorithm for the management of women diagnosed with abnormal cervical smears. HPV DNA PCR test results were not provided to the investigators (an exception was made for one case) or study

subjects until after study completion. Study sites and GSK personnel (except the US medical monitor who was the contact person with the CRO Delft Diagnostic Laboratory who performed the PCR analysis) directly involved in the conduct of the study were blinded to HPV PCR results throughout the study. The clinical management of subjects was conducted within the local standards of care or under the recommended guidelines outlined in the protocol and was based solely on cervical cytology or biopsy results (not HPV PCR test results).

Prior and concomitant medications were to be reported.

The **efficacy variables** assessed were:

- The presence of HPV type specific DNA detected by PCR in cervicovaginal (self-obtained) and cervical (physician-obtained) specimens.
- Cytologically confirmed (physician-obtained cervical specimens) or histopathologically confirmed (biopsy samples) LSIL, HSIL, squamous cell cancer, or adenocarcinoma (note: histopathlogically confirmed lesions were described according to the cervical intraepithelial neoplasia (CIN) classification system.

Laboratory assays and time points

Cervical Samples: During the pelvic examination at screening and at months 6, 12 and 18, a cervical sample for cytology was collected by the physician. In addition, women provided self-obtained cervical samples at months 0, 6, 9, 12, 15 and 18, and for subjects participating in the blinded extended follow-up at months 21, 24 and 27.

Polymerase chain reaction (PCR): One aliquot for HPV DNA PCR testing was forwarded to Delft Diagnostic Laboratory, Delft, The Netherlands. The second aliquot was archived. Aliquots sent to Delft Diagnostic Laboratory were first tested in parallel by:

- ----------b(4)----------
- ----------b(4)----------
- Reverse line probe assay (LiPA). The LiPA is a strip of nitrocellulose with HPV probes fixed on it. The probes detect 14 high risk HPV types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and 11 low risk HPV types (6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74). LiPA testing may not detect some HPV types when there is multiple HPV infection or a low viral load AND BY
- Type-specific PCR assay for HPV-16 and type-specific PCR assay for HPV-18 (these assays use specific primers sets for HPV-16 or HPV-18) to confirm absence of HPV-16 and HPV-18, thus affording maximum test sensitivity. The decision to test any HPV DNA positive specimens by type-specific PCR for HPV-16 and HPV-18 in addition to LiPA was added in the 4th protocol amendment (5/6/02). HPV DNA positive specimens collected before implementation of this amendment were tested by LiPA only. After the protocol amendment, Delft Diagnostic Laboratory tested specimens collected prior to the amendment by type-specific PCR for HPV-16 and for HPV-18. However, due to insufficient material, 12 samples could not be tested. A *post hoc* analysis of HPV DNA detected by PCR in biopsy tissue for histopathologically confirmed cases of LSIL (referred to as CIN 1 in this report) and HSIL (referred to as CIN 2 or CIN 3 in this report) was made. Any samples testing positive using the "generic" PCR assay were then tested by LiPA and by type-specific PCR assays for HPV-16 and for HPV-18 as described above.

Cytology Testing: Cervical cytology was performed by Quest Diagnostics (Teterboro, NJ, USA), using the ThinPrep® PapTest™ (Cytyc Corporation, Boxborough, MA, USA). The ThinPrep 2000 Processor was used to transfer cells on to glass slides and fixing.The slides were stained and evaluated by laboratory personnel using the Bethesda System 1999 for reporting cervical cytology diagnoses.

Biopsy and Histopathology: Guidance on how women with abnormal cervical cytologies were to be assessed by colposcopy and biopsy was provided in the protocol in a management algorithm. (See Table 6.

Table 6- Study HPV-001: Management of women with cervical lesions

Abnormal Cytology	Management of cervical lesions
ASCUS	For a single observation: repeat pelvic examination and cervical smear at next scheduled study visit (in 6 months) For two observations at a six month interval: referral for colposcopy* For two full colposcopy* examinations preceded by ASCUS if a normal biopsy is observed, NO further colposcopy was to be conducted
LSIL	For a single observation: immediate referral for colposcopy*. All and any lesions will be biopsied if observed For repeat LSIL observations following normal biopsy at colposcopy*: a thorough vaginal, vulvar and anal colposcopic examination will be performed
AGUS	For a single observation: immediate referral for colposcopy*. All and any lesions will be biopsied if observed For repeat AGUS observations: referral for a LEEP/cone procedure to determine the disease state
HSIL	For a single observation: immediate referral for colposcopy*. All and any lesions will be biopsied if observed For repeat HSIL observations: referral for a LEEP/cone procedure to determine the disease state

Source: STN 125259/0, CSR 001, Table 5, p. 62

Subjects referred for colposcopy were asked to sign a supplement to the study informed consent and assent forms describing the colposcopy procedures.

Pathology Panel: Biopsy samples obtained under the protocol were referred to Dr Ronald Luff (Quest Diagnostics). Dr Luff headed an expert panel of three gynecologic pathologists. Two pathologists from the expert panel independently evaluated each case and involved the third group member to resolve any discrepancy by consensus. Stained tissue sections were made available to any site for local review if requested. In addition, biopsies were tested for HPV DNA by PCR after completion of the study (post hoc analysis). A final consensus diagnosis was issued by the expert panel following review of the biopsy sections prepared for HPV DNA PCR analysis. For the analysis of study data, the results were expressed using the cervical intraepithelial neoplasia (CIN) classification system where CIN 1 corresponds to LSIL and CIN 2 and CIN 3 correspond to HSIL but during the study, results were communicated using the SIL classification.

Immunogenicity variables

Laboratory assays and time points: At screening and at months 0, 1, 6, 7, 12 and 18, 10 ml of whole blood was taken from each subject for serology testing. Serological assays were performed at GSK Biologicals laboratories, Rixensart, Belgium, using standardized validated procedures with adequate controls.

Anti-HPV-16 and anti-HPV-18 ELISA: Anti-HPV-16 and anti-HPV-18 ELISAs were performed for blood samples from all subjects using the methodology developed by ---b(4)----- ---------- The ELISA assays were used at screening (between days –90 and day 0) to determine eligibility of subjects and at the study visit 1 (month 0) to assess serostatus at study entry. Additional ELISA assays were performed on blood samples taken at months 1, 6, 7, 12 and 18 to evaluate vaccine response. If there was an insufficient blood sample volume to perform assays for both antibodies, anti-HPV-16 ELISA testing took priority over anti-HPV-18 ELISA.

V5/J4 monoclonal inhibition enzyme immuno-assays: Sera from a randomly defined set of 100 subjects who had received three HPV vaccine doses and 50 subjects who had received three doses of control according to protocol, and who had serum available for visits 1, 4 and 8 (months 0, 7 and 18) were selected for testing for HPV-16 and HPV-18 antibodies using V5/J4 monoclonal antibody inhibition enzyme immuno-assays. To maintain the blinding of the study the subset of sera was selected by a prespecified procedure. Seropositivity was defined as a titer greater than or equal to the assay cut-off value. The assay cut-off for anti-HPV-16 V5 antibodies was 41 ELISA units/ml and the assay cut-off for anti-HPV-18 J4 antibodies was 110 ELISA units/ml.

Neutralization assay for detection of human neutralizing antibodies to HPV-16 or HPV-18 L1 VLPs: Sera from the same subset of subjects who had their sera tested by the V5/J4 monoclonal inhibition enzyme immunoassays were tested for HPV-16 and HPV-18 neutralizing antibodies. HPV-16 and HPV-18 neutralizing antibodies were assayed using an -------b(4)---------- ----------. HPV-16 or HPV-18 infection of cultured human keratinocytes were determined by the presence of a HPV-specific messenger ribonucleic acid (mRNA) detected by -------b(4)----------. Neutralization titers were reported as endpoint titers, defined as the highest serum dilutions that inhibited the synthesis of the viral transcript. A PCR product consistent with the expected size of the HPV spliced transcript that could be amplified from cells exposed to the infectious virus indicated no neutralization antibodies. In contrast, the inability to amplify the expected PCR product reflected the neutralization of the HPV virus by specific antibodies. The assay cut-off for neutralizing antibodies was 1/10 dilution.

Assessment of safety variables

Adverse events

Solicited adverse events: Solicited adverse events were collected for seven days following administration of a study vaccine/control dose (days 0-6). These solicited local and general signs and symptoms were recorded by the subjects on standard diary cards supplied by the sponsor.

- **Solicited Local (Injection Site) Adverse Events** included pain, redness, and swelling at the injection site.
- **Solicited General (or Systemic) Adverse Events** included fatigue, fever, GI symptoms (nausea, vomiting, diarrhea, and/or abdominal pain), headache, rash, and pruritus. Temperature (by oral, axillary or rectal route) was to be recorded in the evening. If temperature measurement was additionally performed at another time of day, the highest temperature was to be recorded.

Unsolicited adverse events: All unsolicited adverse events occurring within one month (minimum 30 days) following administration of each dose of study vaccine or control were recorded. The nature of each event, onset, outcome, intensity and relationship to vaccination was recorded. Any medically significant adverse events (including new onset of chronic diseases, unscheduled gynecological procedures or emergency room visits) which occurred outside the 30

day follow-up period following administration of each dose of study vaccine or control were also recorded.

Assessment of intensity (grading): The intensity of solicited adverse events was assessed as specified in Tables 7 and 8 below.

Table 7 – Study HPV-001: Solicited adverse events and assessment of their intensity

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	Absent
	1	Painful on touch
	2	Painful when limb is moved
	3	Spontaneously painful
Redness at injection site	0	None
	1	> 0 mm to ≤ 20 mm
	2	>20mm to ≤ 50 mm
	3	> 50 mm
Swelling at injection site	0	None
	1	> 0 mm to ≤ 20 mm
	2	>20mm to ≤ 50 mm
	3	> 50 mm
Fever*	0	< 37.5 °C
	1	≥ 37.5 °C to ≤ 38.0 °C
	2	> 38.0 °C to ≤ 39.0 °C
	3	> 39.0 °C
Headache	0	Normal
	1	Headache that is easily tolerated
	2	Headache that interferes with normal activity
	3	Headache that prevents normal activity
Fatigue	0	Normal
	1	Fatigue that is easily tolerated
	2	Fatigue that interferes with normal activity
	3	Fatigue that prevents normal activity
Gastrointestinal symptoms	0	Normal (no gastrointestinal symptoms)
	1	Gastrointestinal symptoms that are easily tolerated
	2	Gastrointestinal symptoms that interfere with normal activity
	3	Gastrointestinal symptoms that prevent normal activity
Rash	0	No rash
	1	Rash which is easily tolerated
	2	Rash which interferes with daily activities
	3	Rash which prevents daily activities
Pruritus (itching)	0	No pruritus (itching)
	1	Itching which is easily tolerated
	2	Itching which interferes with daily activities
	3	Itching which prevents daily activities

*Fever was defined as oral temperature ≥99.5°F (37.5°C) / axillary temperature ≥99.5°F (37.5°C) / rectal temperature
≥100.4°F (38°C) / tympanic temperature on oral setting ≥99.5°F (37.5°C) / tympanic temperature on rectal setting ≥100.4°F (38°C)
Source: STN 125259/0, CSR 001, Table 7, p. 67

Table 8 – Study HPV-001: Assessment of intensity of unsolicited symptoms

Intensity Grade	
0	No adverse event.
1	An adverse event which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2	An adverse event which was sufficiently discomforting to interfere with normal everyday activities.
3	An adverse event which prevented normal, everyday activities.

Source: STN 125259/0, CSR 001, Table 8, p. 68

Assessment of causality: Causality was assessed by the investigator.

Follow-up of adverse events and assessment of outcome: Investigators were to follow up subjects with serious adverse events until the event had resolved, subsided, stabilized, disappeared, the event was otherwise explained, or the subject was lost to follow-up; or, in the case of non-serious adverse events, the subject completed the study. Clinically significant laboratory abnormalities were to be followed up until they returned to normal, or a satisfactory explanation was provided. Outcomes were as follows: recovered; recovered with sequelae; ongoing at subject study conclusion; died; or unknown.

Serious adverse events (SAEs): defined as any untoward medical occurrence that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, required in-patient hospitalization or prolongation of existing hospitalization or was a congenital anomaly/birth defect in the offspring of a study subject. In addition, an important medical event that jeopardized the patient or required intervention to prevent one of the outcomes listed below was considered serious. Although not considered as 'serious adverse events', cancers were to be reported in the same way as serious adverse events.

SAEs were to be reported during the period during the period starting from the day of administration of the first dose of study vaccine or control and ending with the last study visit (up to month 27).

Pregnancy: Pregnancy was an exclusion criterion for enrollment and all subjects were tested for pregnancy (using a urine human chorionic gonadotrophin (HCG test) during screening. A pregnancy test was also performed on all subjects prior to each vaccination at months 0, 1 and 6 and had to be negative in order for the subjects to receive a dose of vaccine/control. Although subjects who became pregnant during the study were not to receive any further doses of vaccine/control they could continue other study procedures at the discretion of the investigator (or designate). Each pregnancy was to be followed to term and outcome reported.

Clinical laboratory evaluations: Biochemical and hematology analyses were performed for subjects enrolled in centers 10, 17, 18, 23, 40, 70, 100 and 130 at months 0, 1, 6, and 7. The tests at months 1, 6, and 7 were compared with those taken at month 0 (baseline). These tests included biochemistry tests- ALT (SGPT), Cr, and Total proteins; and hematology tests - WBC, hematocrit, and platelet count.

Data Quality Assurance: Significant deficiencies in the frequency of site monitoring were reported as important audit findings at two Brazilian study sites, center 23 and 24. Additional findings were made with respect to the investigator's responsibilities to adequately communicate with the ethics committee, deficiencies in the completion of the sites' FDA Form 1572 and in the quality of source documentation.

Responses from GSK Brazil to the audit findings provided assurances that appropriate corrective actions were to be implemented. However, subsequent audits reported ongoing issues (Country Medical Department audit for Brazil, 9/04 and audits for ongoing HPV vaccine studies in 12/04). GSK Biologicals management then formed a task force with the objective of evaluating compliance with GCP, GSK SOPs and regulatory requirements in order to validate the integrity of HPV-001 study data and make recommendations to GSK management. The task force requested re-monitoring of all Brazilian study sites to be performed by a sub-team to assess the status of clinical and regulatory study documentation with regards to accuracy and completeness by performing 100% source documentation verification for all HPV-001 data.

The re-monitoring exercise confirmed that there were no concerns with vaccination logs or subject randomization. Study sites showed evidence of good general compliance with the protocol and cytology/colposcopy management guidelines (comparable to that observed at North American study sites) and no issues were identified that may have impacted the laboratory data generated at central laboratories. There was no evidence of intentional misconduct at any of the study sites and no study subjects were exposed to undue risk.

The re-monitoring exercise revealed some findings common to all Brazilian sites including issues related to regulatory and GCP compliance (including incomplete dating of informed consents; assent forms available but consent from legally accepted representative missing; inconsistencies with vaccine destruction logs; long intervals between monitoring visits; late reporting of a few pregnancies and SAEs; screening log deficiencies); regulatory issues (including lack of annual ethics committee re-approvals; issues with FDA form 1572 with respect to financial disclosures); and source data issues (source data discrepancies).

At one study site (study site 22), the source document issues were more difficult to correct than at the other Brazilian sites. At this site, the original source worksheet was supplemented with a new source worksheet during the study. In some cases, this had resulted in discrepancies between the original and supplemented source records and the data encoded in the remote data entry (RDE) application. The procedure for documenting source data was not managed appropriately at this site.

Following consideration of the findings from all of the Brazilian sites, the HPV-001 task force considered that, given the nature of the discrepancies, the impact on the overall safety and efficacy of the Brazilian data was not likely to be significant. To confirm this assumption and validate the integrity of the original HPV-001 analysis, GSK conducted a confirmatory re-analysis of a new study dataset which incorporated the following changes compared with the original study dataset: 1) correction of all source data discrepancies identified during the re-monitoring activities; 2) exclusion of data from one study site (study center 22); 3) re-validation of all laboratory databases. Prior to running the re-analysis the approach was discussed with three of the study investigators and external experts who participated in the study and who were also involved with development of the Lancet publication to obtain an independent viewpoint on the merits of the plan. The rationale for maintaining the original analysis as the "primary" and to consider the re-analysis as "confirmatory" included the following considerations: (1) the original analysis was completed prior to creating the revised database; it was felt that the original analysis was not subject to potential bias that might be introduced with late changes in the dataset; (2) the specific nature of the changes made to the database were considered unlikely to impact key study conclusions (3) the statistical approach applied to the re-analysis was the same as that for the initial analysis. The final decision concerning the positioning of the re-analysis was taken prior to initiating this analysis and was supported by the investigators and external experts consulted.

This re-analysis focused on the key safety, immunogenicity and efficacy data and is provided in an annex to the HPV-001 study report. An additional analysis for safety on data from center 22 alone was also conducted. The validity of the conclusions made upon the original efficacy analysis was confirmed by the re-analysis, therefore, the original efficacy analysis (including center 22) is presented as the principal trial data. The reanalysis of the re-monitored data (excluding center 22) provides a complete and valid dataset for reporting of safety and reactogenicity and confirmatory datasets for efficacy and immunogenicity. The safety data for center 22 alone is presented in the annex report separately for completeness. Quest Diagnostics Clinical Trials (--b(4)-), Quest Diagnostics (Teterboro) and Delft Diagnostics Laboratory were employed to perform sample processing and laboratory analyses. --b(4)-- was employed to perform statistical analyses according to agreed contracts. The CRO responsibilities were conducted according to their own SOPs.

Independent audit statement: This study was subject to audit by GlaxoSmithKline's department of Worldwide Regulatory Compliance (WWRC). Two study sites in Brazil were audited (center 23 and center 24) in and two study sites in US were audited (center 110 in 5/01 and center 40 and 11/01). Audit certificates were included in the submission.
Reviewer's Comment: The re-analysis with and without data from center 22 was reviewed, and the results of the study and conclusions did not change even when data from center 22 were excluded.

STATISTICAL CONSIDERATIONS: The analyses were performed according to the protocol except that some additional analyses were defined post hoc; and some analyses described in the protocol have not yet been completed and will be presented as annexes to the clinical report.

Primary endpoint: Incident cervical infection with HPV-16 and/or HPV-18. HPV-16 and/or HPV-18 incident infection was defined as at least one positive HPV-16 or HPV-18 DNA PCR assay. HPV-16 and/or HPV-18 infection (by PCR) was determined for both self-obtained cervicovaginal and physician-obtained cervical specimens. The primary efficacy endpoint was analyzed using all HPV-16 and/or HPV-18 DNA results determined for both self-obtained cervicovaginal and physician-obtained cervical specimens combined. In addition, a separate analysis of physician-obtained cervical specimens only was conducted.
Reviewer's Comment: CBER presented the results for the cervical specimens since this was considered most specific as to identifying HPV infection as they may relate to cervical dysplasias.

Secondary endpoints

- Persistent cervical infection with HPV-16 and/or HPV-18 defined as at least two positive HPV DNA PCR assays for the same viral genotype over a minimum interval of six months.
- Cytologically confirmed or histopathologically confirmed LSIL, HSIL, squamous cell cancer, or adenocarcinoma concurrently associated with HPV-16 and/or HPV-18 cervical infection. *Note: Cytologically confirmed ASCUS as an endpoint was added post hoc and histopathological lesions were described according to the cervical intraepithelial neoplasia (CIN) classification system.*
- Incident cervical infection with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic types such as HPV-31, 33, 35, 39, 45, 52, 58 and 68. *Note: In the report analysis plan (RAP dated 8/29/02 with amendment on 1/31/03, HPV-16 related types were defined as HPV-16, 31, 35, 58 and HPV-18 related types were defined as HPV-18, 45 and 59. The RAP also specified an analysis of infection with individual high risk HPV types; HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 and individual low risk HPV types; HPV- 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74. Post hoc analyses were performed using an additional extended definition of*

HPV-16 related phylogenetic types (to include HPV-33 and HPV-52) and additional analyses of related phylogenetic types which excluded HPV-16 and 18 were performed.

- Persistent cervical infection with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic types such as HPV-31, 33, 35, 39, 45, 52, 58 and 68. *Note: As indicated above, the definitions of related phylogenetic HPV types and individual high risk and low risk HPV types were specified in the RAP. Post hoc analyses were performed using an additional extended definition of HPV-16 related phylogenetic types (to include HPV-33 and 52) as well as analyses of phylogenetic types which excluded HPV-16 and 18.*
- Cytologically confirmed or histopathologically confirmed LSIL, HSIL, squamous cell cancer, adenocarcinoma concurrently associated with cervical infection with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic types such as HPV-31, 33, 35, 39, 45, 52, 58 and 68. *Note: Cytologically confirmed ASCUS as an endpoint was added post hoc and histopathological lesions were described according to the cervical intraepithelial neoplasia (CIN) classification system. As indicated above, the definitions of related phylogenetic HPV types and individual high risk and low risk HPV types were specified in the RAP. Post hoc analyses were performed using an additional extended definition of HPV-16 related phylogenetic types (to include HPV-33 and 52) and additional analyses of phylogenetic types which excluded HPV-16 and 18 were performed.*
- Determination of viral load for HPV-16 and HPV-18 (by PCR) for both cervicovaginal specimens and physician-obtained cervical specimens. *Note: positive specimens to be tested by type-specific PCR to quantify the level of DNA.*

Reviewer's Comment: The viral load endpoint was not reported due to technical difficulties with the assay.

Other endpoints

- Occurrence, nature, intensity and relationship to vaccination of any solicited local or solicited general symptoms within 7 days (days 0-6) after each vaccination and after any vaccination; occurrence of unsolicited symptoms within 30 days after any vaccination (months 0-7) and occurrence of serious adverse events throughout the entire study (month 0 up to month 27).
- HPV-16 and HPV-18 ELISA (all study subjects), neutralizing titers and V5/J4 monoclonal antibody competition tests (both in a randomly defined set of 100 volunteers who received all HPV vaccine doses, and in 50 volunteers who received all control doses, according to protocol, and who have serum available for visits 1, 4 and 8 (months 0, 7 and 18) plus all women infected with HPV-16 or HPV-18 during the course of the study).

Sample Size Determination: The primary objective of this study was to evaluate vaccine efficacy in the prevention of incident infection with HPV-16 and/or HPV-18 between months 6 and 18 in adolescent and young adult women who were initially HPV-16 and HPV-18 seronegative (by ELISA) and high risk HPV DNA negative (by PCR) and also negative by PCR for the infecting HPV type at month 6. HPV-16 and/or HPV-18 incident infection was defined as at least one positive HPV-16 or HPV-18 DNA PCR assay. The primary efficacy endpoint was analyzed using all HPV-16 and/or HPV-18 DNA results determined for both self-obtained cervicovaginal specimens and physician-obtained cervical specimens combined. In addition, a separate analysis of physician-obtained cervical specimens only was conducted. The study was designed to demonstrate that the administration of 3 doses of candidate HPV-16/18 L1/AS04 vaccine reduced the incidence of HPV-16 and/or HPV-18 infection compared with the administration of 3 doses of control.

The sample size was calculated to have 80% power for the primary endpoint analysis ($\alpha = 0.023$, one-sided test), i.e., to demonstrate a difference between vaccine and control groups assuming an

attack rate of HPV-16 and/or HPV-18 incident infection of 6% over 12 months in the control group and an expected vaccine efficacy of 70%.

Target sample size = 1000

- Number of subjects planned per group (vaccine or control) = 500.
- Number of subjects planned per region (North America or Brazil) = 500 (425 in the USA 75 in Canada).
- Number of evaluable subjects per group (vaccine or control) = 385.
- Total number of evaluable subjects = 770.
- A total of 385 evaluable subjects per group would provide 80% power to demonstrate a difference between vaccine and control groups assuming an attack rate of HPV-16 and/or HPV-18 of 6% over 12 months in the control group and an expected vaccine efficacy of 70%.

Study Cohorts Analyzed

- **The ATP cohort months 6-18 and ATP cohort months 6-27** assessed the efficacy of three vaccine doses and the ATP cohort months 0-18 and ATP cohort months 0-27 assessed the efficacy of at least one vaccine dose. The analyses of the protocol-defined cohorts were the primary analysis.
- **ATP cohort for analysis of safety** included all subjects who: had been enrolled; had received at least one dose of study vaccine/control according to their random assignment; with sufficient data to perform an analysis of safety (i.e. at least one solicited or unsolicited symptom sheet available); and had not received a vaccine not specified or forbidden by the protocol within 1 week before or after a dose of study vaccine. (The sponsor notes that the above time interval (presented in the RAP but not the protocol) for this criterion was not consistent with that in a study elimination criterion (presented in the protocol and in the RAP) which stated "Administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before each dose of vaccine and ending 30 days after". For the analyses the elimination criterion was applied but the interval was adapted to "from less than or equal to 28 days before each dose of vaccine and ending 30 days after"; without randomization failure or code broken; for whom injection site or route of vaccine/control administration was known and correct.
- **ATP cohort for analysis of efficacy** for primary analysis of efficacy included all subjects meeting all eligibility criteria, complying with the procedures defined in the protocol; and for whom data concerning efficacy endpoint measures were available. As most of the efficacy endpoints were assessed between months 6 and 18, the endpoint should not have been observed before the month 6 visit. The following criteria applied to all ATP cohorts for analysis of efficacy against HPV-16 and/or HPV-18 infection except the last criterion, which applied only to the ATP 6- 18 month and 6-27 month cohorts. The ATP cohort excluded all subjects:
  - excluded from the ATP cohort for analysis of safety
  - who had not received three doses of vaccine/control
  - with protocol violation
  - with concomitant infection unrelated to HPV vaccine which may influence immune response;
  - with baseline blood sample lost or unable to test
  - with obvious incoherence or abnormality or error in data
  - for efficacy between months 6-18 (primary endpoint) and between months 6-27, for whom the considered event had occurred before the month 6 visit
  - who did not complete the final study visit
  - seropositive for HPV-16 or HPV-18 at month 0

- DNA positive by PCR at month 0 for HPV-16, HPV-18, or any other high risk type (i.e. HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68)
- For efficacy analyses between months 6-18 (primary endpoint) and between months 6-27, DNA positive for HPV-16 or HPV-18 at month 6.

For the **analysis of efficacy against HPV-16/18-related phylogenetic types** (analyzed by related phylogenetic group) and against individual HPV types (high and low risk) all of the above criteria were applied except the last two which were replaced by:

- DNA positive by PCR at month 0 for the specific HPV type or group of HPV types considered in the analysis;
- For the ATP cohorts months 6-18 and months 6-27, DNA positive by PCR at month 6 for the specific HPV type or group of HPV types considered in the analysis.

For the **analysis of efficacy against combined high risk types** (HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 or HPV-16, 18, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) all of the above criteria were applied except the last two which were replaced by:

- DNA positive by PCR at month 0 for any high risk HPV type;
- For the ATP cohorts months 6-18 and months 6-27, DNA positive by PCR at month 6 for any high risk HPV type.

For the **analysis of efficacy against combined low risk HPV types** (HPV-6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74) all of the above criteria were applied except the last two which were replaced by:

- DNA positive by PCR at month 0 for any low risk HPV type;
- For the ATP cohorts months 6-18 and months 6-27, DNA positive by PCR at month 6 for any low risk HPV type.

ATP cohort for analysis of immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol and fulfilling requirements for analysis) for whom pertinent data were available. This included any subjects for who assay results were available for antibodies at any blood sampling time point.
The ATP cohort for immunogenicity analysis excluded the subjects:

- excluded from the ATP cohort for analysis of safety
- who had not received three doses of vaccine/control
- with protocol violation
- with concomitant infection related or unrelated to HPV vaccine which may have influenced immune response
- with non compliance with vaccination schedule
- subjects who had no pre-vaccination data or did have pre-vaccination data but who had no data for either month 7 or month 18
- with obvious incoherence or abnormality or error in data

ITT cohort was the population used for the secondary analysis. The purpose of the two types of analyses was to ensure that protocol violations, subject dropouts and withdrawals were not treatment related and did not lead to any selection bias in the efficacy results.
Total (ITT) cohort included all enrolled subjects who received at least one dose of study vaccine.

- **ITT analysis of safety** included all vaccinated subjects for whom safety data were available.
- **ITT analysis of efficacy** included vaccinated subjects for whom data concerning efficacy endpoint measures were available.

- **ITT analysis of immunogenicity** included vaccinated subjects for whom data concerning immunogenicity measures were available.

Derived and transformed data:
Immunogenicity- The assay cut-off values for each of the antibodies were defined by the laboratory before the analysis. A seronegative subject was defined as a subject whose antibody titer was below the assay cut-off value. A seropositive subject was defined as a subject whose antibody titer was greater than or equal to the assay cut-off value. The Geometric Mean Titers (GMTs) calculations were performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation. The immunogenicity analysis excluded subjects with missing or non-evaluable measurements.
Safety - Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were not considered as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively) and therefore were not considered in the denominator.
Efficacy - Censored subjects at month 0 were considered as non-cases. In the analysis of efficacy of HPV-16 or HPV-18 for the ITT cohort any subject positive for any high risk HPV type at entry (month 0) was censored. Any such subject was not counted as a case but was included in the denominator (N).

Analysis of efficacy: The analysis of efficacy against cervical infection with HPV-16 and/or HPV-18 was performed on five different cohorts as summarized in Table 9. The primary cohorts for analysis were the ATP cohorts months 6-18 and months 6-27 which assessed the efficacy of three vaccine doses.

Table 9- Study HPV-001: Cohorts for analysis of efficacy (infection with HPV-16 and/or HPV- 18)

Cohort (Evaluation period)	Population
ATP (months 6-18) ATP (months 6-27)	Included ATP subjects who had received 3 vaccine doses, who were seronegative for HPV-16 or HPV-18 at month 0 and who were negative for high risk DNA at entry (month 0) and negative for HPV-16 or HPV-18 DNA at month 6, i.e. "post dose 3 efficacy"
ATP (months 0-18) ATP (months 0-27)	Included ATP subjects who had received 3 vaccine doses, who were seronegative for HPV-16 or HPV-18 at month 0 and were negative for high risk DNA at entry (month 0) i.e. "efficacy following administration of at least 1 vaccine dose for ATP subjects".
ITT (months 0-27)	Included ITT subjects who had received at least 1 vaccine dose, were negative for high risk DNA at entry (month 0), i.e. "efficacy following administration of at least 1 vaccine dose for ITT subjects".

Source: STN 125259/0, CSR 001, Table 11, p. 82

For **Analysis of efficacy against infection with HPV-16 and/or HPV-18 related phylogenetic types** (analyzed by related phylogenetic group) and individual high risk or low risk HPV types, the cohorts were the same as in Table 9 except that the negative or positive DNA status at months 0 and 6 was defined with respect to the specific HPV type or group of HPV types considered in the analysis.

For **analysis of efficacy against infection with combined high risk types** (HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 or HPV-16, 18, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) the cohorts were the same as in Table 9 except that the negative or positive DNA status at months 0 and 6 was defined with respect to any high risk HPV type.

For **analysis of efficacy against infection with combined low risk types** (HPV-6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74) the cohorts were the same as in Table 9 except that the negative or positive DNA status at months 0 and 6 was defined with respect to any low risk HPV type.

For each of the efficacy objectives the analysis was divided into two parts, a description of observed events and the calculation of vaccine efficacy.

Descriptive analyses were as follows**:**

- Incidence and number of incident infections with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 stratified by type of lower genital tract specimen (i.e. self-obtained cervicovaginal specimen or physician-obtained cervical specimen or both combined).
- Incidence and number of persistent infections with HPV-16, HPV-18 and HPV-16 and/or HPV-18 stratified by type of lower genital tract specimen.
- Incidence and number of ASCUS (post hoc) LSIL, HSIL, squamous cell cancer, or adenocarcinoma associated with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 infection stratified by cytology or histopathology diagnosis (histopathology results were expressed using the cervical intraepithelial neoplasia (CIN) classification system where CIN 1 corresponds to LSIL and CIN 2 and CIN 3 correspond to HSIL).
- Incidence and number of infections with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic types, high risk types and low risk types (as defined in RAP and post-hoc section).
- Incidence and number of persistent infections with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic types, high risk types and low risk types (as defined in RAP and post hoc).
- Incidence and number of ASCUS (post hoc), LSIL, HSIL, squamous cell cancer, or adenocarcinoma associated with HPV-16, HPV-18 and/or HPV-16/18-related phylogenetic types, high risk types and low risk types infection (as defined in RAP and post hoc see section) stratified by cytology or histopathology diagnosis (histopathology results were expressed using the CIN classification system where CIN 1 corresponds to LSIL and CIN 2 and CIN 3 correspond to HSIL).
- HPV DNA detected in biopsy tissue (post hoc) for histopathologically confirmed cases of CIN 1, CIN 2 or CIN 3.

Inferential Analyses: Comparison of attack rates: A comparison was made between the vaccine and control groups of the attack rates of HPV infection for the ATP 6-18 months and ATP 0 to 18 months efficacy cohorts. Attack rate = number of cases/number of non-cases + number of cases

- **Vaccine Efficacy (VE)** was defined as the percent reduction in the frequency of the relevant endpoint in vaccine recipients compared with those subjects who received control. This was calculated as: 1-[the attack rate in vaccine recipients/the attack rate in control recipients] with two-tailed 95% confidence intervals.
- **Statistical hypothesis:** The null hypothesis was: “the expected attack rates during the considered period were similar in both groups”. If the null hypothesis was rejected, the alternative hypothesis, that the expected attack rate was different between the 2 groups was accepted.

- **Statistical analysis:** Attack rates (and 95% exact confidence limits) for HPV infection in vaccine and control recipients were calculated. Rates were compared between groups using a Fisher's exact test. The null hypothesis was rejected if the Fisher's exact p-value was < 0.046. The attack rate comparison between groups was also stratified by covariates. The following factors, recorded on the month 18 exit questionnaire as indicated below, were considered separately: Geographical region (North America, Brazil) (baseline); Number of new sexual partners since study start (0, 1-3, 4-6, and > 6); Frequency of sexual contact per month: 0-5, 6-10, and >10; Hormonal contraception for at least 3 months consecutively (Yes, No); Smoking (Yes, No); Occurrence of another lower genital tract infection (Yes, No).

The attack rate was given by the above covariates for each group. Vaccine efficacy (and 95% CI) adjusted by the covariates was calculated using logistic regression.

Inferential Analyses: Comparison of time to occurrence.
For the cohorts where the duration of follow up was not identical for all subjects (due to some subjects participating in the optional blinded extension phase after month 18) endpoints were analyzed by "time to occurrence of infection". A comparison was made between the vaccine and control groups of the time to occurrence of HPV infection for the ITT month 0-27, ATP month 0-27 and ATP month 6-27 cohorts.

- **Statistical hypothesis:** The null hypothesis was: "the distribution of time to occurrence was the same in each group". The null hypothesis was rejected if the p-value of the log rank test was < 0.046.
- **Statistical analysis**
  - The **main comparison** of subjects between groups was in terms of time to occurrence analyzed by means of the Log-rank test. The magnitude of vaccine effect was estimated in terms of vaccine efficacy (95% confidence interval), obtained from a Cox regression. Kaplan-Meier plots were drawn for each vaccine group.
  - A **secondary comparison** was the time to occurrence analysis was adjusted for covariates in a stratified Log-rank test. This analysis assessed the vaccine effect in delaying the occurrence of HPV infection, controlling for other covariates defined by risk factors identified in exploratory analyses using the month 18 exit questionnaires (e.g. measures of exposure such as number of new sexual partners, frequency of sexual contact, hormonal contraception, smoking, occurrence of other sexually transmitted diseases, etc).
  - **Vaccine efficacy (VE)** was based on time to occurrence was equal to 1 minus the hazard ratio, where the hazard ratio was estimated by the coefficient of the Cox regression model. This estimate takes into account the time to exposure for each individual subject and is therefore applicable for the cohorts (ITT month 0-27, ATP month 0-27 and ATP month 6-27) where the duration of follow up was not identical for all subjects (due to some subjects participating in the optional blinded extension phase after month 18).

Analysis of safety
The analysis of safety was performed on the ATP cohort (primary analysis) and the ITT cohort.
Descriptive analyses

- The percentage of documented vaccine or control doses followed by any symptoms (and further stratified by local and general symptoms) during the 30 day-follow up after each dose was tabulated with exact 95% confidence intervals per dose and overall.
- The percentage of documented vaccine or control doses followed by solicited local adverse events (pain, redness and swelling) and solicited general adverse events (temperature, headache, fatigue, gastrointestinal symptoms, rash, pruritis) during the 7-day follow-up period

(Day 0 to Day 6) after each dose were tabulated with exact 95% confidence intervals (per dose and overall) by intensity and for general solicited adverse events, also according to their relationship to vaccination.

- The verbatim reports of unsolicited symptoms were coded by use of the World Health Organization's (WHO) Dictionary for Adverse Reaction Terminology. Every verbatim term, as stated by the reporter, was matched to the appropriate WHO term. The percentage of subjects with at least one report of an unsolicited adverse event, classified by the WHO Body system and Preferred Terms (latter not presented in this report) to 30 days after vaccination were tabulated. The same tabulation was performed for unsolicited adverse events that were causally related to vaccination, for grade 3 unsolicited adverse events and for grade 3 unsolicited adverse events that were causally related to vaccination.
- Reports of unsolicited events considered as medically significant (including new onset of chronic disease) which occurred outside the 30 day follow-up period were also tabulated.
- Any pregnancies occurring during the study and the outcome of these pregnancies were tabulated per group.
- The number and type of unscheduled gynecological visits per treatment group was tabulated and a description of the visits provided in a supplementary table.
- The results of biochemical and hematology laboratory tests with respect to normal laboratory ranges were tabulated.
- All serious adverse events reported during the study were listed.

Inferential analyses: The incidence between groups of solicited local symptoms and solicited general symptoms calculated on the number of symptom sheets was compared using Fisher's exact tests.

Analysis of immunogenicity

The analysis of immunogenicity was performed on the ATP cohort (primary analysis) and the ITT cohort. The humoral response was assessed by the measurement of serum antibody levels to HPV-16 and HPV-18 as assessed by ELISA. Ig-anti J4-HPV18 and Ig-anti-V5-HPV16 titers were also measured in a subset of subjects.

A **seropositive** subject was defined as a subject whose titer was greater than or equal to the assay cut-off value:

- 8 ELISA units/ml for anti-HPV-16 antibodies
- 7 ELISA units/ml for anti-HPV-18 antibodies
- -b(4)- ELISA units/ml for anti- V5-HPV16 antibodies
- -b(4)- ELISA units/ml for anti- J4-HPV18 antibodies
- -b(4)- dilution for neutralization assays for neutralizing antibodies to HPV-16 and HPV-18 L1 VLPs

Descriptive analysis: The seropositivity rates and their exact 95% confidence intervals were calculated.

Changes in the conduct of the study or planned analyses: There were six amendments.

1st protocol amendment (8/9/00): This amendment was made to include recommendations made by CBER following a teleconference on the 7/31/00 telecon. The major changes were as follows:

- **Long-term follow-up:** Following CBER recommendations, the planned long-term follow-up was designed as a separate protocol including both vaccine and control recipients, with the objectives of evaluating:
  - The long-term course of high-risk HPV infection and viral clearance

- Persistence of vaccine-induced immune responses. (In addition, an option to randomly select a subset of vaccine recipients who had not developed HPV-16 or HPV-18 infection for booster immunization was added.)

The follow-up study was to be conducted under a separate protocol and could be further extended, if appropriate.

- **Primary Endpoint:** For the primary efficacy endpoint analysis all HPV-16 and/or HPV-18 DNA results for both self-obtained cervicovaginal specimens and physician-obtained cervical specimens combined were to be used. Following CBER recommendations, a separate analysis of physician-obtained cervical specimens was added.
- **Interim Analysis:** CBER requested an adjustment to the alpha value for the primary endpoint analysis since an interim analysis was to be performed, (even though the results of this analysis were not to be used to make decisions about early termination of the trial, i.e., no "stopping rules" were described). The O'Brien and Fleming method was used to adjust the alpha value for the final analysis. A table summarizing the power calculated for observed vaccine efficacy of 70%, 75%, 80%, 85% and 90% was added.

2nd protocol amendment (12/19/00): The major changes were as follows:

- **Cervical cytology samples and samples for HPV DNA by PCR:** At the time of finalization of the original protocol, it was not known which transportation medium would be selected for extraction of HPV DNA from the cervical specimens for PCR. --b(4)--- was selected as the transport medium for all cervical specimens.
- **Biopsies:** In order to ensure consistency of evaluation, biopsy material from sites was to be processed by a central laboratory.
- **Intervals between study visits and vaccinations:** Inconsistencies in the allowable intervals between study visits and the allowable intervals between administrations of corresponding vaccine doses were corrected.
- **Subject information and informed consent:** The subject information and informed consent were clarified to indicate that subjects completing the epidemiology study (999910/106) more than 90 days prior to enrolment in the present study would need to undergo screening.

3rd protocol amendment (6/15/01): The major changes were as follows:

- **Colposcopy:** All subjects with abnormal cervical cytologies indicating the presence of LSIL, AGUS or HSIL were to be referred for colposcopy and appropriate medical follow-up. Subjects referred for colposcopy were now to be asked to sign an addendum to the study informed consent describing the colposcopy procedures. Subjects electing to have colposcopy performed outside of the study were to be asked if study staff could access their medical records to obtain results of their colposcopy for evaluation. Subjects not agreeing to sign the addendum were still to be referred for further evaluation but data resulting from the evaluation was not to be used in the analyses.
- **Subject information and informed consent:** Supplemental subject information sheets and informed consents were added.

4th protocol amendment (5/6/02): The major changes were as follows:

- **Increase in the duration of follow-up:** In the original protocol the duration of individual participation was 18 months. In order to ensure sufficient statistical power if the attack rate was lower than expected the study was extended. All subjects completing the initial follow up (at month 18) before 2/1/03 were asked to return for visits (or participate in telephone interviews and return self samples) at regular intervals until the last subject enrolled completed the initial study period. Subjects completing their month 18 visit (visit 8) on or after 2/1/03

were not eligible to participate in the blinded extended phase. This blinded extended phase was different from the planned long-term follow-up study (HPV-007).

- **Change in timing and scope of interim analysis:** In the original protocol an interim analysis was planned at month 12. In this amendment it was specified that **two interim analyses** were planned for internal planning purposes only.
  - A **safety analysis** was to be conducted on all available (but not validated) safety data up to the 5/2/02 to evaluate solicited adverse events after each and any vaccine dose, by treatment group; the number and proportion of enrolled volunteers receiving doses 1, 2, 3 and all doses, by treatment group. This safety analysis was to be carried out in order to assess the tolerability of the vaccine.
  - The **second interim analysis of immunogenicity and efficacy** was to be carried out when all subjects had completed their month 7 visit (visit 4) and the ITT cohort had 28 incident HPV16/18 infections after dose 1 to establish vaccine efficacy >0. This interim analysis was to evaluate vaccine efficacy (VE) in order to show VE>0, assuming a true VE = 80% with a power of 70% and an alpha = 0.5%and immunogenicity at month 7.
  - **PCR testing** testing algorithm was modified. Any specimen testing positive using the "generic" PCR assay was also to be tested by type-specific PCR for HPV-16 and HPV-18 in addition to LiPA .

5th protocol amendment (6/13/02): This amendment obliged investigators to report any subject's pregnancy throughout the study including the blinded extension phase. The amendment also clarified that only pregnancy-related adverse experiences had to be recorded in the SAE screen of the eCRF.

6th protocol amendment (1/30/03): In this amendment a **second interim efficacy analyses** was planned for internal purposes when all subjects had completed their month 12 visit (visit 6) and when the number of results available for month 18, were at least equal to 50% of the results available for month 12. This second interim efficacy analysis was to evaluate vaccine efficacy (VE) in the prevention of infection with HPV-16 and/or HPV-18 in order to show VE>0, assuming a true VE =70% with a power of 90% and an alpha = 0.5%.

Other Changes

Miscellaneous changes and deviations

This study was conducted according to the protocol except for the following:

- Subjects who participated in the epidemiology study 999910/106 were eligible to be enrolled directly in this current study without screening provided that the interval between completion of study 999910/106 and enrolment in this study did not exceed 90 days. An exception was granted for four subjects for whom completion of study 999910/106 took place up to 96 days before enrolment in study 580299/001.
- In the protocol, 32 centers were planned but one center (030 in US) was closed because none of the six subjects screened at this center ultimately enrolled in this present study.
- An addendum to the informed consent was to be signed by all subjects (or in the case of subjects below the age of consent, the addendum to the Consent Form was to be signed by a parent/guardian and an addendum to the Assent Form by them) who opted to participate in the blinded extended follow-up to the study. In one center (No. 320) there was confusion between the two types of addendum forms. In this center all the subjects were presented with and signed the Assent addendum forms for participation in the blinded extension phase even though most of them were over 18 years of age. The content of both forms was exactly the same, the only difference related to the signature page. A letter of notification was sent to the

IRB. As this deviation had no impact on study procedures, the subjects concerned were not eliminated from the ATP analysis.

- In the five Brazilian study sites, several irregularities concerning informed consent were noted during the re-monitoring exercise. All subjects gave their written consent prior to study start. Corrective actions were taken subsequent to the re-monitoring activities, appropriate documentation of the corrective actions was added to the local study files and the respective ethical committees were informed.

Reviewer's Comment: The sponsor's explanations for these events were reviewed. In each instance, the discrepancies were noted and rectified, with ethics committees being informed and not deeming the events to be in violation of ethical procedure. These events did not appear to impact on the integrity of data collected.

Changes to analyses

Analyses were performed as planned and described in the protocol and the report analysis plan (RAP dated 8/29/02 amended on 1/31/03) except for the following:

- Both methods proposed to compute the 95% confidence intervals for the vaccine efficacy (comparison of attack rates and Cox-regression) did not provide a lower limit when there were no cases in the vaccine group. Therefore in these cases a lower limit of the 95% confidence interval was calculated using the asymptotic version of a method. Both exact and asymptotic methods calculate confidence intervals for the difference in proportions and are based on a standardized score statistic. They both lead to very similar confidence intervals with large sample sizes (as in this study). However, the computation time for the exact method is considerably longer as compared to the asymptotic method, and that is why the asymptotic method was used for this analysis.
- The time to occurrence used to estimate the vaccine efficacy by the Cox regression was approximated based on the time point as follows: for the month 6 visit, an approximate value of 182 days; for the month 9 visit, an approximate value of 273 days; for the month 12 visit, an approximate value of 365 days; for the month 15 visit, an approximate value of 456 days; for the month 18 visit, an approximate value of 547 days; for the month 21 visit, an approximate value of 639 days; for the month 24 visit, an approximate value of 730 days.
- HPV-16 and HPV-18 related phylogenetic types were not specified in the protocol but examples were listed (such as HPV-31, 33, 35, 39, 45, 52, 58 and 68). In the RAP HPV-16 related phylogenetic types were defined as HPV-16, 31, 35, and 58 and HPV-18 related phylogenetic types were defined as HPV-18, 45 and 59. An additional extended *post hoc* definition for phylogenetic types related to HPV-16 (HPV-16, 31, 35, 58, 33 and 52) was used for the analysis. Also it was decided *post hoc* to do an additional analysis for HPV-16 related phylogenetic types excluding HPV-16 and an analysis for HPV-18 related phylogenetic types excluding HPV-18.
- As indicated in the RAP an exploratory analysis of efficacy against individual high risk types was performed. In addition the incidence and efficacy for combined high risk types (HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 or HPV-16, 18, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and combined low risk types (HPV-6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74) were calculated *post hoc.*
- The definitions of the ATP cohorts for efficacy against HPV-16/18-related phylogenetic types, individual high risk and low risk HPV types, combined high risk and combined low risk HPV types were made *post hoc*.
- In addition to the protocol specified incidence of LSIL, HSIL, squamous cell cancer, or adenocarcinoma based on cytological analysis of cervical specimens and associated with HPV-16 and/or HPV-18 or related phylogenetic type, high risk or low risk type infections, a *post hoc* descriptive analysis was performed of the incidence of ASCUS associated with these

infections. The RAP specified "overall incidence" (i.e. any cytological lesion) also incorporated ASCUS and was referred to as "≥ ASCUS".

- Samples of biopsy material were tested for HPV DNA *post hoc* by PCR.
- To establish a link between PCR testing and results obtained in cytology and histopathology the following *post hoc* algorithm was constructed:
  - Some subjects had more than one cytology specimen tested for one time point. In the majority of cases this was because the initial specimen was inadequate. However in some cases there were two or more valid cytology results for the same subject and the same time point. In these cases, the highest grade of pathology was considered (worst case result obtained).
  - The result obtained for PCR on the cervical specimen retained for cytology was the one taken into consideration. However if the PCR results for the same subject and the same time-point gave contradictory results for HPV detection then any positive result was considered.
- As requested by CBER an analysis of co-infection cases (infection with both HPV-16 and HPV-18) was performed.
- A *post hoc* analysis of the duration of local solicited symptoms in the vaccine group was performed.
- Due to maintenance of blinded status unsolicited symptoms were presented for vaccine and control groups by WHO Body System rather than by WHO Preferred Term. This was to avoid breaking the blind for some individuals who might have been identifiable on assignment of WHO Preferred Terms. The overall frequencies of serious adverse events (SAEs) and pregnancies are presented per group but details of the individual SAEs or pregnancies are presented as "blinded cases" without indication of the study group.
- Unscheduled gynecologic visits were classified into the following categories which were established post hoc: follow-up to study visits, visits associated with an adverse event involving the lower genital tract and gynecologic visits associated with an adverse event not involving the lower genital tract.
- Although indicated in the protocol but not described in the RAP, an analysis of immunogenicity by geographical region and center was performed.
- An error by a laboratory technician in the labeling of ELISA plates led to the incorrect reporting of anti-HPV-18 titers for seventy two samples (33 from the control and 39 from the vaccine group). Sixty nine of these were month 6 samples and three were month 12 samples. These seventy two titer values were not included in the immunogenicity analyses at month 6 or 12.
- Following completion of the immunogenicity analyses it was discovered during a quality control check of serum samples that nine of the subjects included in the ATP analysis should have been excluded due to inconsistencies in the dates noted for month 7 and month 18 serum samples. A re- analysis of anti-HPV-16 and anti-HPV-18 ELISA titers which excluded these nine subjects was performed. The exclusion did not affect the overall results and so the original ATP analysis was maintained.
- The analysis of viral load for HPV-16 and HPV-18 (by PCR) for both cervicovaginal specimens and physician-obtained cervical specimens (secondary efficacy endpoint), preliminary testing was performed with non-validated method on a limited number of heterogenous .
- Other exploratory analyses described in the protocol but for which limited data are available or analysis has not yet been performed and which may lead to additional future annexes to this report are:
  - Clearance of HPV infection for subjects positive for high risk at month 0 (limited data)
  - Duration of high risk HPV DNA positivity by HPV type (limited data)

- HPV-16 and HPV-18 molecular variants (limited data)
- Identification of a possible correlate of protection by analysis of breakthrough infections and decile of antibody response at month 7 (analysis still pending).

- A confirmatory re-analysis of the study data was performed on a re-monitored dataset with the exclusion of all data from study site 22 (Curitiba, Brazil). This re-analysis is presented in an annex report.

RESULTS

SUBJECTS ANALZYED

Number and distribution of subjects: A total of 1000 subjects (500 in each group) were planned to be enrolled in this study to provide at least 770 evaluable subjects (385 per group). Subsequently, 1113 subjects (560 in the HPV-16/18 L1/AS04 vaccine group and 553 in the control group) were enrolled in the study. Subjects were enrolled at 31 centers in the USA, Canada and Brazil. 506 (45.5%) subjects were enrolled in Brazil and The number and percentages of enrolled subjects vaccinated per center and 607 subjects (54.5%) were enrolled in North America.

Study completion and withdrawal from study: There were two phases for the study, an initial phase which concluded at month 18 (visit 8) and a blinded extension phase which concluded at month 21, 24 or 27 (visit 9, 10 or 11) depending on the enrollment date in this extension phase. The blinded extension phase was optional and only offered to subjects who had completed their month 18 visit before 2/1/03. Of the 1113 subjects enrolled, 958 subjects (86%) completed the initial part of study with the concluding visit at month 18. The number of withdrawals was comparable for both groups. There were four withdrawals related to adverse events, one due to a serious adverse event in the vaccine group and three due to non serious adverse events in the control group. The most common reasons for withdrawal were loss to follow up of subjects who had completed the vaccination course and consent withdrawal, as shown in Table 10.

Table 10 – Study HPV-001: Subjects entered, completed, or dropped-out and reason for dropout from months 0- 18 (ITT cohort)

	Number of Subjects			Reason for drop-out							
	Enrolled	Completed	Dropped out	A	B	C	D	E	F	G	H
Overall	1113	958	155	1	3	1	32	29	26	42	21
Vaccine	560	480	80	1	0	0	18	17	15	18	11
Placebo	553	478	75	0	3	1	14	12	11	24	10

Enrolled = number of subjects who where enrolled in the study
Completed = number of subjects who completed the concluding visit for the initial part of the study (visit 8)
Dropped out = number of subjects who did not come for the concluding visit for the initial part of the study (visit 8)
Reasons for drop-out (Reasons C-H: not related to any adverse event):
A – Serious Adverse Event
B – Non-Serious Adverse Event
C – Protocol Violation
D – Consent Withdrawal
E – Migration from study area
F – Lost to Follow-up (subject with incomplete vaccination course)
G – Lost to Follow-up (subject with complete vaccination course)
H – Others
Source: STN 125259/0, CSR 001, Table 12, p. 272

The number of subjects who participated in the blinded extension phase and who attended the visits at month 21 (visit 9), month 24 (visit 10) and month 27 (visit 11) were comparable between the two groups, as shown in Table 11.

Table 11- Study HPV-001: Subjects who Participated in the Blinded Extension Phase and Completed Visits 9, 10, and 11 (Months 21, 24 and 27 respectively) (ITT cohort)

Number of subjects:	Vaccine		Placebo	
	n	%	n	%
Randomized (initial study phase)	560		553	
Completed Visit 1 (initial study phase)	560	100	553	100
Completed Visit 8 (initial study phase)	480	85.7	478	85.4
Completed Visit 9 (extension phase)	403	72.0	392	70.0
Completed Visit 10 (extension phase)	267	47.7	247	41.1
Completed Visit 11 (extension phase)	95	17.0	82	14.6

Source: STN 125259/0, CSR 001, Table 13, p. 273

Protocol deviations leading to exclusion of subjects from an analysis: The number of subjects excluded from the ATP analyses and the reasons for exclusion are shown in Table 12 for the safety and efficacy analyses and in Table 13 for the immunogenicity analysis.

Table 12 – Study HPV-001: Number of Subjects and Reason for Elimination from Safety and Efficacy Analyses

	Total	Percent	Vaccine	Placebo
Randomization numbers created	1608		804	804
Subject or vaccine number not allocated (code 1010)	495		244	251
Number of subjects enrolled	1113	100	560	553
Administration of vaccine(s) forbidden in the protocol (code 1040)	21		10	11
Randomisation failure (code 1050)	9		9	
Randomisation code broken at the investigator site (code 1060)	2		1	1
Number of subjects in the ATP cohort for safety	**1081**	**97.12**	**540**	**541**
Underlying medical condition forbidden by the protocol at screening (code 3010)	8		2	6
Seropositive for HPV-16 or 18, high risk HPV DNA positive or abnormal cytology result at entry (code 3020)	152		79	73
Administration of any medication forbidden by the protocol (code 3040)	1			1
Non compliance with vaccination schedule (code 3080)	86		41	45
Subjects without HPV DNA results or serology results at month 0 (code 3100)	21		9	12
Subjects dropout from first conclusion (up to month 18) (code 3110)	67		36	31
Number of subjects in the ATP cohort month 0-18 and 0-27 for efficacy against HPV-16 and/ or 18	**746**	**67.03**	**373**	**373**
Subjects with positive HPV-16 or 18 DNA results at Month 6 (code 4020)	25		7	18
Number of subjects in the ATP cohort month 6-18 and 6-27 for efficacy against HPV-16 and/ or 18	**721**	**64.78**	**366**	**355**

Percent = percentage of subjects in the considered ATP cohort relative to the ITT cohort.
Subjects may have one or more elimination code(s) assigned in which case the lowest code number is listed in the figure. Codes are listed based on a ranking order.
Source: STN 125259/0, CSR 001, Table 14, p. 103

Table 13 – Study HPV-001: Number of Subjects and Reason for Elimination from Immunogenicity Analysis

	Total	Percent	Vaccine	Placebo
Number of subjects in the ATP cohort for safety	**1081**	**97.12**	**540**	**541**
Protocol violation (inclusion/exclusion criteria) (code 2010)	8		2	6
Initially seropositive or initially unknown antibody status (code 2020)	43		23	20
Administration of any medication forbidden by the protocol (code 2040)	1			1
Concomitant infection related or unrelated to the vaccine which may influence immune response (code 2060)	125		40	85
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	103		52	51
Non compliance with blood sampling schedule (including wrong and unknown date) (code 2090)	64		35	29
Essential serological data missing (code 2100)	9		4	5
Number of subjects in the ATP cohort for immunogenicity	**728**	**65.41**	**384**	**344**

Percent = percentage of subjects in the considered ATP cohort relative to the ITT cohort.
Subjects may have one or more elimination code(s) assigned in which case the lowest code number is listed in the figure. Codes are listed based on a ranking order.
Source: STN 125259/0, CSR 001, Table 15, p. 104

Protocol deviations not leading to exclusion of subjects from an analysis: There were two types of protocol intervals which were adapted prior to the analysis so that deviations from the protocol did not lead to exclusion of subjects from analyses: intervals between study visits and intervals for administration of a vaccine not foreseen by the protocol.
Reviewer's Comment: Minor changes were made to allow for varying intervals, and time between another vaccine was changed from within 30 days to within $\geq$ 28 days before and 30 days after.

Demographic characteristics: The demographic profile of the vaccine and control groups was similar with respect to age, racial distribution, height and weight. The mean ages of the two groups were 20.2 and 20.5 years. The majority of subjects were white (68.4%), with 7.2% of the subjects black, and 22.6% other. (See Table 14).

Table 14 – Study HPV-001: Demographic Characteristics (ATP Cohort Months 6-18 and Months 6-27 for efficacy)

Characteristic	Parameter	Vaccine N=366		Aluminum hydroxide Control N=355		Total N=721	
		Value or n	%	Value or n	%	Value or n	%
Age (yrs)	Mean (SD)	20.2 (2.9)		20.5 (2.79)		20.3 (2.85)	
	Median	20		20		20	
	Min-Max	15-26		15-26		15-26	
Race	White	244	66.7%	249	70.1%	493	68.4%
	Black	30	8.2%	22	6.2%	52	7.2%
	Oriental	9	2.5%	4	1.1%	13	1.8%
	Other	83	22.7%	80	22.5%	163	22.6%
Height (cm)	Mean (SD)	162.5 (7.57)		162.7 (7.76)		162.6 (7.70)	
	Median	163		163		163	
	Min-Max	143-183		142-185		142-185	
Weight (kg)	Mean (SD)	62.7 (13.52)		62.2 (12.77)		62.5 (13.20)	
	Median	60		60		60	
	Min-Max	36-120		38-116.8		36-120	

Source: STN 125259/0, CSR 001, from Tables 16 and 17, p. 105-106

Demographic characteristics for other cohorts are also provided (ATP cohort months 0-18 and 0-27 for efficacy; ITT cohort; ATP cohort for safety; and ATP cohort for immunogenicity). The characteristics are comparable across the different analysis populations.

EFFICACY RESULTS

Analysis of efficacy was performed on the ATP cohort (primary analysis) and the ITT cohort. After the month 18 visit only self-obtained cervicovaginal specimens were collected. However, in some cases following an abnormal result, a repeat cervical specimen was taken by the physician after month 18. Data from these specimens are included in the analysis of the ATP month 0 to 27 and month 6 to 27 cohorts.

According-To-Protocol (ATP) analysis, Vaccine efficacy in the prevention of *incident infection* with HPV-16 and/or HPV-18: The primary endpoint of the study was prevention of HPV-16 and/or HPV-18 incident infection after three doses of vaccine during the period between months 6 to 18. The analysis stratified by type of specimens shows that more infections were detected by cervicovaginal than by cervical specimens. Cervical specimens, which were also evaluated for cytology, can be considered as the more medically relevant because they assess the tissue where neoplasia develops. Cervicovaginal specimens assess the entire lower genital tract and may be less predictive of cervical disease. Vaccine efficacy based on all specimens (i.e. combined self-obtained cervicovaginal specimens and physician-obtained cervical specimens) and cervical specimens only was also presented. Since the alpha level allotted to this analysis was 0.046, the observed vaccine efficacy (VE) against HPV-16 and/or HPV-18 based on all specimens (VE = 78.4%, $p < 0.001$) was statistically significant. There was evidence of protection against HPV-16 infection alone (VE = 88.4%, $p < 0.001$) and HPV-18 infection alone (VE = 67.7%, $p = 0.020$). The analysis based on cervical specimens only also demonstrated statistically significant vaccine efficacy against HPV-16 and/or HPV-18 (VE = 91.6%, $p < 0.001$) and HPV-16 infection alone (VE = 100%, $p < 0.001$). There were too few cases of HPV-18 infection to observe statistically significant efficacy based on cervical specimens only. Analysis of cervical specimens only and all specimens (combined cervicovaginal and cervical specimens) are presented in Table 15.

Table 15 – Study HPV-001: Vaccine efficacy against incident infection with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 for cervical specimens and all specimens (combined cervical and cervicovaginal specimens) (ATP cohort months 6-18)

Specimen Type	Infection Type	Attack Rate						Vaccine Efficacy
		Vaccine			Alum control			% (95% CI)
		N	n	AR	N	n	AR	
Cervical specimens	HPV 16°	366	0	0.0	355	18	5.1	100 (79.4, 100%)
	HPV 18°	366	2	0.6	355	7	6.5	72.3% (-32.5, 94.2%)
	HPV 16 &/or 18°	366	2	0.6	355	23	6.5	91.6% (64.5, 98%)
All specimens (combined CV and Cervical specimens)	HPV 16°	366	3	0.8	355	25	7.0	88.4% (61.8, 96.5%)
	HPV 18°	366	5	1.4	355	15	4.2	67.7% (12.0, 88.1%)
	HPV 16 &/or 18°	366	8	2.2	355	36	10.1	78.4% (54.3, 89.8%)

N = number of subjects in specific cohort
n = number of subjects with at least one episode of incident infection with corresponding HPV type
AR = Attack rate = n / N
95% CI = 95% confidence interval
p-value = result of comparison of attack rates between groups by Fisher's exact test (two sided)
° = without considering other HPV types
Source: STN 125259/0, CSR 001, from Tables 19, p. 109

ATP cohort months 6-27: Results from these analyses (by incidence and vaccine efficacy by 'time to occurrence') are similar to those of the ATP cohort months 6-18. (Source: STN 125259/0, CSR 001, Tables 20 and 21, p. 110-111, not shown here).
Reviewer's Comment: As compared to incidence of endpoints from the 6-18 month time period, there were several additional endpoints that accrued. Point estimates of efficacy are similar for all endpoints.

ATP cohort month 0-27: The analyses of vaccine efficacy for this cohort are presented in Table 16.

Table 16- Study HPV-001: Vaccine efficacy based on time to occurrence of incident infection with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 for cervical specimens and all specimens (combined cervical and cervicovaginal specimens) (ATP cohort months 0-27).

		HPV Vaccine = 373 Aluminum hydroxide = 373
Specimen Type	Infection Type	Vaccine Efficacy (95% CI)
Cervical specimens	HPV 16°	84.0% (54.0, 94.4%)
	HPV 18°	77.3% (21.0, 93.5%)
	HPV 16 &/or 18°	82.3% (57.8, 92.5%)
All specimens (combined CV and Cervical specimens)	HPV 16°	75.9% (53.2, 87.6%)
	HPV 18°	65.4% (25.8, 83.8%)
	HPV 16 &/or 18°	70.0% (49.6, 82.1%)

95% CI= 95% confidence interval obtained from Cox regression
p-value = result of comparison of Kaplan-Meier survival curves between groups by Log-rank test
°= without considering other HPV types
Source: STN 125259/0, CSR 001, Supplement 14, p. 281

Reviewer's Comment: In the month 0-27 cohort, the point estimates of efficacy are somewhat lower for the HPV 16 endpoints as compared to the 6-18 month period. These analyses count cases from day 0 (i.e., contain prevalent infections already present at the time of dose 1, and/or before receipt of the entire series of vaccinations.) However, all analyses of vaccine efficacy reach statistical significance, possibly related to the higher number of cases that have accrued in each time period.

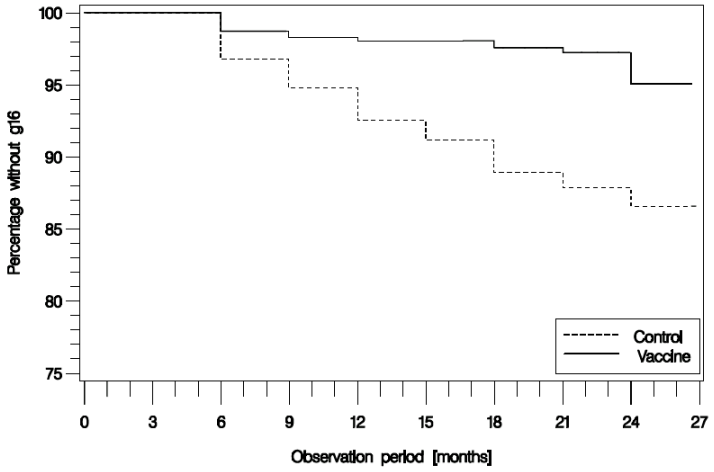
Analyses of Incident Infection, ITT Cohort: Vaccine efficacy analyses and time to occurrence curves were also presented in the ITT cohort. These analyses were conducted on subjects who received at least one dose of vaccine through Month 27. These analyses are presented in Table 17 and Figures 7, 8 and 9 below.

Table 17 – Study HPV-001: Vaccine efficacy based on time to occurrence of incident infection with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 for cervical specimens and all specimens (combined cervical and cervicovaginal specimens) (ITT cohort)

		Vaccine N=560 Aluminum hydroxide control = 553
Specimen Type	Infection Type	Vaccine Efficacy % (95% CI)
Cervical specimens	HPV 16°	82.7% (55.2, 93.3%)
	HPV 18°	82.1% (38.8, 94.7%)
	HPV 16 &/or 18°	83.0% (62.0, 92.4%)
All specimens (combined CV and Cervical specimens)	HPV 16°	75.2% (55.3, 86.2%)
	HPV 18°	59.5% (22.7, 78.8%)
	HPV 16 &/or 18°	67.6% (48.9, 79.4%)

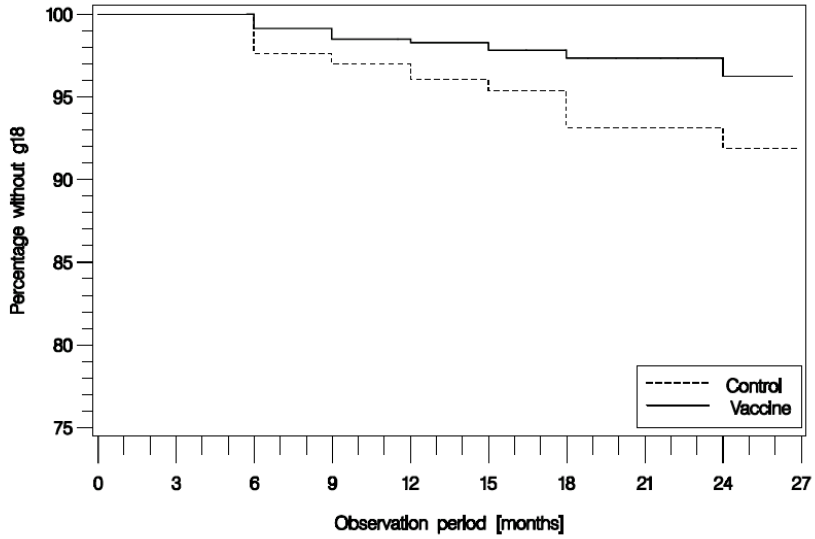
Source: STN 125259/0, CSR 001, Table 66, p. 165

Figure 7 – Study HPV-001: Time to occurrence of first incident infection with HPV-16 (Kaplan-Meier plot) (all specimens) (ITT cohort)



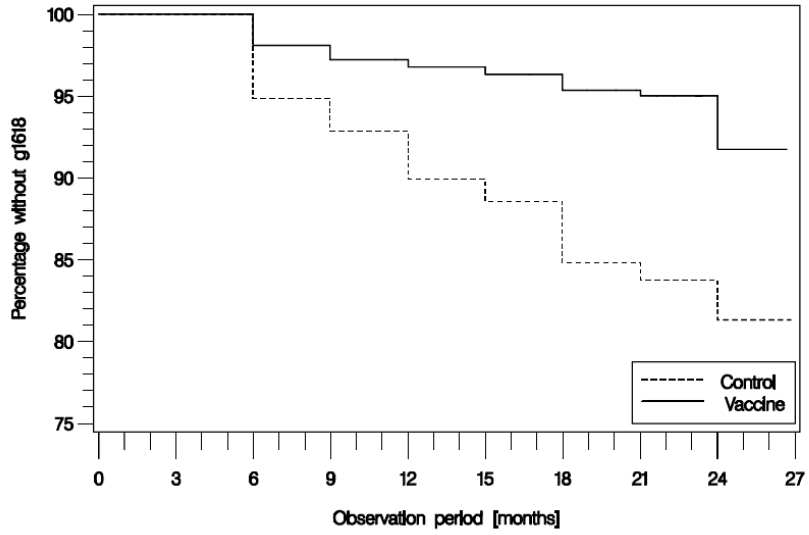
Source: STN 125259/0, CSR 001, Figure 2, p. 165

Figure 8- Study HPV-001: Time to Occurrence of First Incident Infection with HPV-18 (Kaplan-Meier Plot) (All Specimens) (ITT Cohort)



Source: STN 125259/0, CSR 001, Figure 3, p. 166

Figure 9-Study HPV-001: Time to occurrence of first incident infection with HPV-16 and/or 18 (Kaplan-Meier plot) (all specimens) (ITT cohort)



Source: STN 125259/0, CSR 001, Figure 4, p. 166

Vaccine efficacy in the prevention of persistent infection with HPV-16 and/or HPV-18: Persistent infection was defined in the protocol as "at least 2 positive specimens over a minimum interval of 6 months". This definition included consecutive and intermittently detected infections (for example specimens positive at months 9 and 18 but negative at months 12 and 15).

ATP cohort months 6-18: The analysis for the ATP cohort months 6 to 18 for efficacy against persistent infection (6-month definition) is shown in Table 18. During this period there were no cases of persistent infection with HPV-18 alone in the ATP cohort.

Table 18- Study HPV-001: Vaccine efficacy against persistent infection (2 positive specimens over a minimum of 6 months) with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 for cervical specimens and all specimens (combined cervical and cervicovaginal specimens) (ATP cohort months 6-18)

Specimen Type	Infection Type	Attack Rate						Vaccine Efficacy
		Vaccine			Alum control			% (95% CI)
		N	n	AR	N	n	AR	
Cervical specimens	HPV 16°	366	0	0.0	355	7	2.0	100% (47.0, 100%)
	HPV 18°	366	0	0.0	355	0	0.0	-
	HPV 16 &/or 18°	366	0	0.0	355	7	2.0	100% (47.0, 100%)
All specimens (combined CV and Cervical specimens)	HPV 16°	366	0	0.0	355	10	2.8	100% (63.0, 100%)
	HPV 18°	366	0	0.0	355	0	0.0	-
	HPV 16 &/or 18°	366	0	0.0	355	10	2.8	100% (63.0, 100%)

N = number of subjects in specific cohort
n = number of subjects with persistent infection with corresponding HPV type
AR = Attack rate = n / N
95% CI = 95% confidence interval
p-value = result of comparison of attack rates between groups by Fisher's exact test (two sided)
° = without considering other HPV types
Source: STN 125259/0, CSR 001, Table 23, p. 113

ATP cohort months 6-27: The incidence of persistent infection and vaccine efficacy were presented for the time period from 6-27 months.
Reviewer's Comment: In the time period out to 27 months, there were several additional cases which accrued as compared to the 6-18 month time period, and the point estimate for efficacy is 100% for HPV 16 (either with cervical only specimens and combined specimens). For HPV 18, 4 cases of persistent infection accrued for combined specimens in the control group and 0 in the vaccine group, and the point estimate of efficacy is 100% and reached statistical significance. (Source: STN 125259/0, CSR 001, Tables 24-25, p. 114-115, not shown here).

ATP cohort months 0-27: The results for prevention of persistent infection (6-month) for the 0-27 month period are shown in Table 19.

Table 19- Study HPV-001: Vaccine Efficacy Based on Time to Occurrence of Persistent Infection (2 Positive Specimens Over a Minimum of 6 Months) with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 for Cervical Specimens and All Specimens (Combined Cervical and Cervicovaginal Specimens) (ATP Cohort Months 0-27)

		HPV Vaccine = 373 Aluminum hydroxide control = 373
Specimen Type	Infection Type	Vaccine Efficacy (95% CI)
Cervical specimens	HPV 16°	92.4% (41.6, 99.0%)
	HPV 18°	100% (23.5, 100%)
	HPV 16 &/or 18°	94.2% (56.3, 99.2%)
All specimens (combined CV and Cervical specimens)	HPV 16°	81.3% (45.4, 93.6%)
	HPV 18°	90.1% (22.9, 98.7%)
	HPV 16 &/or 18°	85.5% (58.6, 94.9%)

V.E. = Vaccine efficacy obtained from Cox regression
95% CI= 95% confidence interval obtained from Cox regression
p-value = result of comparison of Kaplan-Meier survival curves between groups by Log-rank test
°= without considering other HPV types
Source: STN 125259/0, CSR 001, Supplement 18, p. 283

Reviewer's Comment: A higher number of cases of 6-month persistent infection accrued when cases are counted from time 0, in part due to cases related to prevalent infection and cases counted prior to administration of the full vaccine course. Although the point estimates of efficacy are not 100%, all are >80%. The point estimates for efficacy for the time 0-27 month

period are slightly higher when compared to the 0-18 month time period, in part due additional time in which new cases of persistent infection can accrue and are apparently prevented by the vaccine. (Source: STN 125259/0, CSR 001, Supplements 15 and 16, p. 282, not shown here.)

Analyses of Persistent Infection, ITT cohort: Analyses are also presented for prevention of persistent infection for the ITT cohort (after at least 1 vaccine dose, counting cases after Month 0). All analyses were statistically significant.

Table 20- Study HPV-001: Vaccine Efficacy Based on Time to Occurrence of Persistent Infection (2 Positive Specimens Over a Minimum of 6 Months) with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 for Cervical Specimens and All Specimens (Combined Cervical and Cervicovaginal Specimens) (ITT cohort)

		Vaccine N=560 Aluminum hydroxide control = 553
Specimen Type	Infection Type	Vaccine Efficacy % (95% CI)
Cervical specimens	HPV 16°	93.9% (53.2, 99.2%)
	HPV 18°	100% (24.4, 100%)
	HPV 16 &/or 18°	95.1% (63.5, 99.3%)
All specimens (combined CV and Cervical specimens)	HPV 16°	84.4% (55.2, 94.6%)
	HPV 18°	91.1% (31.0, 98.9%)
	HPV 16 &/or 18°	87.5% (64.6, 95.6%)

N= Number of subjects in specific cohort
V.E. = Vaccine efficacy obtained from Cox regression
95% CI= 95% confidence interval obtained from Cox regression
p-value = result of comparison of Kaplan-Meier plots between groups by Log-rank test
°= without considering other HPV types
Source: STN 125259/0, CSR 001, Table 68, p. 168

Vaccine efficacy in the prevention of LSIL, HSIL, squamous cell cancer, or adenocarcinoma associated with HPV-16 and/or HPV-18 infection. No cases of adenocarcinoma or squamous cell cancer were diagnosed during the study period.

Cytology results: In addition to LSIL and HSIL a *post-hoc* descriptive analysis was performed of the incidence of ASCUS associated with HPV-16 and/or HPV-18 infection. Association with HPV-16 and/or HPV-18 infection was defined by the HPV DNA type(s) detected by PCR in the cervical or cervicovaginal specimens obtained at the time of diagnosis of the cytological lesion. Incidence rates are shown for the 6-18 month ATP cohort in Table 21.

Table 21- Study HPV-001: Number and Percentage of Subjects with Cytologically Confirmed ASCUS, LSIL or Any Cytologically Confirmed Lesion (Greater Than or Equal to ASCUS) Associated with HPV-16 and/or HPV-18 Infection (ATP Cohort Months 6-18)

Lesion Type	Infection Type	Vaccine (N= 366)					Placebo (N= 355)				
		n	n*	%	95% CI		n	n*	%	95% CI	
ASCUS	HPV-16°	0	0	0.00	0.00	1.00	5	5	1.41	0.46	3.26
	HPV-18°	0	0	0.00	0.00	1.00	5	5	1.41	0.46	3.26
	HPV-16 and/or HPV-18°	0	0	0.00	0.00	1.00	8	8	2.25	0.98	4.39
LSIL	HPV-16°	0	0	0.00	0.00	1.00	8	9	2.25	0.98	4.39
	HPV-18°	1	1	0.27	0.01	1.51	0	0	0.00	0.00	1.03
	HPV-16 and/or HPV-18°	1	1	0.27	0.01	1.51	8	9	2.25	0.98	4.39
≥ ASCUS	HPV-16°	0	0	0.00	0.00	1.00	12	14	3.38	1.76	5.83
	HPV-18°	1	1	0.27	0.01	1.51	5	5	1.41	0.46	3.26
	HPV-16 and/or HPV-18°	1	1	0.27	0.01	1.51	15	17	4.23	2.38	6.87

There were no cases of HSIL, squamous cell cancer or adenocarcinoma associated with HPV-16 or HPV-18.
N = number of subjects in specific cohort
n = number of subjects with corresponding lesion associated with corresponding HPV type
% = (n/N)
n* = number of reported episodes of corresponding lesion associated with corresponding HPV type
95% CI = 95% confidence interval for rate (percentage)
°= without considering other HPV types
Source: STN 125259/0, CSR 001, Table 26, p. 117

The point estimates of efficacy in prevention of HPV 16 related ASC-US and LSIL were 100% (reach statistical significance). The point estimate for HPV 18 related ASC-US and LSIL is 80.6% but does not reach statistical significance. (Source: STN 125259/0, CSR 001, Table 27, p. 118, not shown here).

Reviewer's Comment: Concerns regarding use of cytology as a surrogate for prevention of cervical cancer were raised at the VRBPAC in November 2001 and in the WHO document. Pap testing sensitivity has been reported to be < 100%, and is considered a screening tool, which may lead to further investigation (such as colposcopy). It is acknowledged that if an abnormal Pap test is prevented, this may potentially reduce the need for colposcopy and possibly invasive treatment. Similar results are also presented for the 0-18 month cohort (which includes prevalent infection), and one case of HPV 16 related HSIL is reported for an aluminum hydroxide control recipient as compared to 0 in the vaccine group.

Vaccine efficacy against cytologically confirmed ASCUS, LSIL, HSIL or any cytologically confirmed lesion (Greater than or equal to ASCUS) associated with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 infection: Analyses of vaccine efficacy in prevention of cytological abnormalities associated with HPV 16 and/or 18 infections in the ITT cohort are also presented.

Table 22 - Vaccine Efficacy Against Cytologically Confirmed ASCUS, LSIL, HSIL or Any Cytologically Confirmed Lesion (Greater Than or Equal to ASCUS) Associated with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 Infection (ITT cohort)

Lesion type	Infection Type	Attack Rate						Vaccine Efficacy
		Vaccine			Aluminum hydroxide control			% (95% CI)
		N	n	AR	N	n	AR	
ASC-US	HPV 16°	560	1	0.18	553	9	1.63	89.2% (15.0, 98.6%)
	HPV 18°	560	0	0.00	553	9	1.63	100% (13.7, 100%)
	HPV 16 &/or 18°	560	1	0.18	553	15	2.71	93.6% (51.3, 99.1%)
LSIL	HPV 16°	560	1	0.18	553	13	2.35	92.6% (43.1, 99.0%)
	HPV 18°	560	1	0.18	553	2	0.36	51.1% (-439, 95.6%)
	HPV 16 &/or 18°	560	2	0.36	553	14	2.53	86.1% (39.0, 96.9%)
HSIL	HPV 16°	560	0	0.00	553	1	0.18	100% (-706, 100%)
	HPV 18°	560	0	0.00	553	0	0.00	-
	HPV 16 &/or 18°	560	0	0.00	553	1	0.18	100% (-706, 100%)
≥ASC-US	HPV 16°	560	1	0.18	553	20	3.62	95.2% (64.0, 99.4%)
	HPV 18°	560	1	0.18	553	11	1.99	91.2% (31.7, 98.9%)
	HPV 16 &/or 18°	560	2	0.36	553	27	4.88	92.9% (70.0, 98.3%)

N= number of subjects in specific cohort
n = number of subjects with corresponding lesion associated with infection with corresponding HPV type
AR = Attack rate = n / N expressed in percent
Vaccine efficacy by Cox regression
95% CI= 95% confidence interval
p-value =result of comparison of attack rates between groups by log rank test
°= without considering other HPV types
Source: STN 125259/0, CSR 001, Table 70, p. 171

Histopathology results: The histopathology results are expressed using the cervical intraepithelial neoplasia (CIN) classification system where CIN 1 corresponds to LSIL and CIN 2 and CIN 3 correspond to HSIL. Association with HPV-16 and/or HPV-18 infection was defined by the HPV DNA type(s) detected by PCR in the cervical and cervicovaginal specimens obtained at the time of diagnosis of the cytological lesion which led to the biopsy. Table 23 presents the histopathological lesions diagnosed in the ATP cohort months 6-18

Table 23 - HPV-001: Number and percentage of subjects with histopathologically confirmed lesions associated with HPV-16 and/or HPV-18 infection (ATP cohort months 6-18)

Lesion Type	Infection Type	Vaccine (N=366)					Placebo (N=355)				
		n	n*	%	95% CI		n	n*	%	95% CI	
CIN 1	HPV-16°	0	0	0.00	0.00	1.00	2	2	0.56	0.07	2.02
	HPV-18°	1	1	0.27	0.01	1.51	0	0	0.00	0.00	1.03
	HPV-16 and/or HPV-18°	1	1	0.27	0.01	1.51	2	2	0.56	0.07	2.02
CIN 2	HPV-16°	0	0	0.00	0.00	1.00	1	1	0.28	0.00	1.60
	HPV-18°	0	0	0.00	0.00	1.00	0	0	0.00	0.00	1.03
	HPV-16 and/or HPV-18°	0	0	0.00	0.00	1.00	1	1	0.28	0.00	1.60

There were no cases of CIN 3, squamous cell cancer or adenocarcinoma associated with HPV-16 and/or HPV-18.
N = number of subjects in specific cohort
n = number of subjects with corresponding lesion associated with infection with corresponding HPV type
% = (n/N)
n* = number of reported episodes of corresponding lesion associated with corresponding HPV type
95% CI = 95% confidence interval for rate (percentage)
°= without considering other HPV types
Source: STN 125259/0, CSR 001, Table 28, p. 119

The sponsor also notes that this CIN 1 case was also associated with persistent infections with HPV-51 and HPV-56. Biopsy PCR performed on the lesion revealed the presence of HPV-51 but not HPV-18 or HPV-56 DNA. In a similar analysis when counting cases from months 0-18, there were 2 additional cases of HPV 16 related CIN 2 in the control group. (Source: STN 125259/0, CSR 001, Supplement 20, p. 284, not shown here).

Histopathology results (ITT cohort): In the ITT cohort the following histopathological lesions were diagnosed:

- One case of CIN 1 associated with HPV-18 infection in the vaccine group and three cases associated with HPV-16 infection in the in the control group.
- No cases of histopathologically confirmed CIN 2 in the vaccine group and three cases associated with HPV-16 infection in the control group.

Table 24 – Study HPV-001: Number and Percentage of Subjects with Histopathologically Confirmed Lesions Associated with HPV-16 and/or HPV-18 Infection (ITT cohort)

Lesion Type	Infection Type	Vaccine (N= 560)					Placebo (N=553)				
		n	n*	%	95% CI		n	n*	%	95% CI	
CIN 1	HPV-16°	0	0	0.00	0.00	0.66	3	3	0.54	0.11	1.58
	HPV-18°	1	1	0.18	0.00	0.99	0	0	0.00	0.00	0.66
	HPV-16 and/or HPV-18°	1	1	0.18	0.00	0.99	3	3	0.54	0.11	1.58
CIN 2	HPV-16°	0	0	0.00	0.00	0.66	3	3	0.54	0.11	1.58
	HPV-18°	0	0	0.00	0.00	0.66	0	0	0.00	0.00	0.66
	HPV-16 and/or HPV-18°	0	0	0.00	0.00	0.66	3	3	0.54	0.11	1.58

There were no cases of CIN 3, squamous cell cancer or adenocarcinoma associated with HPV-16 and/or HPV-18.
N = number of subjects in specific cohort
n = number of subjects with corresponding lesion associated with corresponding HPV type
% = (n/N); n* = number of reported episodes of corresponding lesion associated with corresponding HPV type
95% CI = 95% confidence interval for rate (percentage); °=without considering other HPV types
Source: STN 125259/0, CSR 001, Table 71, p. 172

PCR analysis of biopsies: The HPV DNA detected by PCR in cervicovaginal/cervical specimens and in biopsy tissue (*post hoc* analysis) for the four histopathologically confirmed lesions associated with HPV-16 or 18 in the ATP cohort are presented in Table 25.

Table25– Study HPV-001: HPV DNA Detected by PCR in Cervicovaginal/Cervical Specimens and in Biopsy Tissue for Histopathologically Confirmed Lesions Associated with HPV-16 and/or HPV-18 (ATP cohort Months 6-18)

Group	Diagnosis and Specimen analysis by PCR	Months							
		6	9	12	15	18	21	24	27
Vaccine	Cytology/Histopathology diagnosis	Normal		LSIL/ **CIN 1**		Normal	§		
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N	N/-	N/18	N/-	N/N	N/-		
	Cervicovaginal/Cervical Other HPV by PCR	N/N	51,56/-	51,56/51,56	51/-	N/N	51/-		
	Biopsy Tissue HPV type by PCR			**51**					
Placebo	Cytology/Histopathology diagnosis	Normal		ASCUS		LSIL/**CIN 1**		§	
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N	N/-	16/16	16/-	16/16	16/-	16/-	
	Cervicovaginal/Cervical Other HPV by PCR	N/N	N/-	N/N	N/-	N/N	N/-	N/-	
	Biopsy Tissue HPV type by PCR					**16**			
Placebo	Cytology/Histopathology diagnosis	Normal		Normal		LSIL/ **CIN 1** §			
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N	N/-	16/16	16/-	16/16			
	Cervicovaginal/Cervical Other HPV by PCR	N/N	N/-	58/58	58,39/-	58/58			
	Biopsy Tissue HPV type by PCR					**16,58**			
Placebo	Cytology/Histopathology diagnosis	Normal		Normal		LSIL/**CIN 2**	§		
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N	16/-	-/16	16/-	16/16	16/-		
	Cervicovaginal/Cervical Other HPV by PCR	N/N	N/-	-/N	N/-	N/N	N/-		
	Biopsy Tissue HPV type by PCR					**16**			

Cervicovaginal specimens (self-obtained) were collected for PCR analysis at months, 6, 9, 12, 15 and 18 and also at months 21, 24 and 27 for participants in the *optiona*l blinded extended follow-up. § = Last study visit for subject. Cervical specimens (physician-obtained) were collected for cytology and PCR analysis at months 6, 12 and 18.
Biopsy was recommended for all subjects with two cytological observations (with a 6 month interval) indicating the presence of ASCUS or with a single cytological observation indicating the presence of LSIL, AGUS or HSIL.
High risk HPV types = 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Low risk HPV types = 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74.
- = test not performed. N = Negative result.
Source: STN 125259/0, CSR 001, Table 29, p. 121

Reviewer's Comment: For the one CIN 1 lesion which occurred in the vaccine group but was associated with an incident HPV 18 infection, the biopsy contained HPV 51 DNA by PCR but not HPV 18, and HPV 51 was noted to be present at baseline and throughout PCR testing of cervicovaginal secretions. It is probable that HPV 51 was associated with this lesion and not HPV 18. In study HPV-008, the results for multiple non-vaccine HPV types will be reviewed in more detail. In the alum control group, 3/3 of the subjects did not have HPV 16 at baseline, but developed persistent HPV 16 infection and subsequently developed a CIN 1 or CIN 2 lesion related to HPV 16 (one also associated with an acquired HPV 58 persistent infection.)

PCR analysis of biopsies (ITT Cohort): The HPV DNA detected by PCR in cervicovaginal/cervical specimens and (as indicated in the protocol) in biopsy tissue (post hoc analysis) for histopathologically confirmed lesions associated with HPV-16 or 18 in the ITT cohort. There were seven cases of CIN 1 or CIN 2 associated with HPV-16 and/or HPV-18 infection in the ITT cohort, four of these cases have already been described for the ATP cohort.

The histopathological lesions diagnosed during the study were associated with persistent high risk HPV type infections. The one lesion in the vaccine group is presented as associated with the incident HPV-18 infection based on the pre-specified definition of association (defined by the HPV DNA type(s) detected in the cervical and cervicovaginal specimens obtained at the time of diagnosis of the cytological lesion which led to the biopsy). However it is possible that this vaccine CIN 1 case was caused by the persistent infection with high risk HPV-51 rather than by the incident HPV-18 infection; this was supported by the detection of only HPV-51 DNA in the biopsy tissue by PCR. Of the six cases of CIN 1 or CIN 2 in the control group, all were likely due to persistent HPV-16 infections either alone or concomitant with other high risk HPV type infections. This was confirmed by the PCR analysis of biopsy tissues which detected only HPV-

16 DNA in five of the control cases and HPV-16 DNA together with HPV-58 DNA in the remaining control case.

Table 26: Study HPV-001: HPV DNA Detected by PCR in Cervicovaginal/cervical Specimens and in Biopsy Tissue for Histopathologically Confirmed Lesions Associated with HPV-16 and/or HPV-18 (ITT Cohort)

Group	Diagnosis and Specimen analysis by PCR	Months							
		6	9	12	15	18	21	24	27
Vaccine (also ATP cohort)	Cytology/Histopathology diagnosis	Normal		LSIL/ **CIN 1**		Normal	§		
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N		N/18	N/-	N/N	N/-		
	Cervicovaginal/Cervical Other HPV by PCR	N/N	51,56/-	51,56/51,56	51/-	N/N	51/-		
	Biopsy Tissue HPV type by PCR			**51**					
Placebo (also ATP cohort)	Cytology/Histopathology diagnosis	Normal		ASCUS		LSIL/**CIN 1**		§	
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N	N/-	16/16	16/-	16/16	16/-	16/-	
	Cervicovaginal/Cervical Other HPV by PCR	N/N	N/-	N/N	N/-	N/N	N/-	N/-	
	Biopsy Tissue HPV type by PCR					**16**			
Placebo (also ATP cohort)	Cytology/Histopathology diagnosis	Normal		Normal		LSIL/ **CIN 1** §			
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N	N/-	16/16	16/-	16/16			
	Cervicovaginal/Cervical Other HPV by PCR	N/N	N/-	58/58	58,39/-	58/58			
	Biopsy Tissue HPV type by PCR					**16,58**			
Placebo	Cytology/Histopathology diagnosis	Normal		Normal		LSIL/-	-/ **CIN 1**		Normal §
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N	N/-	N/N	16/-	16/16	16/-	16/-	16/16
	Cervicovaginal/Cervical Other HPV by PCR	39/39	39/-	39/39	N/-	N/N	6/-	N/-	N/N
	Biopsy Tissue HPV type by PCR						**16**		
Placebo (also ATP cohort)	Cytology/Histopathology diagnosis	Normal		Normal		LSIL/**CIN 2**	§		
	Cervicovaginal/Cervical HPV 16,18 by PCR	N/N	16/-	-/16	16/-	16/16	16/-		
	Cervicovaginal/Cervical Other HPV by PCR	N/N	N/-	-/N	N/-	N/N	N/-		
	Biopsy Tissue HPV type by PCR					**16**			
Placebo	Cytology/Histopathology diagnosis	Normal		HSIL/ **CIN 2**		Normal		§	
	Cervicovaginal/Cervical HPV 16,18 by PCR	16/16	16/-	16/16	16/-	N/N	N/-	N/-	
	Cervicovaginal/Cervical Other HPV by PCR	66,68/66	66/-	N/N	N/-	39,66/39,66	90*/-	66/-	
	Biopsy Tissue HPV type by PCR			**16**					

Group	Diagnosis and Specimen analysis by PCR	Months							
		6	9	12	15	18	21	24	27
Placebo	Cytology/Histopathology diagnosis	Normal		ASCUS		LSIL/ **CIN 2**			§
	Cervicovaginal/Cervical HPV 16,18 by PCR	16/16	16/-	16/16	16/-	16/16	16/-	N/-	N/-
	Cervicovaginal/Cervical Other HPV by PCR	N/N	N/-	N/N	39/-	59,74/39	59,39,74/-	51,74/-	51,74/-
	Biopsy Tissue HPV type by PCR					**16**			

Cervicovaginal specimens (self-obtained) were collected for PCR analysis at months, 6, 9, 12, 15 and 18 and also at months 21, 24 and 27 for participants in the *optiona*l blinded extended follow-up. § = Last study visit for subject. Cervical specimens (physician-obtained) were collected for cytology and PCR analysis at months 6, 12 and 18 (it should be noted that subjects with specimens collected after 18 months were included in the ITT cohort).
Biopsy was recommended for all subjects with two cytological observations (with a 6 month interval) indicating the presence of ASCUS or with a single cytological observation indicating the presence of LSIL, AGUS or HSIL.
*HPV-90 was detected by DNA sequencing.
High risk HPV types = 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.
Low risk HPV types = 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74.
- = test not performed. N = Negative result
Source: STN 125259/0, CSR 001, Table 72, p. 175-176

Vaccine efficacy in the prevention of *incident infection* with HPV-16/18-related phylogenetic types, high risk and low risk HPV types: The sponsor indicates that for the analyses presented for non-vaccine HPV types, the number of subjects (N) included in each of the cohorts (HPV-16 and/or HPV-18 related phylogenetic groups, individual or combined high risk or low risk HPV types) varies. They state that this is due to the different definitions of these ATP cohorts with respect to negative or positive status for the different HPV types or groups of HPV types at months 0 and 6.

Reviewer's Comment: These are type-specific analyses, and this explains the different Ns for analysis of different types.

Vaccine efficacy for HPV-16/18-related phylogenetic types, combined high risk and combined low risk HPV types: The sponsor notes that the analysis for the HPV-16/18 related phylogenetic types and high risk HPV types was performed with and without *(post hoc)* inclusion of HPV-16 and 18 types. Two definitions for HPV-16 related phylogenetic types were also used; the pre-specified definition (HPV-31, 35 and 58) and the extended *post hoc* definition (HPV-31, 35, 58, 33 and 52). Analyses were also made post hoc for combined high risk HPV types (HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 or HPV-16, 18, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and combined low risk HPV types (HPV- 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74).
Reviewer's Comment: In Table 27, combined self-obtained cervicovaginal specimens and physician-obtained cervical specimens were used. There is evidence of efficacy in prevention of HPV 16 and 18 incident and 6 month persistent infection from the earlier data reported for study HPV-001, as well as a trend towards prevention of dysplastic lesions associated with HPV 16. It is possible that the vaccine's effect in preventing vaccine HPV type incident infection might be "driving" the analyses in which the vaccine HPV types are included. It is somewhat problematic to combine all high-risk types if one is attempting to assess evidence of cross-protection for individual non-vaccine HPV types which are phylogenetically related to vaccine HPV types. However, there is evidence of reduction in incident high risk non-vaccine HPV infections. With inclusion of HPV 16/18, assessment of impact on a wider group of HPV-related genital disease may be possible, especially if only high-risk types are included. In Table 27, the overall reduction of incident infection with any tested high-risk HPV type (vaccine and non-vaccine HPV types) would be 42.3% (95% CI: 22.9, 56.8%). In the pivotal Phase III study, HPV-008, results are presented from a larger database.

Table 27- Study HPV-001: Vaccine Efficacy Against Incident Infection with HPV-16/18 Related Phylogenetic Types, Combined High Risk and Combined Low Risk HPV Types for All Specimens (Combined Cervical and Cervicovaginal Specimens) (ATP Cohort Months 6-18)

	Attack rate						Vaccine Efficacy
Infection type	Vaccine			Aluminum hydroxide control			% (95% CI)
	N	n	AR	N	n	AR	
Analyses excluding HPV 16 and/or 18							
HPV-16 related	412	11	2.7	410	26	6.3	57.9% (15.9, 78.9%)
HPV-related extended	403	28	6.9	394	48	12.2	43.0% (11.0, 63.5%)
HPV-18 related	421	10	2.4	420	15	3.6	33.5% (-46.3, 69.8%)
HPV-16 &/or 18 related	407	18	4.4	401	37	9.2	52.1% (17.2, 72.2%)
HPV-16 &/or 18 related extended	399	32	8.0	388	54	13.9	42.4% (12.8, 61.9%)
High Risk	356	55	15.5	340	81	23.8	35.2% (11.7, 52.4%)
Low risk	378	45	11.9	377	52	13.8	13.7% (-25.3, 40.5%)
Analyses including HPV 16 and/or 18							
HPV-16 related	399	13	3.3	392	50	12.8	74.5% (53.7, 85.9%)
HPV-related extended	392	30	7.7	379	66	17.4	56.1% (33.9, 70.8%)
HPV-18 related	414	15	3.6	405	32	7.9	54.1% (16.6, 74.8%)
HPV-16 &/or 18 related	389	24	6.2	375	61	16.3	62.1% (40.5, 75.8%)
HPV-16 &/or 18 related extended	383	37	9.7	365	74	20.3	52.3% (31.2, 67.0%)
High Risk	356	58	16.3	340	96	28.2	42.3% (22.9, 56.8%)

N= number of subjects in specific cohort; n = number of subjects with HPV incident infection
AR = Attack rate = n / N
95% CI= 95% confidence interval
HPV-16 related = 31, 35 and 58; HPV-16 related extended = 31, 35, 58, 33 and 52
HPV-18 related = 45 and 59
HPV-16 and/or HPV-18 related = 31, 35, 45, 58, 59
HPV-16 and/or HPV-18 related extended = 31, 33, 35, 45, 52, 58, 59
High risk = 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68
Low risk = 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74
Source: STN 125259/0, CSR 001, Table 31, p. 125

Efficacy was also calculated for physician collected cervical specimens. This is shown in Table 28. The number of positive specimens is lower (since these are collected by the physician with pelvic exam). Similar trends are noted, but point estimates of efficacy are somewhat higher when considering cervical specimens only as compared to combined specimens, except for low-risk HPV type incident infection. It is noted that the vaccine only includes HPV 16 and HPV 18.

Table 28- Study HPV-001: Vaccine Efficacy Against Incident Infection With HPV-16/18 Related Phylogenetic Types, Combined High Risk and Combined Low Risk HPV Types for Cervical Specimens Only (ATP Cohort Months 6-18)

	Attack rate						Vaccine Efficacy
Infection type	Vaccine			Aluminum hydroxide control			% (95% CI)
	N	n	AR	N	n	AR	
Analysis excluding HPV 16 and/or 18							
HPV-16 related	412	6	1.5	410	17	4.1	64.9% (11.8, 86.0%)
HPV-related extended	403	16	4.0	394	32	8.1	51.1% (12.4, 72.7%)
HPV-18 related	421	4	1.0	420	7	1.7	43.0% (-93.3, 83.2%)
HPV-16 &/or 18 related	407	10	2.5	401	24	6.0	58.9% (15.3, 80.1%)
HPV-16 &/or 18 related extended	399	19	4.8	388	36	9.3	48.7% (12.1, 70.0%)
High Risk	356	32	9.0	340	53	15.6	42.3% (12.9, 61.8%)
Low risk	378	28	7.4	377	25	6.6	-11.7% (-87.9, 33.6%)
Analysis including HPV 16 and/or 18							
HPV-16 related	399	6	1.5	392	33	8.4	82.1% (57.8, 92.4%)
HPV-related extended	392	16	4.1	379	43	11.3	64.0% (37.3, 79.4%)
HPV-18 related	414	6	1.4	405	14	3.5	58.1% (=8.0, 83.7%)
HPV-16 &/or 18 related	389	11	2.8	375	39	10.4	62.1% (40.5, 75.8%)
HPV-16 &/or 18 related extended	383	19	5.0	365	48	13.2	52.3% (31.2, 67.0%)
High Risk	356	32	9.0	340	64	18.8	52.2% (28.9, 67.9%)

N= number of subjects in specific cohort
n = number of subjects with HPV incident infection
AR = Attack rate = n / N
95% CI= 95% confidence interval
p-value =result of comparison of attack rates between groups by Fisher's exact test
HPV-16 related = 31, 35 and 58
HPV-16 related extended = 31, 35, 58, 33 and 52
HPV-18 related = 45 and 59
HPV-16 and/or HPV-18 related = 31, 35, 45, 58, 59
HPV-16 and/or HPV-18 related extended = 31, 33, 35, 45, 52, 58, 59
High risk = 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68
Low risk = 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74
Source: STN 125259/0, CSR 001, Table 33, p. 127

Vaccine efficacy is also reported for the 6-27 month ATP cohort for combined specimens. The point estimates of efficacy are similar to those seen in the 6-18 month period. It is noted that additional cases accrue in both treatment groups over time for the non-vaccine HPV types. (Source: STN 125259/0, CSR 001, Table 35, p. 129, not shown here).

Point estimates of vaccine efficacy for combined specimens from 0-18 months (both including and excluding HPV 16 and/or HPV 18) are lower than the point estimates reported for 6-18 month time period, and this may be related to the impact of prevalent disease present at baseline. When only cervical specimens are considered, point estimates of efficacy are in general are lower, although there is less of a difference in point estimates of efficacy, and statistical significance is maintained for specific analyses. Source: STN 125259/0, CSR 001, Supplements 22 and 24, p. 286 and 288).

An analysis of vaccine efficacy in the 0-27 month cohort for combined specimens was also conducted. Point estimates of efficacy are in general somewhat lower in the 0-27 month ATP

cohort as compared to the 6-18 month ATP cohort, with retention of statistical significance for specific analyses, and again might be in part due to the impact of prevalent HPV infection. These results are shown in Table 29.

Table 29 –Study HPV-001: Vaccine Efficacy Against Incident Infection with HPV-16/18 Related Phylogenetic Types, Combined High Risk Types and Combined Low Risk Types for all specimens (Combined Cervical and Cervicovaginal Specimens) (ATP Cohort Months 0-27)

	Attack rate						Vaccine Efficacy
Infection type	Vaccine			Aluminum hydroxide control			% (95% CI)
	N	n	AR	N	n	AR	
Analysis excluding HPV 16 and/or 18							
HPV-16 related	426	30	7.0	421	46	10.9	39.8% (4.2, 62.2%)
HPV-related extended	420	57	13.6	415	81	19.5	35.1% (8.9, 53.8%)
HPV-18 related	425	18	4.2	425	24	5.7	27.4% (-33.9, 60.6%)
HPV-16 &/or 18 related	423	43	10.2	417	63	15.1	38.7% (9.2, 58.7%)
HPV-16 &/or 18 related extended	417	65	15.6	412	91	22.1	35.7% (11.4, 53.3%)
High Risk	391	107	27.4	386	140	36.3	31.6% (12.0, 46.9%)
Low risk	394	79	20.1	394	89	22.6	13.9% (-16.6, 67.0%)
Analysis including HPV 16 and/or 18							
HPV-16 related	416	37	8.9	416	84	20.2	58.8% (39.3, 72.0%)
HPV-related extended	412	63	15.3	411	112	27.3	
HPV-18 related	419	25	6.0	417	48	11.5	52.6% (22.6, 71.0%)
HPV-16 &/or 18 related	407	52	12.8	406	104	25.6	54.8% (36.8, 67.7%)
HPV-16 &/or 18 related extended	404	73	18.1	402	127	31.6	48.3% (31.1, 61.3%)
High Risk	391	112	28.6	386	160	41.5	37.4% (20.3, 50.9%)

N= number of subjects in specific cohort
n = number of subjects with HPV incident infection
AR = Attack rate = n / N
95% CI= 95% confidence interval
Vaccine efficacy by Cox regression
p-value =result of comparison between groups by Log Rank test
HPV-16 related = 31, 35 and 58
HPV-16 related extended = 31, 35, 58, 33 and 52
HPV-18 related = 45 and 59
HPV-16 and/or HPV-18 related = 31, 35, 45, 58, 59
HPV-16 and/or HPV-18 related extended = 31, 33, 35, 45, 52, 58, 59
High risk = 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68
Low risk = 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74
Source: STN 125259/0, CSR 001, Supplement 26, p. 290

Cytology results: In *post-hoc* analyses, the overall efficacies against any cytological lesion (≥ ASC-US) were 72.8% (95% CI: 27.6, 89.8%) for infection with HPV-16 related phylogenetic types (extended definition), 66.0% (95% CI: 20.4, 85.4%) for infection with HPV-16 and/or HPV-18 related phylogenetic types (extended definition) and 68.2% (95%CI: 35.9, 84.2%) for infection with combined high risk types. (Source: STN 125259/0, CSR 001, Table 55, p. 148, not shown here).

Histopathology results are presented as they relate to non-vaccine HPV types.
Reviewer's Comment: Very few histopathological cases in study HPV-001 and it is difficult to discern impact on lesions associated with non-vaccine HPV types. The lower prevalence of non-vaccine HPV types and the small number of histopathological endpoints related to non-vaccine HPV types renders meaningful interpretation difficult. Further analyses of non-vaccine HPV types will be discussed in the large Phase 3 study HPV-008.

Overview of all histopathologically confirmed lesions (ITT Cohort) through Month 27: A summary is presented of all histopathologically confirmed lesions in the ITT cohort. The table shows the number of cases associated or not associated with HPV-16 and/or HPV-18 infection. Association with HPV-16 and/or HPV-18 infection or related phylogenetic type or low risk or high risk HPV type infection was defined by the HPV DNA type(s) detected by PCR in the cervical or cervicovaginal specimens obtained at the time of diagnosis of the cytological lesion which led to the biopsy. However, the sponsor notes that cases which involved a high risk HPV type detected at Month 0 were not included in these totals. Table 30 includes the totals when all cases have been included.

Table 30-Study HPV-001: Cases of histopathologically confirmed lesions and association with HPV DNA detected by PCR in cervicovaginal or cervical specimens obtained at the time of diagnosis of the cytological lesion which led to the biopsy (ITT cohort plus cases added in which subject was HR HPV positive at Month 0) [CBER modified]

Lesion type	Infection type	Total	Vaccine	Control
CIN 1	Associated with HPV 16 and/or 18 at time of diagnosis	4	1*	3
	Not associated with HPV 16 and/or 18 but associated with phylogenetic, high-risk or low risk HPV types at time of diagnosis	9+2=11	4+2=6	5
	Not associated with HPV 16 and/or 18 or any other HPV type at the time of diagnosis	2+1=3	0	2+1=3
	Total	15+2=17	5+2=7	10
CIN 2	Associated with HPV 16 and/or 18 at time of diagnosis	3	0	3
	Not associated with HPV 16 and/or 18 but associated with phylogenetic, high-risk or low risk HPV types at time of diagnosis	1	1+2=3	0
	Not associated with HPV 16 and/or 18 or any other HPV type at the time of diagnosis	0	0	0
	Total	4+2=6	1+2=3	3

*The one case of CIN 1 associated with HPV-18 in the vaccine group had cervical infection with multiple HPV types. These included a persistent HPV-51 (detected at months 9, 12, 15 and 21), a HPV-56 infection (detected at months 9 and 12) and an incident HPV-18 infection (detected at month 12 only). The PCR testing on the biopsy indicated the presence of HPV-51 but not HPV-18 DNA.

Note: there were five subjects with lesions associated with phylogenetic, high risk or low risk HPV type infection at the time of diagnosis who were positive for high risk HPV DNA at study entry, and these subjects were not eligible for inclusion in the ITT analyses. However they are added (after + signs). Vaccine group: 1 51-CIN 1; 1 66-CIN 1; 1 56-CIN 2; 1-33&35 CIN 2. Control group: 1 CIN 1 (no HPV identified).

Source: STN 125259/0, CSR 001, Table 96, p. 205 and Supplement 59, p. 313

Incident or persistent co-infection with both HPV-16 and HPV-18 is also presented. These data are presented in the ITT cohort (data for the ATP 6-27 month cohort show no co-infection cases in the vaccine group and 3 in the control group).

Table 31 – Study HPV-001: Number and Percentage of Subjects with Co-infection with Both HPV- 16 and HPV-18 (All Specimens) (ITT Cohort)

Vaccine		Aluminum hydroxide control	
n/N	% (95% CI)	n/N	% (95% CI)
2/560	0.36% (0.04, 1.28%)	11/553	1.99% (1.00, 3.53%)

N = number of subjects in specific cohort

n = number of subjects reporting at least one episode of co-incident infection with HPV-16 and HPV-18

% = n/N

95% CI = 95% confidence interval for rate (percentage)

Source: STN 125259/0, CSR 001, Table 97, p. 207

Table 32- Study HPV-001: Number and Percentage of Subjects with Persistent Co-Infection (2 Positive Specimens Over a Minimum of 6 Months) with Both HPV-16 and HPV-18 (All Specimens) (ITT cohort)

Vaccine		Aluminum hydroxide control	
n/N	% (95% CI)	n/N	% (95% CI)
1/560	0.18% (0.00, 0.99%)	5/553	0.9% (0.29, 2.10%)

N = number of subjects with information available per group
n = number of subjects reporting at least one episode of persistent co-incident infection with HPV-16 and HPV-18
% = n/N
95% CI = 95% confidence interval for rate (percentage)
Source: STN 125259/0, CSR 001, Table 99, p. 208

SAFETY RESULTS

Data sets analyzed: Analysis of safety was performed on the ATP cohort (primary analysis) and the ITT cohort.

According-To-Protocol (ATP) analysis: The vaccine and control groups in the ATP cohort for safety were similar with respect to the number of doses administered. Over 96% of subjects in both groups received dose 2 and over 92% received dose 3. Similarly, compliance for the return of symptom sheets was high (over 96% in both groups).

In the 30 day follow-up period after administration of each dose of vaccine or control, the incidence of any symptoms (compared by two sided Fisher exact test see reported per subject was similar between groups ($p = 0.432$) but there were more symptoms in the vaccine group than in the control group in the overall/dose analysis ($p < 0.001$). This was primarily due to a higher incidence of local symptoms in the vaccine group ($p < 0.001$, overall/dose). There was no difference between the groups with respect to the incidence of general symptoms ($p = 0.280$, overall/dose). There was no evidence that the incidence of local or general symptoms increased with subsequent doses; indeed in both groups the highest incidence of symptoms was associated with the first dose. The majority of local symptoms reported during the 30 day follow up period can be attributed to local solicited symptoms reported during the 7 day follow up. The overall/dose incidence of solicited local symptoms was 85% in vaccine group and 73.3% in control group).

Table 33- Study HPV-001: Incidence and Nature of Any Symptoms (Solicited and Unsolicited) Reported During the 30 Days Follow-up Period After Each Dose and Overall (ATP cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Dose 1	V	528	498	94.3% (92, 96.1%)	528	366	69.3% (65.2, 73.2%)	528	477	90.3% (87.5, 92.7%)
	C	535	478	89.3% (86.4, 91.8%)	535	376	70.3% (66.2, 74.1%)	535	429	80.2% (76.6, 83.5%)
Dose 2	V	503	434	86.3% (83, 89.2%)	503	287	57.1% (52.6, 61.4%)	503	407	80.9% (77.2, 84.3%)
	C	512	401	78.3% (74.5, 81.8%)	512	289	56.4% (52, 60.8%)	512	343	67% (62.7, 71.1%)
Dose 3	V	493	434	88% (84.8, 90.8%)	493	310	62.9% (58.4, 67.2%)	493	410	83.2% (79.6, 86.4%)
	C	493	400	81.1% (77.4, 84.5%)	491	277	56.4% (51.9, 60.9%)	493	356	72.2% (68, 76.1%)
Overall/dose	V	1524	1366	89.6% (88, 91.1%)	1524	963	63.2% (60.7, 65.6%)	1524	1294	84.9% (83, 86.7%)
	C	1540	1279	83.1% (81.1, 84.9%)	1538	942	61.2% (58.8, 63.7%)	1540	1128	73.2% (71, 75.4%)
Overall/subject	V	531	513	96.6% (94.7, 98%)	531	458	86.3% (83, 89.1%)	531	499	94% (91.6, 95.8%)
	C	538	514	95.5% (93.9, 97.1%)	538	462	85.9% (82.6, 88.7%)	538	472	87.7% (84.7, 90.4%)

V=Vaccine; C=Control
For each dose and overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects presenting at least one type of symptom during the 30 days follow-up period (day 0 to day 29)
For overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by a given type of symptom
Source: STN 125259/0, CSR 001, Table 101, p. 213

Table 34- Study HPV-001: Incidence and Nature of Symptoms Reported During the 30 Day follow-up Period After **Each Vaccine Dose and Overall: Summary Statistics (Fisher's Exact Test) (ATP cohort)**

Dose	Symptoms	p-values
Dose 1	Any symptoms	0.003
	General symptoms	0.739
	Local symptoms	< 0.001
Dose 2	Any symptoms	< 0.001
	General symptoms	0.850
	Local symptoms	< 0.001
Dose 3	Any symptoms	0.004
	General symptoms	0.044
	Local symptoms	< 0.001
Overall/Dose	Any symptoms	< 0.001
	General symptoms	0.280
	Local symptoms	< 0.001
Overall/subject	Any symptoms	0.432
	General symptoms	0.860
	Local symptoms	< 0.001

Source: STN 125259/0, CSR 001, Table 102, p. 214

Solicited local adverse events: The incidence of solicited local symptoms (any intensity and grade 3) is presented for each dose, for all doses (overall/dose) and for all subjects (overall/subject). The overall incidences (compared by two sided Fisher exact test) for each of the three local symptoms were statistically significantly higher ($p < 0.001$) in the vaccine group compared to the control group. The most frequently reported solicited local symptom reported in both groups was pain (reported following 84% of vaccine and 72.4% of control doses). Most of the pain was mild to moderate in intensity, as grade 3 pain was only reported following 11.1% of vaccine and 7.9% of control doses ($p = 0.002$). Grade 3 redness (0.2% of vaccine and 0.1% of control doses $p = 0.372$) and swelling (0.3% of vaccine and 0.0% of control doses $p = 0.030$) occurred at low frequencies in both groups. The majority of the solicited local symptoms resolved within 3-4 days. (Source: STN 125259/0, CSR 001, Supplement 79, p. 330, not shown here). The difference in incidence observed between the groups had no impact on compliance for completion of the vaccination course.

Table 35- Study HPV-001: Incidences of Solicited Local Symptoms During the 7-Day Follow-up Period Following the Administration of Each Vaccine Dose (ATP cohort)

Dose		Dose 1				Dose 2				Dose 3			
Group		Vaccine		Control		Vaccine		Control		Vaccine		Control	
#SS		527		535		503		511		493		493	
Pain	Any	474	89.9%	422	78.9%	404	80.3%	339	66.3%	402	81.5%	353	71.6%
	Gr 3	64	12.1%	49	9.2%	49	9.7%	31	6.1%	56	11.4%	41	8.3%
Redness	Any	90	17.1%	61	11.4%	105	20.9%	58	11.4%	141	28.6%	76	15.4%
	Gr 3	1	0.2%	1	0.2%	1	0.2%	0	0.0%	1	0.2%	0	0.0%
Swelling	Any	92	17.5%	53	9.9%	111	22.1%	52	10.2%	123	24.9%	57	11.6%
	Gr 3	1	0.2%	0	0.0%	3	0.6%	0	0.0%	1	0.2%	0	0.0%

Vaccine = HPV 16/18 vaccine; Control = aluminum hydroxide
SS = symptom sheets
For each dose n/% = number/percentage of subjects reporting a specified symptom
95%CI = Exact 95% confidence interval. LL = Lower Limit; UL = Upper Limit
Grade 3 pain: spontaneously painful
Grade 3 redness/swelling: > 50 mm
Source: STN 125259/0, CSR 001, Table 103, p. 215

Reviewer's Comment: There was some increase in proportion of subjects with redness and swelling with progressive doses of Cervarix, and very low proportions of Grade 3 intensity for any of the solicited local symptoms.

Table 36-Study HPV-001: Incidences of Solicited local Symptoms During the 7-Day Follow-up Period Following the Administration of Each Vaccine Dose for All/Dose and All/Subject (ATP cohort)

Dose		All/Dose				All/Subject			
Group		Vaccine		Aluminum hydroxide control		Vaccine		Aluminum hydroxide control	
#SS		1523		1539		531		538	
Pain	Any	1280	84%	1114	72.4%	496	93.4%	469	87.2%
	Gr 3	169	11.1%	121	7.9%	116	21.8%	89	16.5%
Redness	Any	336	22.1%	195	12.7%	189	35.6%	131	24.3%
	Gr 3	3	0.2%	1	0.1%	3	0.6%	1	0.2%
Swelling	Any	326	21.4%	162	10.5%	182	34.3%	113	21.0%
	Gr 3	5	0.3%	0	0.0%	5	0.9%	0	0.0%

Vaccine = HPV 16/18 vaccine
SS = symptom sheets
For all/subject: n/% = number/percentage of subjects reporting a specified symptom
For all/dose: n/% = number/percentage of doses with reports of a specified symptom
95%CI = Exact 95% confidence interval. LL = Lower Limit; UL = Upper Limit
Grade 3 pain: spontaneously painful
Grade 3 redness/swelling: > 50 mm
Source: STN 125259/0, CSR 001, Table 104, p. 216

Table 37- Study HPV-001: Incidence of Any Solicited Local Symptoms Reported During the 7-Day Follow-up Period After Each Vaccine Dose and Overall: Summary Statistics (Fisher's Exact Test) (ATP Cohort)

Dose	Symptoms	p-values
Dose 1	Pain	< 0.001
	Redness	0.008
	Swelling	< 0.001
	Any local symptoms	< 0.001
Dose 2	Pain	< 0.001
	Redness	< 0.001
	Swelling	< 0.001
	Any local symptoms	< 0.001
Dose 3	Pain	< 0.001
	Redness	< 0.001
	Swelling	< 0.001
	Any local symptoms	< 0.001
Overall/dose	Pain	< 0.001
	Redness	< 0.001
	Swelling	< 0.001
	Any local symptoms	< 0.001
Overall/subject	Pain	< 0.001
	Redness	< 0.001
	Swelling	< 0.001
	Any local symptoms	< 0.001

Source: STN 125259/0, CSR 001, Table 105, p. 217

Table 38-Study HPV-001: Incidence of Grad 3 Solicited Local Symptoms Reported During the 7-Day Follow-up Period After Each Vaccine Dose and Overall: Summary Statistics (Fisher's Exact Test) (ATP cohort)

Dose	Symptoms	p-values
Dose 1	Pain	0.135
	Redness	1.000
	Swelling	0.496
	Any local symptoms	0.115
Dose 2	Pain	0.036
	Redness	0.496
	Swelling	0.122
	Any local symptoms	0.027
Dose 3	Pain	0.134
	Redness	1.000
	Swelling	1.000
	Any local symptoms	0.134
Overall/dose	Pain	0.002
	Redness	0.372
	Swelling	0.030
	Any local symptoms	0.002
Overall/subject	Pain	0.030
	Redness	0.371
	Swelling	0.030
	Any local symptoms	0.020

Source: STN 125259/0, CSR 001, Table 106, p. 217

Reviewer's Comment: The majority of local adverse events were mild to moderate in intensity. Source: STN 125259/0, CSR 001, Supplement 80, p. 331, not shown here).

Solicited general adverse events: The incidence of solicited general symptoms (any intensity, grade 3 and with causal relationship to vaccination as assessed by investigators) is presented for each dose and for all doses (overall/dose) and all subjects (overall/subject). The most frequently reported solicited general symptoms reported in both groups were headache (reported following 35.7% of vaccine and 36.4% of control doses) and fatigue (reported following 35.9% of vaccine and 31.9% of control doses). Grade 3 symptoms occurred at low frequencies in both groups (maximum of 2.2% of doses for fatigue in the vaccine group and 2.1% of doses for headache in the control group). The incidences of each solicited general symptom were comparable between the vaccine and control groups except for fatigue where the difference was statistically significant (overall/dose p=0.024). The incidence of fatigue considered as related to vaccination was however comparable between the groups as was the incidence of grade 3 fatigue. There was no evidence that the incidence of solicited general symptoms increased with subsequent doses. It was noted that the incidence of Grade 3 elevated temperature was higher in the aluminum hydroxide control group as compared to the Cervarix group. Additional data on the intensity of solicited general symptoms are also shown.

Table 39- Study HPV-001: Incidences of Any Solicited General Symptoms During the 7-Day Follow-up Period Following the Administration of Each Vaccine Dose (ATP Cohort)

Dose		Dose 1				Dose 2				Dose 3			
Group		Vaccine		Aluminum hydroxide control		Vaccine		Aluminum hydroxide control		Vaccine		Aluminum hydroxide control	
#SS		527		535		503		511		493		491	
Fatigue	Any	220	41.7%	200	37.4%	160	31.8%	145	28.4%	166	33.7%	146	29.7%
	Gr 3	16	3.0%	12	2.2%	10	2.0%	9	1.8%	8	1.6%	10	2.0%
Gastrointestinal	Any	111	21.1%	118	22.1%	74	14.7%	63	12.3%	74	15.5%	57	11.6%
	Gr 3	4	0.8%	2	0.4%	6	1.2%	2	0.4%	3	0.6%	3	0.6%
Headache	Any	210	39.8%	220	41.1%	157	31.2%	176	34.4%	177	35.9%	163	33.2%
	Gr 3	12	2.3%	12	2.2%	6	1.2%	10	2.0%	7	1.4%	11	2.2%
Itching	Any	58	11.0%	59	11.0%	45	8.9%	45	8.8%	66	13.4%	47	9.6%
	Gr 3	0	0.0%	2	0.4%	1	0.2%	1	0.2%	0	0.0%	1	0.2%
Rash	Any	20	3.8%	28	5.2%	20	4.0%	22	4.3%	34	6.9%	15	3.1%
	Gr 3	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.4%	0	0.0%
Temperature	Any	25	4.7%	26	4.9%	36	7.2%	27	5.3%	43	8.7%	30	6.1%
	Gr 3	0	0.0%	1	0.2%	0	0.0%	3	0.6%	0	0.0%	2	0.4%

Vaccine=HPV 16/18 vaccine
SS = symptom sheets.
n/% = number/percentage of doses with reports of a specified symptom
Grade 3: adverse event which prevents normal, everyday activities (for temperature grade 3 intensity is defined as temperature axillary/orally > 39.0 oC)
Source: STN 125259/0, CSR 001, Table 107, p. 219-220

Table 40-Study HPV-001: Incidences of Any Solicited General Symptoms During the 7-Day Follow-up Period Following the Administration of Each Vaccine Dose for All/Dose and All/Subject (ATP cohort)

Dose		All/Dose				All/Subject			
Group		Vaccine		Aluminum hydroxide control		Vaccine		Aluminum hydroxide control	
#SS		1523		1537		531		538	
Fatigue	Any	546	35.9%	491	31.9%	308	58.0%	289	53.7%
	Gr 3	34	2.2%	31	2.0%	29	5.5%	26	4.8%
Gastrointestinal	Any	259	17.0%	238	15.5%	178	33.5%	172	32.0%
	Gr 3	13	0.9%	7	0.5%	13	2.4%	7	1.3%
Headache	Any	544	35.7%	559	36.4%	331	62.3%	329	61.2%
	Gr 3	25	1.6%	33	2.1%	23	4.3%	29	5.4%
Itching	Any	169	11.1%	161	9.8%	130	24.5%	109	20.3%
	Gr 3	1	0.1%	4	0.3%	1	0.2%	3	0.6%
Rash	Any	74	4.9%	65	4.2%	60	11.3%	54	10.0%
	Gr 3	2	0.1%	0	0.0%	2	0.4%	0	0.0%
Temperature	Any	104	6.8%	83	5.4%	88	16.6%	73	13.6%
	Gr 3	0	0.0%	6	0.4%	0	0.0%	6	1.1%

SS = symptom sheets.
n/% = number/percentage of subjects reporting a specified symptom
For all/dose: N = number of doses for which at least one symptom sheet was completed.
n/% = number/percentage of doses with reports of a specified symptom. 95%CI = Exact 95% confidence interval.
Grade 3: adverse event which prevents normal, everyday activities (for temperature grade 3 intensity is defined as axillary/orally temperature > 39.0 oC)
Source: STN 125259/0, CSR 001, Table 108, p. 221-222

Reviewer's Comment: The majority of general adverse events were mild to moderate in intensity. Source: STN 125259/0, CSR 001, Supplement 81, p. 332-33, not shown here).

Unsolicited adverse events

Any unsolicited adverse events reported during the 30 day follow-up: A summary of the percentage of subjects presenting at least one report of an unsolicited symptom (any grade)

following each dose and overall is presented. The percentage of subjects reporting unsolicited symptoms during the follow-up period (30 days after each study vaccine or control administration) was similar in both groups (47.3% for vaccine group and 48.5% control group). There was no evidence that the incidence of unsolicited symptoms increased with subsequent doses; in both groups the highest incidence of symptoms was associated with the first dose.

The percentage of doses followed by at least one report of an unsolicited symptom (any grade) classified by WHO Body System is also presented. The incidence was similar in both groups with 21.9% in the vaccine group and 23.9% in the control group.

Table 41-Study HPV-001: Percentage of All Documented Doses Followed by at Least One Report of an Unsolicited Symptom Within 30 days After Vaccination (ATP cohort)

WHO Body System	Vaccine D=1524		Control =1540	
	d	%	d	%
At least one symptom	336	22.0%	369	24.0%
Application site	16	1%	13	0.8%
Autonomic Nervous System	1	0.3%	0	0.0%
Body as a whole general	56	3.7%	55	3.6%
Cardiovascular general	1	0.1%	2	0.1%
Central & peripheral nervous system	63	4.1%	91	5.9%
Endocrine	1	0.1%	1	0.1%
Gastrointestinal system	58	3.8%	57	3.7%
Hearing and vestibular	3	0.2%	4	0.3%
Heart rate & rhythm	1	0.3%	0	0.0%
Metabolic and nutritional	2	0.1%	2	0.1%
Musculoskeletal system	39	2.6%	50	3.2%
Neoplasm	1	0.1%	2	0.1%
Psychiatric	17	1.1%	17	1.1%
Red blood cell	2	0.1%	1	0.1%
Reproductive female	39	2.6%	47	3.1%
Resistance mechanism	36	2.4%	49	3.2%
Respiratory system	55	3.6%	63	4.1%
Skin and appendages	20	1.3%	18	1.2%
Urinary system	18	1.2%	14	0.9%
Vascular extracardiac	1	0.3%	0	0.0%
Vision	5	0.3%	2	0.1%
White cell & reticuloendothelial system	2	0.1%	1	0.1%

At least one symptom = at least one symptom experienced (regardless of the preferred term)
D = number of documented doses
d/% = number/percentage of doses followed at least once by a specified symptom within 30 days after vaccination day 0 to day 29
* One case which remains blinded so as not to compromise the blinding of long-term follow-up study 580299/007
Source: STN 125259/0, CSR 001, Table 112, p. 226 and wunsol.xpt

Grade 3 Unsolicited adverse events reported during the 30 day follow-up: The percentage of subjects reporting grade 3 unsolicited symptoms was low (5.1% vaccine group and 5.4% control group). The percentages of doses followed by at least one report of a grade 3 unsolicited symptom classified by WHO Body System were low (less than 2%) in both the vaccine and control groups.

Table 42-Study HPV-001: Percentage of All documented Doses and Percentage of Subjects With at Least One Report of Grade 3+ Unsolicited Symptom Within 30 Days After Vaccination (ATP cohort)

WHO Body System	Vaccine D=1524 N=531	Control D=1540 N=538
	d (%) [N (%)]	d (%) [N (%)]
At least one symptom	28 (1.8%) [5.3%]	29 (1.9%) [5.4%]
Body as a whole general	3 (0.2%) [0.6%]	4 (0.3%) [0.7%]
Central and peripheral nervous system	3 (0.2%) [0.6%]	6 (0.4%) [1.1%]
Gastrointestinal system	8 (0.5%) [1.5%]	6 (0.4%) [1.1%]
Musculoskeletal system	1 (0.1%) [0.2%]	4 (0.3%) [0.7%]
Psychiatric	3 (0.2%) [0.6%]	2 (0.1%) [0.4%]
Reproductive female	4 (0.3%) [0.8%]	2 (0.1%) [0.4%]
Resistance mechanism	7 (0.5%) [1.3%]	1 (0.1%) [0.2%]
Respiratory system	2 (0.1%) [0.4%]	5 (0.3%) [0.9%]
Skin and appendages	0 (0.0%) [0.0%]	2 (0.1%) [0.4%]
Urinary system	0 (0.0%) [0.0%]	1 (0.1%) [0.2%]
Vascular extracardiac	1 (0.1%) [0.2%]	0 (0.0%) [0.0%]

+Grade 3 defined as adverse events which prevent normal everyday activities.
At least one symptom = at least one symptom experienced (regardless of the preferred term)
D = number of documented doses
d/% = number/percentage of doses followed at least once by a specified symptom within 30 days after vaccination day 0 to day 29 ;* One case which remains blinded so as not to compromise the blinding of long-term follow-up study 580299/007
[95% CI:] % as calculated by subject
Source: STN 125259/0, CSR 001, Table 114, p. 228 and wunsol.xpt

Reviewer's Comment: There were few Grade 3 unsolicited adverse events considered related to study material.

Any unsolicited events reported outside the 30 day follow-up: The percentage of subjects reporting unsolicited symptoms outside the 30 day follow up period after each study vaccine or control administration was similar in both groups (21.2% vaccine subjects and 23.2% control subjects). For WHO Body System, the numbers of doses followed by a specific event were similar in both groups.

Table 43-Study HPV-001: Percentage of All Documented Doses and Percentage of Subjects With at Least One Report of an Unsolicited Symptom Outside the 30 day Follow-up Period After Vaccination (ATP cohort)

WHO Body System	Vaccine D=1530 N=532		Control D=1542 N=538	
	d	% [N %]	d	% [N%]
At least one symptom	132	8.6% [24.8%]	143	9.3% [26.6%]
Autonomic Nervous System	2	0.1% [0.4%]	0	0.0% [0.0%]
Body as a whole general	13	0.8% [0.2%]	15	1.0% [2.8%]
Central & peripheral nervous system	15	1.0% [2.8%]	13	0.8% [2.4%]
Endocrine	0	0.0% [0.0%]	2	0.1% [0.4%]
Foetal	0	0.0% [0.0%]	1	0.1% [0.2%]
Gastrointestinal system	16	1.0% [3.0%]	19	1.2% [3.5%]
Hearing and vestibular	2	0.1% [0.4%]	1	0.1% [0.2%]
Heart rate & rhythm	0	0.0% [0.0%]	1	0.1% [0.2%]
Liver & bilary system	3	0.2% [0.6%]	2	0.1% [0.4%]
Metabolic and nutritional	0	0.0% [0.0%]	1	0.1% [0.2%]
Musculoskeletal system	8	0.5% [1.5%]	6	0.4% [1.1%]
Neoplasm	3	0.2% [0.6%]	2	0.1% [0.4%]
Platelet bleeding and clotting	0	0.0% [0.0%]	2	0.1% [0.4%]
Psychiatric	16	1.0% [3.0%]	15	1.0% [2.8%]
Red blood cell	1	0.1% [0.2%]	3	0.2% [0.6%]
Reproductive female	19	1.2% [3.6%]	31	2% [5.8%]
Resistance mechanism	34	2.2% [6.4%]	26	1.7% [4.8%]
Respiratory system	15	1.0% [2.8%]	21	1.4% [3.9%]
Skin and appendages	13	0.8% [0.2%]	5	0.3% [0.9%]
Urinary system	15	1.0% [2.8%]	9	0.6% [1.7%]
Vascular extracardiac	1	0.1% [0.2%]	0	0.0% [0.0%]
Vision	2	0.1% [0.4%]	0	0.0% [0.0%]
White cell & reticuloendothelial system	0	0.0% [0.0%]	2	0.1%[0.4%]

At least one symptom = at least one symptom experienced (regardless of the preferred term)
D = number of documented doses
d/% = number/percentage of doses followed by at least one symptom outside the 30 day follow-up after each dose. Note that his table does not include the unsolicited symptoms associated with three SAE which were reported after the closure of the clinical database; [95% CI:%] =percentage of subjects with an event
Source: STN 125259/0, CSR 001, Table 120, p. 232 and wunsol.xpt

Total vaccinated (ITT) cohort analysis: The safety results for the ITT cohort were consistent with those obtained for the final ATP cohort analysis. (Source: STN 125259/0, CSR 001, Supplements 83-97, p.336-350, not shown here).

Serious adverse events: The SAE case narratives for each SAE and the SAE Summary Table were presented.

Fatal events: No subject who was vaccinated in the study died. However there was one report of a neonatal death in the control group in a center in North America. This case concerned the neonatal deaths of prematurely delivered (21 week gestation) twins with twin-twin transfusion syndrome. This event was considered as not related to the vaccination of the mother (PID 06236).

Table 44- Study HPV-001: Fatal Serious Adverse Events (ITT cohort)

Case Id	Serious Adverse Event	Causal relationship to vaccination
(b)(6)	Birth premature	No
	Death foetal	No
	Twin-twin transfusion syndrome	
(b)(6)	Birth premature	No
	Death foetal	No
	Twin-twin transfusion syndrome	

Source: STN 125259/0, CSR 001, Table 122, p. 235

Non-fatal events: Data on non-fatal serious adverse events (SAEs) reported during the whole study period are presented. The overall frequency of SAEs in each group was similar, with 22 subjects reporting at least one SAE in the HPV group and 19 subjects reporting at least one SAE in the control group. None of the SAEs were considered by the investigator to be causally related to vaccination. One SAE (PID 08076 case ID A0363938A) led to withdrawal from the study.

Table 45-Study HPV-001: Non-Fatal Serious Adverse Events in Centers in Brazil

PID	Case Id	Serious Adverse Event	Causal relationship to vaccination
07001	B0278953A	Abortion spontaneous	No
07008	B0312173A*	Hypophyseal Adenoma	No
07023	B0256051A	Dysfunctional Uterine Bleeding	No
07060	B0312174A** B0312174B**	Breast fibroadenoma	No
07099	B0262871A	Cholelithiasis	No
07143	B0380552A*	Endometriosis	No
07190	B0269788A	Abortion spontaneous	No
07230	B0302087A	Pyelonephritis	No
07237	B0278499A	Burn of face	No
07249	B0265093A/*** B0265093B*	Talipes Equinovarus Congenital	No
07344	B0295882A	Abortion spontaneous	No
07413	B0267640A	Anxiety Reaction	No
07431	B0265371A	Abortion spontaneous	No

* SAE reported following database closure.
**Two different incidences of fibroadenoma were reported for the same subject. SAE was reported following database closure. ***This was one case (child of subject born with congenital foot malformation) but was recorded with a case ID for both the mother and child. Source: STN 125259/0, CSR 001, Table 123, p. 236.

Table 46-Study HPV-001: Non-Fatal Serious Adverse Events in Centers in North America

PID	Case Id	Serious Adverse Event	Causal relationship to vaccination
06032	B0251648A	Anaphylactic reaction*	No
		Cardiogenic shock	No
06043	B0253269A	Abortion induced	No
06051	B0253270A	Abortion induced	No
06076	A0400234A	Abortion induced	No
06194	A0373901A	Abortion induced	No
06223	A0378714A	Abortion induced	No
06230	B0257834A	Abortion induced	No
06236	B0254979A	Overdose	No
		Suicidal ideation	No
	B0254979B**	Premature labour	No
	B0254979C**	Birth premature	No
		Death foetal	
	B0254979D**	Birth premature	No
		Death foetal	
06261	A0396020A	Basal cell carcinoma	No
06271	B0258570A	Food allergy	No
	B0258570B	Pyelonephritis	No
06288	B0256271A	Infectious mononucleosis	No
06298	B0256997A	Ovarian cyst	No
06370	B0257769A	Abortion induced	No
06399	B0257467B	Nephrolithiasis	No
06636	B0258193A	Abortion induced	No
06378	A0360147A	Premature labour	No
06478	A0365768A	Arterial occlusive disease	No
06530	A0403292A	Tibia fracture	No
06551	A0359184A	Pancreatitis acute	No
06570	A0365816A	Renal surgery	No
06571	A0376392A	Caesarean section	No
06583	A0380334A	Abortion spontaneous	No
06593	A0401289A	Abortion spontaneous	No
06595	A0406238A	Dehydration	No
		Viral infection	No
06596	A0358947A	Migraine	No
06666	B0259172A	Bipolar I disorder	No
06709	A0369957A	Abortion spontaneous	No
08030	A0409617A***	Abortion induced	No
08076	A0363938A	Abortion spontaneous	No

*This subject developed an anaphylactic reaction to the contrast dye used in a CT scanner.
**This is one case involving a premature birth of twins (gestation 21 weeks) who did not survive and presented a twin-twin transfusion syndrome.
***Initial report erroneously made for current study but conception date was after last visit in current study, therefore the SAE is reported in follow-up study HPV-007.
Source: STN 125259/0, CSR 001, Table 124, p. 237

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study:
There were four withdrawals related to adverse events. One was a serious adverse event in the vaccine group (PID 8076, case ID A0363938A). This 18-year-old subject received the second dose of study vaccine on 11/9/01. A pregnancy test on 2/20/02 was positive. Vaccination was discontinued. On ---b(6)---, 132 days after the second dose of study vaccine, the subject experienced a spontaneous abortion. The investigator considered the event unrelated to vaccination and probably associated with natural causes. There were three withdrawals due to non serious adverse events in the control group. Details for these three events are given in Table 47 below.

Table 47-Study HPV-001: Drop Outs Due to Non Serious Adverse Events (ITT cohort)

PID	Centre	Timing of Drop out	Adverse event	Causal relationship to vaccination
6294	080	After visit 3 on 16/11/01	Mental illness	No
6464	110	After visit 1 on 22/5/01, last contact was 12/6/01	Fatigue and migraine	No
6576	340	After visit 2 on 9/11/01, last contact was 8/4/02	Dizziness	No

Source: STN 125259/0, CSR 001, Table 125, p. 238

Concomitant medications/vaccinations: The number and percentage of subjects who received medication were similar in both study groups.

Table 48- Study HPV-001: Concomitant medication (ATP cohort)

Vaccine			Placebo		
N	n	%	N	n	%
540	381	70.6	541	406	75

n = Number of subjects in specific cohort with medication
% = Percentage of subjects in specific cohort with medication = n/N
Medication stopped before study entry or starting after last date of contact was not included in this table .After the 30 day follow-up after each vaccination only restricted medication was documented.
Source: STN 125259/0, CSR 001, Table 126, p. 238

Clinical Laboratory Evaluations: Biochemical and hematology analyses were performed for subjects enrolled in centers 10, 17, 18, 23, 40, 70, 100 and 130. The hematology and biochemistry profiles were similar for both groups and there were no values out of range that were considered as medically relevant. There were 6 subjects in the vaccine group (two prior to vaccination at visit 1, one at visit 2, one at visit 3 and two at visit 4) and 3 subjects in the control group (one at visit 3, two at visit 4) with an absolute neutrophil count below 1500/µl, none of these subjects had a count below 500/µl. (Source: STN 125259/0, CSR 001, Table 127, p. 239; Supplement 98, p. 351-354 ; Supplements 99 and 100, p. 355-356, not shown here).

Pregnancy: During the study 88 pregnancies (44 in the vaccine group, 44 in the control group) were reported. The outcomes of these pregnancies were presented. The number of pregnancy outcomes reported as miscarriages/spontaneous abortions was low and comparable between the two groups. There was one report of a neonatal death reported as an SAE. This case concerned the neonatal deaths of prematurely delivered (21 week gestation) twins with twin-twin transfusion syndrome. All reported complications were considered as not related to vaccination. Pregnancy case narratives were provided as well.

Table 49-Study HPV-001: Outcome of Reported Pregnancies

Outcome	Vaccine	Control	Total
Abnormal child (congenital defect†)			**1**
Healthy baby	**30**	**31**	**61**
Miscarriage/spontaneous abortion	**5**	**3****	**8**
Elective abortion	**5**	**4**	**9**
Neonatal death	**0**	**1**	**1‡**
Pregnancy ongoing	**2**	**4**	**6**
Unknown	**1**	**1**	**2**
Total	**44**	**44**	**88**

Count is made on number of subjects
† Talipes equinovarus.
‡One subject reported two outcomes, Miscarriage/spontaneous abortion and neonatal death of twins. This was counted as only one outcome under neonatal death.
Source: STN 125259/0, CSR 001, Table 128, p. 242

IMMUNOGENICITY RESULTS

Data sets analyzed: Analysis of immunogenicity was performed on the ATP cohort (primary analysis) and the ITT cohort.

According-To-Protocol (ATP) analysis: The ATP cohort for analysis of immunogenicity included all evaluable subjects (those meeting all eligibility criteria, complying with the procedures defined in the protocol, and fulfilling requirements for analysis) for whom immunogenicity data were available (i.e. subjects for who assay results were available for antibodies at any blood sampling time-point). Subjects who acquired HPV-16 and/or HPV-18 infection during the trial were excluded from the analysis.

Reviewer's Comment: As noted in the efficacy results, very few subjects in the ATP cohort who received HPV vaccine developed such an infection. In addition, the ITT cohort included all subjects with data available.

Humoral response: anti-HPV-16/18 measured by ELISA: The immune response (anti-HPV-16 antibody titers and anti-HPV-18 antibody titers as measured by ELISA) following administration of three HPV-16/18 vaccine doses is presented. More than 98% of vaccinees were seropositive at one month following administration of the first vaccine dose. At one month following the administration of the full three dose vaccination course (month 7) all vaccinees were seropositive for HPV-16 and HPV-18 (a laboratory error resulted in one subject being recorded as seronegative for anti-HPV-18 antibodies at month 7; this was discovered after database freeze). The administration of the third dose induced the greatest increase in antibody levels with geometric means titers (GMTs) reaching 5334 ELISA units/ml for HPV-16 and 3364 ELISA units/ml for HPV-18 (these GMTs were greater than those observed in women with natural infections with HPV-18 and HPV-16. One year following the full vaccination course (month 18) all subjects in the vaccine group were seropositive for both HPV-16 and HPV-18 (including the one subject seronegative for HPV-18 at month 7). GMT levels had decreased (801 ELISA units/ml for HPV-16 and 480 ELISA units/ml for HPV-18) but were still higher than those observed in women with natural HPV-16 or HPV-18 infections. Reverse cumulative curves were presented for month 7 and for month18, and curves are superimposable for HPV 16 and for HPV 18. (Source: STN 125259/0, CSR 001, Supplements 101-104, p. 357-358, not shown here).

It was discovered during a quality control check of serum samples that nine of the subjects included in the ATP analysis should have been excluded due to inconsistencies in the dates noted for month 7 and month 18 serum samples. A re-analysis of anti-HPV-16 and anti-HPV-18 ELISA titers which excluded these nine subjects was performed. The results of this analysis demonstrated that the exclusion did not affect the overall results for either anti-HPV-16 ELISA titers or anti-HPV-18 ELISA titers. (Source: STN 125259/0, CSR 001, Supplements 105-106, p. 359-360, not shown here).

The HPV-16 or HPV-18 ELISA data for vaccinees at month 7 stratified by geographical region was presented. This analysis indicates that the GMTs in the North American population tended to be higher than for the population in Brazil. It should be noted that a covariate efficacy analysis showed no effect of geographical region. Data by center for Brazil is also presented. A similar analysis has not been conducted for North America as the subject number per center was lower compared to Brazil.

Table 50-Study HPV-001: Anti-HPV-16 and Anti-HPV-18 Seropositivity Rates and GMTs at Month 7 (by ELISA - Vaccine group) Stratified by Geographical Region (ATP Cohort)

Antibody	Geographical region	N	Seropositivity* rate				GMT			MIN	MAX
			n	%	95% CI L.L.	95% CI U.L.	Value	95% CI L.L.	95% CI U.L.		
ANTI-HPV-16	Brazil	179	179	100	98.0	100	4614	3963.9	5371.0	65.0	49454.0
	North America	172	172	100	97.9	100	6203.8	5260.2	7316.7	59.0	134190.0
ANTI-HPV-18	Brazil†	179	178	99.4	96.9	100	2694.5	2302.8	3152.8	<7.0	86114.0
	North America	172	172	100	97.9	100	4239.8	3661.3	4909.7	37.0	43235.0

* A seropositive subject is a subject whose titre is greater than or equal to the assay cut-off value which is 8 ELISA units/ml for anti-HPV-16 antibodies and 7 ELISA units/ml for anti-HPV-18 antibodies.
† A database error resulted in one subject being recorded as seronegative at month 7 when in fact the subject was seropositive.
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
MIN/MAX = Minimum/Maximum value
Source: STN 125259/0, CSR 001, Table 130, p. 246

Table 51-Study HPV-001: Seropositivity Rates and Geometric Mean Titers (GMT) for Anti-HPV-16 and Anti-HPV-18 Antibody Titers (ATP Cohort for Efficacy (6-27 Months), Breakthrough Cases)

Antibody	Status	Timing	N	Seropositivity* rate				GMT			MIN	MAX
				n	%	95% CI LL	95% CI UL	Value	95% CI LL	95% CI UL		
Anti-HPV-16	Infected HPV-16	PRE	6	0	0.0	0.0	45.9	4.0	4.0	4.0	<8.0	<8.0
		PIII(M7)	6	6	100.0	54.1	100.0	3779.9	2218.7	6439.6	1963.0	7866.0
		PIII(M18)	6	6	100.0	54.1	100.0	450.2	168.5	1202.7	111.0	1233.0
	Infected HPV-18	PRE	6	0	0.0	0.0	45.9	4.0	4.0	4.0	<8.0	<8.0
		PIII(M7)	6	6	100.0	54.1	100.0	3557.9	1638.9	7724.2	1178.0	8035.0
		PIII(M18)	6	6	100.0	54.1	100.0	596.0	246.5	1441.2	264.0	2071.0
Anti-HPV-18	Infected HPV-16	PRE	6	0	0.0	0.0	45.9	3.5	3.5	3.5	<7.0	<7.0
		PIII(M7)	6	6	100.0	54.1	100.0	1886.0	615.0	5784.0	341.0	4738.0
		PIII(M18)	6	6	100.0	54.1	100.0	223.8	56.8	881.7	42.0	2383.0
	Infected HPV-18	PRE	6	0	0.0	0.0	45.9	3.5	3.5	3.5	<7.0	<7.0
		PIII(M7)	6	6	100.0	54.1	100.0	1949.8	640.0	5939.9	495.0	7979.0
		PIII(M18)	6	6	100.0	54.1	100.0	228.1	65.1	798.7	74.0	1605.0

* A seropositive subject is a subject whose titre is greater than or equal to the assay cut-off value which is 8 ELISA units/ml for anti-HPV-16 antibodies and 7 ELISA units/ml for anti-HPV-18 antibodies.
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE =Prevaccination blood sampling at month 0
PIII(M7) = Post dose 3 blood sampling at month 7
PIII(M18) =Post dose 3 blood sampling at month 18
Source: STN 125259/0, CSR 001, Table 131, p. 246

The seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies in the six subjects with HPV-16 infection and the six subjects with HPV-18 infection from the HPV-16/18 vaccine group (breakthrough cases) is also presented. Data is presented for subjects in the ATP cohort for efficacy (months 6-27) as subjects infected prior to month 18 were eliminated from the ATP cohort for immunogenicity. Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies for the breakthrough cases from the HPV-16/18 vaccine group in the ATP cohort for immunogenicity are presented as well.

All subjects that developed HPV-16 or HPV-18 infection had seroconverted by month 7 and remained seropositive up to month 18. For both anti-HPV-16 and anti-HPV-18 antibodies, GMTs

peaked at month 7 with values that were similar regardless of the type of infection (anti-HPV-16 GMTs of 3779.9 and 3557.9 EU/ml for HPV-16 and HPV-18 infected subjects, respectively and anti-HPV-18 GMTs of 1886.0 and 1949.8 EU/ml for HPV-16 and HPV-18 infected subjects, respectively) but which were lower than the GMTs reported for the ATP immunogenicity cohort (5334.5EU/ml and 3364.7 EU/ml for anti-HPV-16 and anti-HPV-18 antibodies), which excluded subjects with infection.

Table 52-Study HPV-001: Anti-HPV-16 and Anti-HPV-18 Seropositivity Rates and GMTs (by ELISA) (ATP Cohort)

Antibody	Group	Timing	N	Seropositivity* rate				GMT			MIN	MAX
				n	%	95% CI		Value	95% CI			
						LL	UL		LL	UL		
ANTI-HPV-16	Vaccine	PRE	352	0	0.0	0.0	1.0	4.0	4.0	4.0	<8.0	<8.0
		PI(M1)	352	348	98.9	97.1	99.7	117.4	104.7	131.6	<8.0	2827.0
		PII(M6)	348	347	99.7	98.4	100	287.9	257.3	322.2	<8.0	7955.0
		PIII(M7)	351	351	100	99.0	100	5334.5	4766.9	5969.6	59.0	134190.0
		PIII(M12)	342	341	99.7	98.4	100	1348.0	1187.0	1530.8	<8.0	57408.0
		PIII(M18)	348	348	100	98.9	100	801.4	706.4	909.2	42.0	41014.0
	Placebo	PRE	310	0	0.0	0.0	1.2	4.0	4.0	4.0	<8.0	<8.0
		PI(M1)	309	3	1.0	0.2	2.8	4.0	4.0	4.1	<8.0	16.0
		PII(M6)	307	8	2.6	1.1	5.1	4.2	4.0	4.3	<8.0	83.0
		PIII(M7)	310	10	3.2	1.6	5.9	4.2	4.0	4.3	<8.0	67.0
		PIII(M12)	308	9	2.9	1.3	5.5	4.2	4.1	4.3	<8.0	61.0
		PIII(M18)	310	10	3.2	1.6	5.9	4.2	4.1	4.3	<8.0	46.0
ANTI-HPV-18	Vaccine	PRE	352	0	0.0	0.0	1.0	3.5	3.5	3.5	<7.0	<7.0
		PI(M1)	352	346	98.3	96.3	99.4	106.2	94.0	119.9	<7.0	7206.0
		PII(M6) °	324	322	99.4	97.8	99.9	314.9	280.7	353.3	<7.0	8794.0
		PIII(M7)†	351	350	99.7	98.4	100	3364.7	3015.1	3754.9	<7.0	86114.0
		PIII(M12) °	340	340	100	98.9	100	871.6	773.1	982.5	67.0	27156.0
		PIII(M18)	348	348	100	98.9	100	480.5	424.5	543.8	23.0	51686.0
	Placebo	PRE	310	0	0.0	0.0	1.2	3.5	3.5	3.5	<7.0	<7.0
		PI(M1)	308	1	0.3	0.0	1.8	3.5	3.5	3.5	<7.0	7.0
		PII(M6)	286°	3	1.0	0.2	3.0	3.6	3.5	3.7	<7.0	57.0
		PIII(M7)	310	4	1.3	0.4	3.3	3.6	3.5	3.7	<7.0	66.0
		PIII(M12)	307	5	1.6	0.5	3.8	3.6	3.5	3.7	<7.0	168.0
		PIII(M18)	308	1	0.3	0.0	1.8	3.5	3.5	3.6	<7.0	18.0

* A seropositive subject is a subject whose titre is greater than or equal to the assay cut-off value which is 8 ELISA units/ml for anti-HPV-16 antibodies and 7 ELISA units/ml for anti-HPV-18 antibodies.
† A database error resulted in one subject being recorded as seronegative at month 7 when in fact the subject was seropositive.
°The number of subjects with available results for the month 6 and 12 time points was reduced because of a labelling error in the laboratory which required exclusion of 26 subjects in the vaccine group (24 at month 6 and 2 at month 12) and 20 subjects in the control group (20 at month 6 and 0 at month 12) from the immunogenicity analysis.
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
MIN/MAX = Minimum/Maximum value
PRE =Prevaccination blood sampling at month 0
PI(M1) = Post dose 1 blood sampling at month 1
PII(M6) = Post dose 2 blood sampling at month 6
PIII(M7) = Post dose 3 blood sampling at month 7
PIII(M12) = Post dose 3 blood sampling at month 12
PIII(M18) =Post dose 3 blood sampling at month 18
Source: STN 125259/0, CSR 001, Table 129, p. 245

Humoral response: V5-HPV-16 and J4-HPV-18 as measured by monoclonal inhibition enzyme immuno-assays: The seropositivity rates and GMTs for anti-V5-HPV-16 and anti J4-HPV-18 antibodies in the selected subset of subjects was presented. At one month following the full vaccination course 98.7% of vaccinees were seropositive and GMTs reached 491 ELISA units/ml for anti-V5 antibodies and 557 ELISA units/ml for anti-J4 antibodies. None of the subjects who received control were seropositive. On year following the full vaccination course,

GMT levels had decreased in the vaccine group but the majority of subjects remained seropositive for anti-V5 and anti-J4 antibodies (85.7% and 51.9% respectively). (Source: STN 125259/0, CSR 001, Table 132, p. 248, not shown here)

The seropositivity rates and GMTs for anti-V5-HPV-16 and anti J4-HPV-18 in the six subjects with HPV-16 infection and the six subjects with HPV-18 infection from the HPV-16/18 vaccine group in the ATP cohort for efficacy (months 6- 27). Similar to the subjects in the ATP cohort, the breakthrough cases were all seropositive for anti-V5-HPV-16 and anti J4-HPV-18 antibodies by month 7, except for one subject infected with HPV-16 that remained seronegative for anti J4-HPV-18 antibodies. The GMTs for the breakthrough cases were nominally lower than those observed for the subjects in the ATP cohort, irrespective of the type of infection. The significance of these findings is unclear. (Source: STN 125259/0, CSR 001, Table 133, p. 249 and Supplement 113, p. 365, not shown here).

Humoral response: neutralization assay for detection of human neutralizing antibodies to HPV-16 or HPV-18 L1 VLPs: Seropositivity rates and GMTs for neutralizing antibodies for HPV 16 and HPV 18 for the selected subset of subjects are presented. The corresponding results for the breakthrough cases are also presented. Neutralizing antibodies for HPV 18 were not measured pre-vaccination and in fewer samples at months 7 and 18 than for neutralizing antibodies against HPV 16 due to the limited amount of reagent (HPV-18 virus) available. One month following the full vaccination course (month 7), all subjects were seropositive for HPV-16 antibodies and all but one subject were seropositive for HPV-18 antibodies. Seropositivity rates remained high up to month 18 with 96% and 100% of subjects seropositive for HPV-16 and HPV-18 antibodies respectively. The GMT values for both antibodies peaked at month 7 (398 and 546 for HPV-16 and HPV-18 antibodies respectively) and then declined (values of 60 and 110 for HPV-16 and HPV-18 antibodies respectively, at month 18). At month 7, all breakthrough cases were seropositive for HPV-16 antibodies and all but one subject was seropositive for HPV-18 antibodies and remained so up to month 18. The GMT values for neutralizing antibodies for HPV-16 were similar for HPV-16-infected subjects as well as HPV-18-infected subjects. The same pattern was observed for neutralizing antibodies for HPV-18. Breakthrough cases tended to have nominally lower GMTs than the values for subjects in the ATP cohort (with neutralizing antibodies) with values of 215.4 and 191.9 for HPV-16-infected subjects and HPV-18-infected subjects versus a value of 398.1 for the ATP cohort (subjects with neutralizing antibodies) subjects, and values of 316.2 and 464.2 for HPV-16-infected subjects and HPV-18-infected subjects versus a value of 546.3 for the ATP cohort.
Reviewer's Comment: There were very few breakthrough cases identified and although GMTs were nominally lower in the few breakthrough cases as compared to the ATP cohort (with neutralizing antibodies), no immune correlate of protection could be identified. (Source: STN 125259/0, CSR 001, Table 134-135, p. 250-251, not shown here)

Total vaccinated (ITT) cohort analysis: The anti-HPV-16/18 ELISA results for month 7 and month 18 for ITT vaccinated cohort were consistent with those obtained for the ATP cohort analysis. (Source: STN 125259/0, CSR 001, Supplement 114, p. 366, not shown here)

CONCLUSIONS FOR STUDY HPV-001
Efficacy Conclusions:
Primary objective: The vaccine prevented incident lower genital tract infection with HPV-16 and/or HPV-18 between months 6 and 18 in adolescent and young adult women who were HPV-16/18 seronegative (by ELISA) and high risk HPV type DNA negative (by PCR) at month 0. The point estimates for efficacy were statistically significant. In addition, the ITT analysis also demonstrated statistically significant efficacy.

Secondary objectives addressed in this study report:

- The vaccine prevented persistent lower genital tract infections with HPV-16 and/or HPV-18 between months 6 and 18 and months 6 and 27 (ATP cohorts) and in the ITT cohort, and point estimates of efficacy reached statistical significance.
- The vaccine prevented of cytological abnormalities ASCUS (post hoc), LSIL and any cytological lesion (≥ ASCUS) associated with lower genital tract infections with HPV-16 and/or HPV-18 between months 6 and 18 (ATP cohort) and in the ITT cohort.

Other efficacy findings:

- Limited data was available from study HPV-001 for the ITT cohort for histopathological lesions (CIN 1 and CIN 2) associated with HPV-16 and/or HPV-18 infections.
- The vaccine efficacy in the prevention of incident infection with phylogenetically related HPV types is of interest, but needs to be reviewed in additional depth and in a larger database (as in study HPV-008).

The sponsor also notes that there was no effect of geographical region or any risk factor for HPV cervical infection or cervical cancer was observed on vaccine efficacy.

Safety conclusions:

- In healthy women aged 15 to 25 years, the reactogenicity/safety profile of the candidate HPV-16/18 vaccine was shown to be similar to that of the control except for a higher incidence of injection site reactions. The majority of these resolved within 3-4 days (post hoc analysis).
- Both groups had similar high rates of compliance with completion of the vaccination course.

Immunogenicity conclusions:

- The results of the immunogenicity analysis for the ATP and ITT cohorts were similar.
- The vaccine was shown to be immunogenic, with all vaccinees becoming seropositive for anti-HPV-16 and for anti-HPV-18 after the third dose. Monoclonal inhibition enzyme immuno-assay data from a subset of subjects indicated that vaccine-induced antibodies could bind to the major neutralizing/conformational epitopes of HPV-16 and HPV-18. The vaccine induced an immune response that resulted in antibodies with neutralizing capacity for HPV-16 and HPV-18 as demonstrated in a subset of subjects for which neutralizing antibodies to HPV-16 and HPV-18 were tested.
- The presence of anti-HPV-16 and anti-HPV-18 antibodies in vaccinees persisted (at levels above those observed in women with natural HPV16/18 infections) up to at least one year following completion of the full vaccination course.

HPV-001, Annex 1: This annex report contains the results of analyses conducted when the Brazilian site (center 22) with previously identified issues was excluded from analysis. In this process, there was correction of all source data discrepancies identified during the re-monitoring activities in Brazil; exclusion of data from center 22; re-validation of all laboratory database. The confirmatory reanalysis of the new database is described in this report. The rationale for maintaining the original analysis as the "primary" and to consider the re-analysis as "confirmatory" included the following considerations: (1) the original analysis was completed prior to creating the revised database; it was felt that the original analysis was not subject to potential bias that might be introduced with late changes in the dataset; (2) the specific nature of the changes made to the database were considered unlikely to impact key study conclusions.

Population: The size of the analysis populations were reduced by approximately 10% as a result of the elimination of data from center 22.

Demography: No material differences between the demographic characteristics of the cohorts in the re-analysis were found as compared with those of the main analysis.
Efficacy: For all primary and secondary efficacy endpoints, the pattern of results of the original analysis was very similar to that of the re-analysis. As a result, the re-analysis supported conclusions similar in all respects to those supported by the main analysis.
Safety: There was a high degree of concordance between the results of the re-analysis and those of the main analysis, supporting the safety conclusions in the main report.
Immunogenicity: There was a high degree of concordance between the results of the re-analysis and those of the main analysis, supporting the immunogenicity conclusions in the main report.
Overall conclusion: The results of the confirmatory re-analysis are in full concordance with those of the main analysis and therefore support the validity of the main analysis.

The sponsor notes that in each point the re-analysis, using the ATPm and ITTm cohorts instead of the ATP and ITT cohorts, led to a similar conclusion. In all cases the pattern of results of the main analysis and the re-analysis was the same. In a few instances the statistical significance achieved in the main analysis was lost (due to smaller sample size). VE and *p* values in the re-analysis indicated a strengthening rather than a weakening of the result of the main analysis. The sponsor concluded that the discrepancies in source documentation in the original dataset had no effect upon the efficacy-related conclusions of this study.

Reviewer's Comment: This study is a Phase IIb study, and demonstrated Cervarix's efficacy in prevention of incident and persistent HPV 16 and/or 18 infection in women naïve for the relevant HPV type at baseline. In review of specific analyses, conclusions have not changed.

HPV-001, Annex 2: The sponsor presents data for pseudovirion analyses for all subjects for HPV 16 and HPV 18.
Reviewer's Comment: At Month 18, 100% Cervarix recipients (group 1) were seropositive for HPV-16 and HPV-18 antibodies by pesudovirion analyses. In comparison, 2.1%-6.3% of subjects in the control group (group 2) were seropositive for HPV-16 or HPV-18 anitbodies, and GMTs were below the cut-off level for the assay.

Table 53-Study HPV-001: Seropositivity Rates and Geometric Mean Titers (GMT) for HPV 16 PsV Ab HPV 18 PsV Ab antibody Titers (Total Cohort)

Antibody	Group	Timing	N	>= 40 ED50				GMT			MIN	MAX
						95% CI		Value	95% CI			
				n	%	L.L.	U.L.		L.L.	U.L.		
HPV16.PsVAb	1	PRE	110	4	3.6	1.0	9.0	23.3	19.4	28.0	<40.0	151394.0
		PIII(M7)	108	108	100.0	96.6	100.0	19899.9	16083.0	24622.8	499.0	655360.0
		PIII(M18)	109	109	100.0	96.7	100.0	3987.5	3231.1	4921.0	317.0	90626.0
	2	PRE	50	1	2.0	0.1	10.6	20.9	19.1	22.9	<40.0	191.0
		PIII(M7)	49	1	2.0	0.1	10.9	21.1	18.9	23.6	<40.0	291.0
		PIII(M18)	48	3	6.3	1.3	17.2	22.1	19.6	25.0	<40.0	180.0
HPV18.PsVAb	1	PRE	110	3	2.7	0.6	7.8	22.1	19.0	25.7	<40.0	62231.0
		PIII(M7)	107	107	100.0	96.6	100.0	13264.9	10651.9	16518.8	273.0	227155.0
		PIII(M18)	109	109	100.0	96.7	100.0	2023.1	1577.1	2595.2	123.0	67030.0
	2	PRE	50	0	0.0	0.0	7.1	20.0	20.0	20.0	<40.0	<40.0
		PIII(M7)	49	0	0.0	0.0	7.3	20.0	20.0	20.0	<40.0	<40.0
		PIII(M18)	48	1	2.1	0.1	11.1	20.3	19.7	21.0	<40.0	42.0

Group 1 : HPV 16/18 (DVLP017A) Group 2 : Control(DVLP018A)
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
MIN/MAX = Minimum/Maximum
Source: STN 125259/0, CSR 001, Annex 2, p. 2

Table 54-Study HPV-001: Seropositivity Rates and Geometric Mean Titers (GMT) for HPV 16 PsV Ab HPV 18 PsV Ab antibody Titers (ATP Cohort for Immunogenicity)

Antibody	Group	Timing	N	>= 40 ED50				GMT			MIN	MAX
						95% CI		Value	95% CI			
				n	%	L.L.	U.L.		L.L.	U.L.		
HPV16.PsVAb	1	PRE	82	2	2.4	0.3	8.5	21.0	19.6	22.5	<40.0	174.0
		PIII(M7)	81	81	100.0	95.5	100.0	22088.3	17237.2	28304.7	499.0	655360.0
		PIII(M18)	81	81	100.0	95.5	100.0	4078.9	3188.6	5217.9	317.0	90626.0
	2	PRE	29	1	3.4	0.1	17.8	21.6	18.4	25.4	<40.0	191.0
		PIII(M7)	29	1	3.4	0.1	17.8	21.9	18.2	26.5	<40.0	291.0
		PIII(M18)	28	0	0.0	0.0	12.3	20.0	20.0	20.0	<40.0	<40.0
HPV18.PsVAb	1	PRE	82	0	0.0	0.0	4.4	20.0	20.0	20.0	<40.0	<40.0
		PIII(M7)	81	81	100.0	95.5	100.0	13928.2	10935.0	17740.6	273.0	227155.0
		PIII(M18)	81	81	100.0	95.5	100.0	2007.2	1499.9	2686.1	123.0	67030.0
	2	PRE	29	0	0.0	0.0	11.9	20.0	20.0	20.0	<40.0	<40.0
		PIII(M7)	29	0	0.0	0.0	11.9	20.0	20.0	20.0	<40.0	<40.0
		PIII(M18)	28	0	0.0	0.0	12.3	20.0	20.0	20.0	<40.0	<40.0

Group 1 : HPV 16/18 (DVLP017A) Group 2 : Control(DVLP018A)
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
MIN/MAX = Minimum/Maximum
Source: STN 125259/0, CSR 001, Annex 2, p. 3

8.5 EXT- HPV-007 (Trial #5-Extension): A phase IIb, blinded, multi-center, long-term follow-up study of the efficacy of candidate HPV-16/18 L1/AS04 vaccine in the prevention of HPV-16 and/or HPV-18 cervical infection in adolescent and young adult women in North America and Brazil vaccinated in primary study 580299/001.
Study Dates: 11/10/03 – 7/11/05 (Efficacy/Immunogenicity) and 7/31/05 (safety)
Study Sites: 28 centers in three countries: Brazil, Canada and US.

Objectives
Primary Objective: Evaluate the long-term vaccine efficacy in the prevention of incident cervical infection with HPV-16 and/or HPV-18 (by PCR) in adolescent and young adult women who received 3 doses of the study vaccine or control in study HPV-001 and who were previously uninfected with HPV-16 or HPV-18.

Secondary Objectives
- Evaluate the long-term vaccine efficacy in the prevention of persistent cervical infections (6 month definition) with HPV-16 and/or HPV-18 (by PCR) in adolescent and young adult women who received 3 doses of the study vaccine/control in study HPV-001 and who previously did not have persistent cervical infection (i.e. 6 months) with HPV-16 or HPV-18 in study HPV-001.
- Evaluate the long-term vaccine efficacy in the prevention of incident cervical infections with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (by PCR) in adolescent and young adult women who received 3 doses of the study vaccine/control in study HPV-001 and who were previously uninfected by that type.
- Evaluate the long-term vaccine efficacy in the prevention of persistent cervical infections (6 month definition) with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (by PCR) in adolescent and young adult women who received 3 doses of the study vaccine/control in study HPV-001 and who previously did not have persistent cervical infection (i.e. 6 months) with that HPV type in study HPV-001.
- Evaluate the long-term vaccine efficacy in the prevention of histopathologically confirmed cervical intraepithelial neoplasia CIN1+ or CIN2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR).

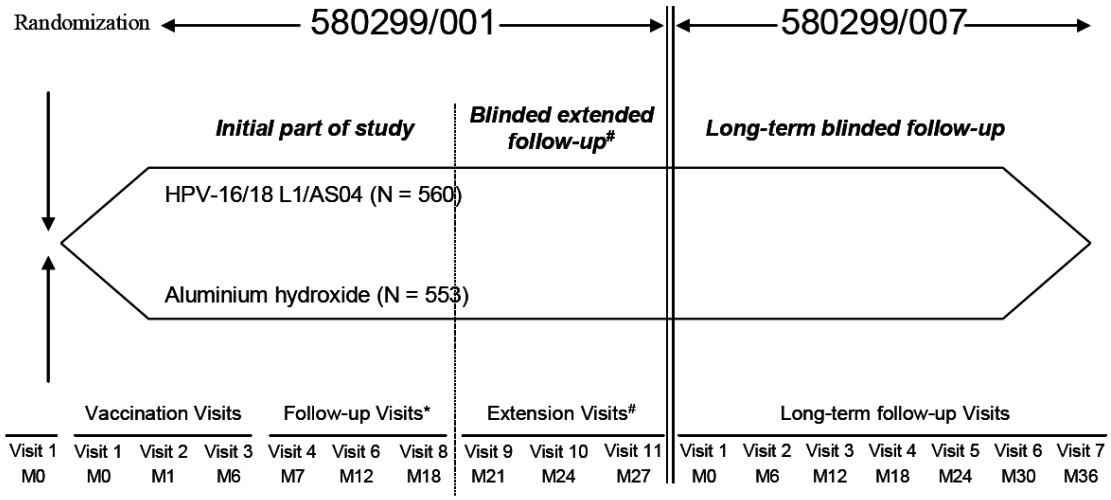
- Evaluate the long-term vaccine efficacy in the prevention of histopathologically confirmed CIN1+ or CIN2+ associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) detected within the lesional component of the cervical tissue specimen (by PCR).
- Evaluate the long-term vaccine efficacy in the prevention of abnormal cytology -atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), atypical squamous cells cannot exclude HSIL (ASC-H) - associated with an HPV-16 and/or HPV-18 cervical infection.
- Evaluate the long-term vaccine efficacy in the prevention of abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (by PCR).

Other Objectives

- Evaluate the long-term vaccine efficacy in the prevention of persistent cervical infections (12 month definition) with HPV-16 and/or HPV-18 (by PCR) in adolescent and young adult women who received 3 doses of the study vaccine/control in study HPV-001 and who previously did not have persistent cervical infection (i.e. 12 months) with HPV-16 or HPV-18 in study HPV-001.
- Evaluate the long-term vaccine efficacy in the prevention of persistent cervical infections (12 month definition) with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (by PCR) in adolescent and young adult women who received 3 doses of the study vaccine/control in study HPV-001 and who previously did not have persistent cervical infection (12 months) with that HPV type in study HPV-001.
- Evaluate long-term vaccine immunogenicity (for all subjects by enzyme-linked immunosorbent assay (ELISA), and in a subset of subjects by V5/J4 monoclonal antibody inhibition tests and/or neutralizing assays).
- Evaluate the safety of the vaccine administered in study HPV-001 during the long-term follow-up period of study HPV-007.

Study design: This study is a blinded long-term efficacy follow-up of study 580299/001 (HPV-001), a multi-center phase IIb study conducted in North America (USA and Canada) and Brazil.

Figure 10-Study HPV-007: Overview of study design



Notes:
The blinded extended follow-up phase of the 580299/001study involved only those subjects who completed their month 18 visit (Visit 8) before 1 February 2003. Month 27 refers to the maximum duration of follow-up in the 580299/001 cohort.
* Visits 5 (M9) and 7 (M15) for study 580299/001 are not shown. These visits to the 580299/001 study site were optional, however, the collection of self-obtained cervical vaginal specimens was required.

Source: STN 125259/0, CSR 007, Figure 1, p. 34

In study HPV-001, 1113 healthy women were enrolled and randomized (1:1) to receive either HPV 16/18 L1 vaccine or 500 mcg aluminum hydroxide control at 0, 1, and 6 months IM.

In study HPV-007, the following was planned:

- Study duration: thirty-six months of long-term follow-up, with seven scheduled visits per subject (at months 0, 6, 12, 18, 24, 30 and 36).
- Number of subjects: all subjects whom the investigator (or designee) could contact of the 1113 subjects initially enrolled in study HPV-001 and who were eligible were invited to participate in this follow-up study.
- Multi-center: 28 study centers located in three countries (USA, Canada and Brazil).
- Blinding was maintained for all subjects and investigators and their study staff with regard to the individual subject treatment assignments allocated in study HPV-001. GSK personnel directly involved in the conduct of this study were also blinded to the individual subject treatment. Site monitors, medical monitors, as well as laboratory and data validation personnel do not have access to any individual unblinded subject data from study 580299/001. In order to maintain the study blind, the interim analyses were performed by an external statistician.
- Blood samples were to be collected at months 0, 12, 24 and 36.
- Cervical liquid-based cytology samples were to be collected at all seven visits for: HPV PCR testing (at 6 month intervals); cytological evaluations (at 1 year intervals, or 6 month intervals if driven by clinical management algorithm).
- Colposcopy was performed according to clinical management algorithms.
- Cervical swabs were collected for *Chlamydia trachomatis* and *Neisseria gonorrhea* testing at study entry, thereafter on a yearly schedule unless this conflicts with national medical recommendations. *Chlamydia trachomatis* and *Neisseria gonorrhea* testing is performed for clinical management only (there are no related study endpoints).
- Behavioural surveys (by questionnaire) were completed at the start of the study and at yearly intervals for 3 years (36 months).

- Data collection: Remote Data Entry (RDE)
- Safety assessments during the study period: Serious Adverse Events (SAEs); new onset chronic diseases (NOCD), e.g. diabetes mellitus, autoimmune diseases; other conditions prompting either emergency room visits or physician visits that are not related to common diseases; pregnancies and their outcome.
- Two interim analyses were planned: at Month 12 and Month 24, and a final analysis at Month 24.

Reviewer's Comment: Separate reports were provided for Months 12, 24, and 36. This review includes the results from Month 36. The sponsor noted that the study design of HPV-007 was similar to that of study HPV-001. All study sites were included.

Outline of Procedures: Visit 1 (Day 0) occurred on any day from September 15, 2003 through July 17, 2004 for all subjects. See Table 55 below.

Table 55-Study HPV-007: Outline of study procedures

Visit Timing	Visit 1 Day 0	Visit 2 Month 6	Visit 3 Month 12	Visit 4 Month 18	Visit 5 Month 24	Visit 6 Month 30	Visit 7 Month 36
Informed consent	●						
Check inclusion/exclusion criteria	●						
Check criteria for the ATP cohorts	●	●	●	●	●	●	●
Collection of demographic data (age, race, weight, height)	●						
History-directed physical examination	●						●
Study staff administers and records behavioural questionnaire	●		●		●		●
Blood sampling for HPV-16 and HPV-18 serology	●		●		●		●
Complete women's health (pelvic) examination according to local practices (may include breast exam)[1]	●		●		●		●
History-directed pelvic examination[1]		●		●		●	
Collection of cervical specimens for:[1] -HPV DNA PCR testing -cervical cytology evaluation[2]	● ● ●	● ● ●[2]	● ● ●	● ● ●[2]	● ● ●	● ● ●[2]	● ● ●
Collection of cervical swab for *Chlamydia trachomatis*/*Neisseria gonorrhea* (CT/NG) screening	●		●[3]		●[3]		●[3]
Reporting of Serious Adverse Events	●	●	●	●	●	●	●
Reporting of new onset chronic diseases, and conditions prompting either emergency room visits that are not related to common diseases or physician visits that are not related to common diseases[4]	●	●	●	●	●	●	●
Recording of all colposcopy results	●	●	●	●	●	●	●
Reporting of all pregnancies and outcomes[5]	●	●	●	●	●	●	●
Recording of immunosuppressants/immune modifying drugs	●	●	●	●	●	●	●
Telephone or e-mail[6] contact to remind subject to return to the site for a visit		○	○	○	○	○	○
Exit Colposcopy[7]							●
Study Conclusion							●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
1 Pelvic examinations for collection of cervical specimens are interrupted in women known to be pregnant and will resume 3 months after resolution of the pregnancy. Missed study procedures are not rescheduled. All routine pregnancy visits are to be conducted according to local medical practice and are not within the scope of this study. During the subject's pregnancy, investigators are to strictly follow the reporting guidelines according to the protocol-specified clinical procedures.
2 Women with abnormal cervical cytologies are evaluated according to an established clinical management algorithm.
3 CT/NG screening was performed at study entry and thereafter on a yearly schedule unless this conflicts with national medical recommendations.
4 The following do not require reporting as long as they are not considered SAEs: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, vaginitis, vulvitis, menstrual cycle abnormalities, injury, visits for routine physical examination/procedures or visits for vaccination. In addition, the following do not need to be recorded: ER visits due to common diseases, physician visits due to common diseases, physician visits for routine physical examinations/procedures or vaccination or physician visits for prescription refills.
5 A Pregnancy Report Form is to be completed for each pregnancy.

6 GSK is NOT to be copied on any correspondence to subjects that would enable GSK to identify them by name.
7 To be performed within 30 days after cytology results of the Month 36 visit have been communicated to the study site on all women who have had cytologically evident abnormalities (ASC-US or LSIL) present in the 12 months preceding, and including, the Month 36 visit.

All subjects were asked for any colposcopy results and whether they experienced any SAEs, new onset chronic diseases and/or pregnancies during the time between their last visit in study HPV-001 and their first visit in study HPV-007.

Intervals between study visits: In order to adequately assess the efficacy and immune response elicited by the vaccine, time intervals were to be strictly followed. These intervals determined a subject's evaluability in the according-to-protocol (ATP) analyses. (Source: STN 125259/0, CSR 007, Table 2, p. 38, not shown here)

Selection of study population: All subjects whom the investigator could contact of the 1113 women initially enrolled in study HPV-001 and who were eligible, were invited to participate in this follow-up study.

Inclusion criteria: All subjects had to satisfy the following criteria at study entry:
- Participated in study HPV-001 and received all three doses of vaccine/control.
- Written informed consent obtained from the subject prior to enrolment (for subjects below the legal age of consent, written informed consent had also to be obtained from a Legally Acceptable Representative of the subject).

Exclusion criteria: The following criterion had to be checked at the time of study entry. If it applied, the subject should not have been included in the study:
- Decoding of the subject's treatment allocation to either the subject or the investigator in study HPV-001.

Elimination criteria: The following criteria were checked at each visit subsequent to the first visit. If any became applicable during the study, it did not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis.
- Use of any investigational or non-registered product (drug or vaccine) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period.
- Administration of immunoglobulins and/or any blood products less than 3 months prior to blood sampling.

Contraindications to subsequent doses of vaccine: Not applicable. No vaccine or control was administered during study HPV-007.

Subject withdrawal from the study: A withdrawal was defined as any subject who did not come back for the concluding visit or was not available for the concluding contact foreseen in the protocol.

Treatment allocation and randomization: No treatment was given in HPV-007. Randomization that occurred in HPV-001 was maintained in HPV-007.

Blinding: The long-term efficacy and safety follow-up in this study was performed in a blinded manner. Blinding was maintained for subjects and investigators and their study staff participating in this study with regard to the individual subject treatment (vaccine or control) assignments allocated in study HPV-001. GSK personnel directly involved in the conduct of the study were

also blinded to the individual subject treatment. Site monitors, the medical monitors for this study, as well as laboratory and data validation personnel did not have access to any individual unblinded subject data from HPV-001. In order to maintain the study blind, the interim analyses (Month 12 and Month 24) and the final analysis (Month 36) were performed by an external statistician.

For the North American cohort, data were unblinded after completion of the statistical analysis of study HPV-007 in order to allow subjects to enroll in the open label fourth dose study HPV-024. The safety data in this report were presented in a blinded manner in order to avoid any risk for unblinding of subjects from the Brazilian cohort participating in a blinded extension study. Partial unblinding of safety data from one cohort could reveal single events that occurred in the other cohort and thus jeopardize the study blind in HPV-023.
Reviewer's Comment: Safety data for adverse events were reviewed from wunsol.xpt dataset.

The sponsor noted that at the end of study HPV-001, HPV DNA PCR test results were disclosed to investigators for clinical management. At the end of study HPV-007, HPV DNA PCR results were only disclosed to North-American investigators. Investigators participating in the extension study HPV-023 were only informed about the presence of oncogenic HPV types in the last sample collected in study HPV-007.

Prior and concomitant medication/vaccinations: All concomitant medication, with the exception of vitamins and/or dietary supplements, which were used for treatment of an adverse event, as well as immunomodulating treatment were recorded.

Assessment of efficacy variables
The efficacy variables assessed were:
- The presence of HPV-type specific DNA detected by PCR in cervical specimen.
- The presence of HPV-type specific DNA detected by PCR in biopsy samples.
- Histopathologically confirmed (biopsy samples) CIN1+ and CIN2+.
- Cytologically confirmed (cervical specimen) ASC-US, LSIL, HSIL, AGC and ASC-H.

Cytology: Cytology was collected every 6 months and processed in a similar fashion to study HPV-001. The slides were stained and evaluated by laboratory personnel using the 2001 Bethesda classification system for reporting cervical cytology diagnoses (as was done with conventionally prepared Pap cytology specimen tests).

HPV DNA PCR testing in --b(4)---- material: To test for HPV DNA, SPF10 primers which amplify a 65 nucleotide region of the HPV L1 gene for most of the known HPV isolates were used; the generic amplification products are detected by hybridization on a microtiter plate. HPV-positive specimens were typed by reverse hybridization line probe assay, using type-specific hybridization probes. This typing process enabled detection of 14 oncogenic HPV types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and 11 low-risk HPV types (HPV-6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74). Any specimen testing positive using the "generic" PCR assay was also tested by HPV-16/18 type-specific PCR. HPV-16 type-specific PCR uses primers that amplified a 92 nucleotide segment of the E6/E7 gene; HPV-18 type-specific PCR used primers that amplified a 126 nucleotide segment of the L1 gene.

Hybrid Capture II testing: "Reflex" testing by Hybrid Capture II (HCII) was performed to guide subject's clinical management in case of ASC-US. After preparation of the ThinPrep® cytology slides, cervical specimens read as ASC-US were automatically tested for HPV DNA

using the residual ---b(4)-------- material. Testing was done by Quest Diagnostics using the HCII test (Digene Corp., Gaithersburg, MD, USA). Probe B was used, designed to detect infections with 13 oncogenic HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). This test does not provide type-specific data, and additional HPV DNA testing by PCR was required to define trial endpoints, as described above.

Histopathology: Protocol-specified management algorithms were provided for specific histopathological abnormalities. Clinical management of women with abnormal cytology within the study was aimed to achieve biopsy diagnosis and excisional treatment in a standardized manner for all high-grade cervical lesions. The algorithms were based on the standards of care accepted for women undergoing screening within a range of national screening programs, including the practices defined by individual countries participating in this study. The algorithms presented in this study were designed to provide a consistent method of detection, clinical management and reporting for cervical lesions. The clinical management algorithms differed slightly from the algorithms used in HPV-001 as medical practice evolved. One of the main differences in the algorithms used in HPV-001 and HPV-007 pertained to the use of HCII: in HPV-007 reflex testing by HCII is performed on all ASCUS cytologies, while in HPV-001 no HCII testing was performed.

Histopathological analysis: Tissue specimens were read as specified in study HPV-001. collected by cervical biopsy or from excisional therapy was fixed in neutral buffered ---b(4)-- and submitted for evaluation to Dr. Ronald Luff (Quest Diagnostics). Dr. Luff headed an expert panel of three gynecologic pathologists. Two pathologists from the expert panel independently evaluated each case. In the cases with discrepant diagnoses, a third pathologist from the panel independently reviewed the diagnosis. A diagnosis agreed by two group members was required to define the endpoint diagnosis. Tissue specimens from women having biopsies performed outside the study HPV-007 or who had a biopsy between the end of study HPV-001 and the beginning of HPV-007 were to be retrieved for histology review by Quest Diagnostics and HPV DNA PCR testing.

HPV DNA PCR testing in tissue: The -----b(4)---------- embedded tissue blocks used for histopathological analysis at Quest Diagnostics were sectioned for PCR examination at DDL. Sections were tested for HPV DNA using PCR methodology. Samples of lesions were selected for further analysis using micro-dissection if appropriate (e.g. if there were multiple lesions in a single section or if there was a small lesion in a large tissue sample). To test for HPV DNA, SPF10 primers were used as described above.

Chlamydia trachomatis and Neisseria gonorrhea testing: An endocervical swab was taken for *Chlamydia trachomatis* and *Neisseria gonorrhea* testing at study entry (Visit 1) and thereafter on a yearly schedule unless this conflicts with national medical recommendations. Quest Diagnostics used the specimen to prepare aliquots for nucleic acid hybridization testing for *Chlamydia trachomatis* DNA and *Neisseria gonorrhoeae* DNA by the ----------b(4)----------

Assessment of immunogenicity variables

Laboratory assays and time points: At months 0, 12, 24 and 36, 10 ml of whole blood (to provide a minimum of 3 ml of serum) was taken from each subject for serology testing. Serological assays were performed at GSK Biologicals' laboratories using standardized validated procedures with adequate controls.

Anti-HPV-16 and anti-HPV-18 ELISA: Anti-HPV-16 and anti-HPV-18 ELISA testing was performed on serum from all subjects using a methodology developed by ----b(4)----------. and modified by GSK Biologicals to evaluate antibody persistence. This assay was described in study HPV-001.

V5/J4 monoclonal inhibition enzyme immunoassay: Sera from a subset of subjects were tested for anti-HPV-16 and anti-HPV-18 antibodies using V5/J4 monoclonal antibody inhibition enzyme immunoassays. These are as described in study HPV-001. The same randomly defined subset of 100 vaccinees and 50 control subjects who had serum samples available in study HPV-007 were tested for the current analysis.

HPV-16 and HPV-18 neutralizing antibodies: At the discretion of GSK, sera from the same subset of subjects who have their sera tested by V5/J4 monoclonal inhibition enzyme immunoassays may have been tested for HPV-16 and HPV-18 neutralizing antibodies.

Assessment of safety variables

Adverse events: Adverse events that occurred between the last visit of study HPV-001 and entry into study HPV-007 and throughout the entire study period of HPV-007 were collected and recorded. The following events are recorded as adverse events: serious adverse events; new onset chronic diseases, (for example diabetes mellitus, autoimmune diseases); other conditions prompting either emergency room visits or physician visits that are not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, vaginitis, vulvitis, menstrual cycle abnormalities, and injury. The following were not recorded as adverse events: physician visits for routine physical examinations/procedures or vaccination, or physician visits for prescription refills.

Grading of intensity: The grading system was the same as noted for unsolicited adverse events in study HPV-001- (mild, moderate, severe).

Relationship to vaccination: The investigator was to assess relationship to vaccination.

Follow-up of adverse events was as noted in study HPV-001 with outcome.

Pregnancy: The investigator was to collect pregnancy information on any subject who became pregnant between the last visit of HPV-001 and before the start of HPV-007, and during the entire study period. Outcome was to be reported.

STATISTICAL CONSIDERATIONS

Primary endpoint: Incident cervical infection with HPV-16 and/or HPV-18.

Secondary endpoints

- Persistent cervical infection (6-month definition) with HPV-16 and/or HPV-18.
- Incident cervical infection with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
- Persistent cervical infection (6-month definition) with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
- Histopathologically-confirmed CIN1+ or CIN2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR). CIN1+ is defined as CIN1, CIN2, CIN3, adenocarcinoma in situ (AIS) and invasive cervical cancer. CIN2+ is defined as CIN2, CIN3, AIS and invasive cervical cancer.

- Histopathologically-confirmed CIN1+ or CIN2+ associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) detected within the lesional component of the cervical tissue specimen (by PCR).
- Abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with an HPV-16 and/or HPV-18 cervical infection.
- Abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) cervical infection.

Other endpoints

- Persistent cervical infection (12-month definition) with HPV-16 and/or HPV-18.
- Persistent cervical infection (12-month definition) with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
- HPV-16 and HPV-18 antibody titers (by ELISA) in all study subjects, and V5/J4 monoclonal antibody inhibition tests and/or neutralizing antibodies in a subset of subjects.
- Occurrence of serious adverse events, new onset chronic diseases (e.g. diabetes mellitus, autoimmune diseases) and other conditions prompting either emergency room visits or physician visits that are not related to common diseases throughout the entire study period. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, vaginitis, vulvitis, menstrual cycle abnormalities and injury.

Determination of sample size: Of the 1113 subjects initially enrolled in study HPV-001, all subjects whom the investigator could contact and who were eligible were invited to participate in this follow-up study. It was estimated that approximately 500 subjects would enroll in this long-term follow-up study. The primary objective of this study was to evaluate the long-term vaccine efficacy in the prevention of incident cervical infection with HPV-16 and/or HPV-18 in adolescent and young adult women who received 3 doses of the study vaccine/control in study HPV-001 and who were previously uninfected with HPV-16 or HPV-18.

Table 56-Study HPV-007: Estimated Attack Rate Incidence in All Specimens

Attack Rate incidence in All Specimens	Placebo	Vaccine
HPV-16 and/or 18	3.50%	1.05%

The number of evaluable subjects needed depended on the attack rate in the control population, anticipated vaccine efficacy, and the power of the study to detect differences between the vaccine and control groups. Even though the calculated sample size gave approximately 80% power to detect a vaccine efficacy level of 70%, the observation of a higher level of efficacy was expected to provide greater statistical power for the primary endpoint analysis.

Table 57-Study HPV-007: The Expected Incidence of Cervical Infections and Power

All	Year 0	Year 1	Year 2	Year 3	Total	Power at end of trial*
N	500	425	361	307		
n HPV-16 and/or HPV-18		10	8	7	25	80%
N	605	514	437	371		
n HPV-16 and/or HPV-18		12	10	8	30	85%
N	720	612	520	442		
n HPV-16 and/or HPV-18		14	12	10	36	90%

*Power to detect a vaccine efficacy level of 70% based on 15% annual attrition, computed by SAS program
N = number of subjects enrolled; n HPV-16 and/or HPV-18 = number of expected cases of HPV-16 and/or HPV-18 positives
Source: STN 125259/0, CSR 007, Table 3, p. 51

Study cohorts/data sets analyzed: For the interim analysis, two study cohorts were defined to perform the data evaluations on: an according-to-protocol (ATP) cohort and a Total cohort. The analysis of the ATP cohort was the primary analysis; the analysis of the Total cohort was the secondary analysis.

- **ATP cohort for analysis of efficacy:** The ATP cohort for primary analysis of efficacy included all subjects meeting all eligibility criteria in studies HPV-001 and HPV-007, complying with the procedures defined in the HPV-007 protocol, and for whom data concerning efficacy endpoint measures were available.
- **ATP cohort for analysis of immunogenicity:** The ATP cohort for primary analysis of immunogenicity included all evaluable subjects: those meeting all eligibility criteria in studies HPV-001 and HPV-007, complying with the procedures defined in the protocol and fulfilling requirements for analysis, and for whom data concerning immunogenicity were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component at least one blood sampling time point.
- **ATP cohort for analysis of safety:** The ATP cohort for primary analysis of safety included all evaluable subjects who did not use any investigational product during the study period.
- **Total cohort:** The secondary cohort/dataset used for statistical analysis was the Total cohort or intention-to-treat (ITT) cohort. The Total cohort included all enrolled subjects who came at first visit.
  - For the **total analysis of efficacy**, this included enrolled subjects for whom data concerning efficacy endpoint measures were available.
  - For the **total analysis of immunogenicity,** this included enrolled subjects for whom data concerning immunogenicity measures were available.
  - For the total **analysis of safety,** this included enrolled subjects for whom safety data were available.

Analysis of demographics: Demographic characteristics (age, race) of each study cohort were tabulated.

Analysis of efficacy: The primary analysis was based on the ATP cohort for analysis of efficacy. The second analysis based on the Total (or ITT) cohort was performed to complement the ATP analysis. The analysis of efficacy was performed on different ATP/ITT cohorts, depending on the HPV types evaluated.

- For the primary analysis of efficacy against infection with HPV-16 and/or HPV-18, the ATP cohort included subjects who had received 3 vaccine doses (in HPV-001), who were seronegative for HPV-16 or HPV-18 at Month 0 (in HPV-001) and who were negative for high-risk HPV DNA at study entry of HPV-001 (Month 0) and negative for HPV-16 or HPV-18 DNA at Month 6 (in HPV-001).

- For the primary analysis of efficacy against infection with any high-risk HPV type (HPV-HR) or any high-risk HPV type excluding HPV-16 and HPV-18 (HPV-HRW), the ATP cohort included subjects who had received 3 vaccine doses (in HPV-001), who were seronegative for HPV-16 or HPV-18 at Month 0 (in HPV-001) and who were negative for high-risk HPV DNA at Month 0 and Month 6 (in HPV-001).
- For the primary analysis of efficacy against infection with each individual high-risk HPV type, the ATP cohort included subjects who had received 3 vaccine doses (in HPV-001) and who were DNA negative for the specific HPV type considered at Month 0 and Month 6 (in HPV-001).
- For the analysis of efficacy against infection with HPV-16 and/or HPV-18, HPV-HR and HPV-HRW, the ITT cohort included subjects who had received at least one vaccine dose and who were negative for high-risk HPV DNA at Month 0 in HPV-001.
- For the analysis of efficacy against infection with each individual high-risk HPV type, the ITT cohort included subjects who had received at least one vaccine dose and who were DNA negative for the specific HPV type considered at Month 0 in HPV-001.

In addition, for each type of endpoint in study HPV-007 (incident infection, persistent (6-month) infection, persistent (12-month infection), cytological abnormality ≥ASC-US, cytological abnormality ≥LSIL, CIN1+ or CIN2+), subjects who encountered the equivalent or higher endpoint associated with the corresponding HPV type in study HPV-001 were not evaluable.

Analysis of HPV-007 efficacy data: For the primary objective, the incidence of HPV-16 and/or HPV-18 cervical infection was compared between the two groups using the Fisher exact test.
- Vaccine efficacy (VE) against all incident cervical infections was measured by the time-to-occurrence approach and the Conditional exact approach (ATP and ITT cohort).
- Vaccine efficacy against all persistent cervical infections was measured by time-to-occurrence approach and Conditional exact approach (ATP and ITT cohort).
- Description of abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with an HPV-16 and/or HPV-18 cervical infection.
- Description of abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with any/each oncogenic HPV type cervical infection.
- Description of histopathologically-confirmed CIN1+ or CIN2+ associated with HPV-16 and/or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR).
- Description of histopathologically-confirmed CIN1+ or CIN2+ associated with any/each oncogenic HPV type detected within the lesional component of the cervical tissue specimen (by PCR).

Pooled analysis between HPV-001 and HPV-007: A pooled analysis between efficacy data of HPV-001 and HPV-007 was performed. The analysis was descriptive. For each endpoint, the point estimate of the vaccine efficacy and 95% confidence interval (CI) were provided.
For incident infection, two kinds of analyses were performed:
- Cervical samples only: analyses were performed on the pooled database using only cervical samples, by applying the same methods as used for the HPV-007 analyses.
- All samples combined: analyses were performed on the pooled database using all samples (i.e. cervical and cervicovaginal) for HPV-001 and cervical samples for HPV-007, by applying the same methods as used for the HPV-007 analyses.

For persistent infection, two kinds of analyses were performed:
- **Cervical samples only:** analyses were performed on the pooled database using only cervical samples, by applying the same methods and definitions as used for the HPV-007 analyses.

- **All samples combined:** analyses were performed on the pooled database using all samples (i.e. cervical and cervicovaginal) for HPV-001 and cervical samples for HPV-007, by applying the same methods and definitions as used for the HPV-007 analyses.

Reviewer's Comment: This review includes the HPV-007 analyses primarily, although the sponsor provided a further statistical adjustment which was used to pool specimens from HPV-001 and HPV-007. A subject was counted once in the pooled analyses.

For abnormal cytology, one analysis was performed by pooling results from HPV-001.

For histopathology, one analysis was performed by pooling results from HPV-001 and HPV-007. For the pooled analysis, association with HPV infection(s) was defined by the HPV DNA type(s) detected by PCR in the cervical biopsy which led to the histopathological diagnosis.

Case definitions for efficacy

- Incident cervical HPV infection is defined as the first detection of an HPV type (by PCR) in a subject previously negative for that HPV type; incident infections may be transient or become persistent.
- Persistent cervical HPV infection (6-month definition) is defined as detection of the same HPV type by PCR in cervical specimens at two consecutive evaluations over a minimum period of five months, with no negative sample in between (must include at least one evaluation in 580299/007; visits are planned at approximately six-month intervals).
- Persistent cervical HPV infection (12-month definition) is defined as detection of the same HPV type by PCR in cervical specimens at all consecutive evaluations over a minimum period of ten months, with no negative sample in between (must include at least one evaluation in 580299/007).
- Previously uninfected with HPV-16 and HPV-18 is defined as a subject who tested HPV-16 and HPV-18 seronegative (by ELISA) prior to vaccination, and HPV-16 or HPV-18 DNA negative (by PCR) for that type in all specimens previously collected in study 580299/001 and study 580299/007.
- Previously uninfected with an oncogenic HPV type is defined as HPV DNA negative (by PCR) for that type in all specimens previously collected in study 580299/001 and study 580299/007.

Primary analysis: Vaccine efficacy for all endpoints was calculated using a Conditional exact method.

Confirmatory analysis: In addition to the primary analysis, VE and its CI were also calculated using a Cox regression model.

Vaccine efficacy using an unconditional asymptotic method: For the endpoints where no cases were accrued in the vaccine group, the unconditional asymptotic method was used to estimate VE and its CI.

Covariate analysis: Exploratory analyses to assess the effect of some covariates on vaccine efficacy for the endpoints related to HPV-16 and/or HPV-18 were planned for both HPV-007 and pooled HPV-001/007 data. At the time of the first interim report, only one covariate analysis was performed evaluating the effect of geographical region.

Reviewer's Comment: Please see statistical review for details.

Analysis of immunogenicity: The primary analysis was based on the ATP cohort for analysis of immunogenicity. A second analysis based on the Total cohort was performed to complement the ATP analysis.

For each treatment group, at each time point that a blood sample result was available:

- seropositivity rates for both HPV-16 and HPV-18 ELISA titers and V5/J4 monoclonal antibody inhibition tests and/or neutralizing antibodies (with exact 95% CI) were calculated by group,
- GMTs with 95% CI were tabulated for antibodies for each antigen and each test,
- antibody titers/concentrations post-vaccination were also investigated by group using reverse cumulative curves for each antigen and each test.

Analysis of safety: The primary analysis was based on the ATP cohort for analysis of safety. A second analysis based on the Total cohort was performed to complement the ATP analysis. The analysis was performed per protocol despite some inconsistencies in the RAP.

Adverse events

- Occurrence of adverse events (AEs), new onset chronic diseases (NOCD) and serious adverse events (SAEs) recorded between the end of study HPV-001 and data lock point of the first interim report (7/31/05) were tabulated.
- The proportion of subjects with at least one report of an adverse event classified by MedDRA (Medical Dictionary for Regulatory Activities), whenever available, was tabulated with exact 95% CI.
- NOCDs were reported (by GSK and investigators.) This review was done using a pre-defined list of potential chronic diseases or signs/symptoms that could evoke NOCD, with their associated MedDRA codes. The list was provided with previous studies, and explained. The proportion of subjects with at least one report of NOCD classified by MedDRA, whenever available, was tabulated with exact 95% CI. A separate table was produced for NOCD based on the Investigator assessment and GSK assessment, respectively.
- Serious adverse events and withdrawal due to adverse event(s) were described in detail.

Pregnancies: Pregnancies and their outcome were described in detail. Pregnancies described in the interim report were recorded between the end of study HPV-001 and data lock point (7/31/05).

Interim analysis: Two interim analyses were planned. The first one was performed after one year of follow-up and is described in the first report. The second interim analysis was performed after two years of follow-up, and described in the second interim report. The purpose of these analyses was to provide an overview of long-term efficacy, immunogenicity and safety data to regulatory authorities. No stopping rule was applied and follow-up continued for all subjects until Month 36.

- The interim analyses evaluated vaccine efficacy (VE) in the prevention of incident cervical infection with HPV-16 and/or HPV-18 in order to show VE>0, assuming a true VE = 70%. In addition, VE in the prevention of incident cervical infection with any/each HPV oncogenic type was evaluated.
- Protection against persistent cervical infection (6-month definition) with HPV-16 and/or HPV-18 as well as with any/each HPV oncogenic type was assessed.
- Cytologically abnormalities or histopathologically confirmed CIN1+ or CIN2+ associated with HPV-16 and/or HPV-18 or with any/each HPV oncogenic type was described.
- An immunogenicity analysis (to assess anti-HPV-16 and anti-HPV-18 levels) was performed.

The sponsor notes that the interim analyses were performed by an external statistician. All GSK personnel directly involved in the conduct of the study, investigators and their study staff remain blinded to individual subject assignments. Alpha values are noted.

Changes in the conduct of the study or planned analyses
Protocol amendments/modifications
Amendment 1 (dated 12/15/04):

- To align the HPV-007 study with respect to the objectives, clinical procedures (including logistics) and clinical management of subjects to the pivotal phase III efficacy study HPV-008.
- To include additional instructions regarding the clinical management algorithm and to clarify the clinical management in the case of missing specimens.
- To specify that subjects will be asked for their consent to allow the study site to obtain tissue for histopathological evaluation and HPV DNA testing (PCR) by a GSK designated laboratory from cervical specimens that are obtained outside study HPV-007, either between the end of study HPV-001 and the beginning of HPV-007 or during HPV-007.
- To clarify the statistical plan for interim analyses.
- To extend enrolment to accommodate the turnaround time of regulatory documents at some sites.

Amendment 2 (dated 10/9/06):
The major changes were as follows:

- Due to the licensure of Merck's HPV vaccine, Gardasil®, the study procedures were revised to determine if subjects had received an HPV vaccine other than that used in study HPV-001. Subjects found to have received an HPV vaccine other than that used in study HPV-001 or unblinded to determine if they would consider immunization with a licensed HPV vaccine outside of the study, were to be withdrawn from further participation in the study.
- Subjects withdrawn because of (1) the administration of an HPV vaccine other than that used in study HPV-001 or (2) following a request to be unblinded were offered an exit gynaecological examination depending on previous results.
- The instructions for exit colposcopy were clarified with respect to cytology results.
- The introduction was updated to include actual safety data.
- An exploratory objective and endpoint were added to describe the occurrence of histopathologically confirmed VIN and VaIN.
- An extension to the long-term efficacy, immunogenicity and safety follow-up was planned (study 109616/109624/109625 [HPV-023 Ext 001]). In order to preserve the blinding in this extension study, HPV-PCR results obtained during study HPV-007 were not to be disclosed at study completion to subjects/sites eligible for participation in study HPV-023. However, subjects and investigators participating in the extension study HPV-023 were to be informed about the presence/absence of oncogenic HPV types after HPV-007 study completion.
- Methods for detection of AEs were updated to allow for autoantibody testing on prevaccination sera and other sera samples collected during the studies HPV-001 and HPV-007, in case an autoimmune disease was diagnosed during the study.
- The concomitant medication section was further clarified to include reporting of any HPV vaccine other than that used in study HPV-001.

Other Changes

Changes to the planned analysis: In study HPV-001, the follow-up period differed among subjects. In addition, subjects were enrolled in study HPV-007 on dates that were independent from the date of their enrolment in study HPV-001. As a result, the proposed attack rates method for the efficacy analysis was not adequate. Therefore, the Cochran-Mantel-Haenszel statistic (as originally planned in the protocol) was replaced by the Conditional exact method. The Cox regression method which models the time-to-occurrence was presented as confirmatory analysis. VE was calculated using incidence rates and using all subjects that had at least one visit in HPV-007 with available efficacy data.

Reviewer's Comment: Please see statistical review for comments.

Modified efficacy endpoint: According to the protocol, abnormal cytology (ASCUS, LSIL, HSIL, AGC, ASC-H) associated with HPV-16 and/or HPV-18 or with any/each oncogenic HPV type was to be evaluated. Prior to the current interim analysis, it was decided to modify the cytological analysis and to evaluate not only vaccine efficacy against cytological abnormalities greater than or equal to ASCUS (associated with HPV-16 and/or HPV-18 or with any/each oncogenic HPV type) but also vaccine efficacy against cytological abnormalities greater than or equal to LSIL.

Additional efficacy endpoints: In addition to the protocol specified efficacy endpoints, a post hoc analysis was performed to evaluate the long-term vaccine efficacy in the prevention of histopathologically-confirmed CIN2+, irrespective of HPV DNA status.

Changes to planned safety analysis: An additional analysis of NOADs (a subset of NOCDs) was performed.

Changes to planned immunogenicity analysis: A post hoc analysis of immunogenicity was performed on the ATP kinetic cohort (all subjects from the vaccine group included in the ATP cohort for immunogenicity and having an ELISA result at all time points in study HPV-001 and at the Months 33-38, 45-50, 57-62 and 69-74 intervals in study HPV-007).

Modified subset for anti-V5 HPV-16 and anti-J4 HPV-18 testing: In the protocol, it is stated that V5/J4 analysis would be performed on study participants who meet the following criteria:

- One hundred randomly selected subjects who received all three doses of vaccine in study HPV-001, who had serum available from visits 1, 4 and 8 (months 0, 7 and 18) in study HPV-001, and who will have serum available from visits 1, 3, 5 and 7 in the current study (HPV-007). This subset will comprise those vaccinated subjects that were already selected for V5/J4 testing in study HPV-001.
- All subjects who become infected with HPV-16 or HPV-18 during study HPV-007.
- Twenty randomly selected subjects who received all three control doses during study HPV-001, who had serum available from visits 1, 4 and 8 (months 0, 7 and 18) in study HPV-001, and who will have serum available from visits 1, 3, 5 and 7 in the current study (HPV-007).

However, for the first interim analysis, V5/J4 analysis was performed on the same subset of subjects who where already selected for V5/J4 testing in study HPV-001 (i.e. randomly selected subjects who received all three doses of vaccine/control and had serum samples available for visits 1, 4 and 8 (months 0, 7 and 18) in study HPV-001) and who had serum samples available in study HPV-007.

RESULTS

HPV-007, Month 36 Report: The study was completed August 9, 2007, and the report was dated March 2008.

Study Population Results

Study dates: Visit 1 (Day 0) of study HPV-007 occurred on any day from 11/10/03 through 7/17/04. The last study-related activity was performed on 8/9/07.

Table 58-Study HPV-007: Number of Subjects by Region (Total Cohort)

Geographical region	HPV	Aluminum hydroxide control	Total (%)
Brazil	230	218	448 (57.7%)
North America	163	165	328 (42.3%)
ALL	393	383	776 (100%)

HPV = HPV-16/18 L1/AS04 (DVLP017A)
Control = Control(DVLP018A)
N = number of subjects included in each group or in total for a given center in each region or for all centers
all = sum of subjects in each region from each group or in total (sum of all groups)
All = sum of all subjects in each group or in total (sum of all groups)
% = n / All x 100
Center = GSK Biologicals assigned center number
Source: STN 125259/0, CSR 007, Table 4, p. 64

Study compliance and follow-up time: An overview of the number of subject who attended each study visit is presented in Table 59. Study compliance with each study visit was high in both groups. Overall, 700 of the 776 enrolled subjects (90.2%) completed the study.

Table 59-Study HPV-007: Number of Subjects Per Visit (Total Cohort)

	Vaccine N = 393		Placebo N = 383		Total N = 776	
Visit	**n**	**%**	**n**	**%**	**n**	**%**
Visit 1	393	100	383	100	776	100
Visit 2	377	95.9	371	96.9	748	96.4
Visit 3	372	94.7	369	96.3	741	95.5
Visit 4	364	92.6	354	92.4	718	92.5
Visit 5	363	92.4	351	91.6	714	92.0
Visit 6	355	90.3	342	89.3	697	89.8
Visit 7	359	91.3	340	88.8	699*	90.1

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
N = total number of subjects with available results
n/% = number / percentage of subjects attending each visit
* Subject no. 7430 did not attend Visit 7 as she moved temporarily out of the study area. However, safety data were collected and therefore this subject was not withdrawn from the study.
Source: STN 125259/0, CSR 007 M36, Table 5, p. 78

The mean follow-up period from the start of study HPV-001 until the end of study HPV-007 (Month 36) was 5.9 years, (2164.1 days-standard deviation of 98.31 days), with a maximum duration of 6.4 years (2341.0 days). (Source: STN 125259/0, CSR 007 M36, Table 6, p. 78, not shown here). The mean follow-up period from Month 6 (after completion of vaccination) of study HPV-001 until the end of study HPV-007 (Month 36) was approximately 5.5 years (66 months) or 1987.0 days (standard deviation of 97.76 days). (Source: STN 125259/0, CSR 007 M36, Table 7, p. 79, not shown here).

Study completion and withdrawal from study: Of the 776 enrolled subjects, 76 subjects prematurely discontinued the study, of whom 34 were in the vaccine group and 42 were in the control group. The main reasons for withdrawal included lost to follow-up (34 subjects), consent withdrawal not due to an AE (17 subjects, reason not specified), migration/move from the study area (10 subjects) and other reasons (10 subjects, including mainly pregnancy and inability to attend the visit). In addition, five subjects were withdrawn due to a protocol violation.

Table 60-Study HPV-007: Number of Subjects Enrolled, Completed and Withdrawn With Reason for Withdrawal (Total Cohort)

	Vaccine	Placebo	Total
Number of subjects enrolled	393	383	776
Number of subjects completed	359	341	700
Number of subjects withdrawn	34	42	76
Reasons for withdrawal :			
Serious Adverse Event	0	0	0
Non-serious adverse event	0	0	0
Protocol violation	3	2	5
Consent withdrawal (not due to an adverse event)	7	10	17
Migrated/moved from study area	4	6	10
Lost to follow-up	16	18	34
Others	4	6	10

Vaccine = HPV-16/18 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
Source: STN 125259/0, CSR 007 M36, Table 8, p. 79

One subject (Subject no. 7430) did not attend the last study visit at Month 36 (Visit 7), but was not withdrawn from the trial. As a result, a total of 699 subjects completed Visit 7, while 700 subjects completed the study. During the course of study HPV-007, Gardasil was licensed for use in women aged 9 to 26 years, and 10 study participants requested information on their treatment allocation (in study HPV-001). The unblinding was performed after the subjects completed their last study visit at Month 36 and therefore these subjects were not withdrawn from the study.

Protocol deviations leading to exclusion of subjects from an analysis: The number of subjects excluded from the ATP analyses and the reasons for exclusion are shown in Table 61 for safety and efficacy analyses and in Table 62 for the immunogenicity analysis. Depending on the endpoints and HPV types evaluated, the number of subjects for each ATP efficacy analysis may differ and be less than the potential number of subjects eligible for the protocol-defined ATP cohort for efficacy. Some subjects were excluded from the ATP analyses based on elimination codes already attributed in study HPV-001. Four subjects did not receive the full vaccination course in HPV-001 and were enrolled by error in HPV-007. In addition, seven subjects had received a replacement vial in HPV-001 (all replacement doses were control in study HPV-001) and thus were to be excluded from the ATP cohort as they were randomized to the HPV vaccine group.

Table 61-Study 007: Number of Subjects Enrolled Into the Study and the Number of Subjects Excluded from ATP Analysis of Safety and Efficacy with Reasons for Exclusion (Total Cohort)

	Total			Vaccine		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Number of vaccines prepared	776			393		383	
Total enrolled cohort	776			393		383	
Total cohort	776		100	393		383	
Administration of vaccine(s) forbidden in the protocol (code 1040)	20	20		9	9	11	11
Randomisation failure (code 1050)*	7	7		7	7	0	0
Randomisation code broken at the investigator site (code 1060)	3	3		1	1	2	2
Did not receive three doses in HPV-001 (code 1500)	4	4		3	3	1	1
ATP safety cohort	**742**		**95.6**	**373**		**369**	
Protocol violations (code 3010)*	6	6		2	2	4	4
Administration of any medication forbidden by the protocol (code 3040)	4	5		1	1	3	4
No compliance with vaccination schedule (code 3080)*	11	17		6	11	5	6
Missing result (HPV DNA or Cyto or Sero) at Month 0 or at screening (code 3100)*	20	21		11	12	9	9
Seropositive (for HPV-16 or HPV-18) or abnormal cytology at screening (code 3900)*	12	16		4	8	8	8
ATP cohort for efficacy	**689**		**88.8**	**349**		**340**	

Vaccine = HPV-16/18 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total cohort
*Elimination code already assigned in study HPV-001 only
Source: STN 125259/0, CSR 007 M36, Table 9, p. 81

In order to evaluate the immune response to the vaccine in naïve subjects, factors possibly influencing the immune response were to be considered. Therefore, subjects developing a concomitant HPV infection, which may influence the HPV antibody levels, were excluded from the ATP cohort for immunogenicity. Due to the vaccine efficacy, more subjects developed HPV-16/18 infections in the control group than in the vaccine group (122 vs. 36 subjects) and thus were eliminated from the ATP cohort for immunogenicity. Of note the Total cohort for immunogenicity includes these subjects.

Reviewer's Comment: Results were reviewed for the Total cohort for immunogenicity.

Table 62-Study 007: Number of Subjects Enrolled Into the Study and the Number of Subjects Excluded from ATP Analyses of Safety and Immunogenicity With Reasons for Exclusion (Total Cohort)

	Total			Vaccine		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Number of vaccines prepared	776			393		383	
Total enrolled cohort	776			393		383	
Total cohort	776		100	393		383	
Administration of vaccine(s) forbidden in the protocol (code 1040)	20	20		9	9	11	11
Randomisation failure (code 1050)*	7	7		7	7	0	0
Randomisation code broken at the investigator site (code 1060)	3	3		1	1	2	2
Did not receive three doses in the HPV-001 (code 1500)	4	4		3	3	1	1
ATP safety cohort	**742**		**95.6**	**373**		**369**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	6	10		2	5	4	5
Initially seropositive or initially unknown antibody status (code 2020)*	25	26		10	11	15	15
Administration of any medication forbidden by the protocol (code 2040)	4	5		1	1	3	4
Concomitant infection related to the vaccine which may influence immune response (code 2060)	141	158		32	36	109	122
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)*	14	31		9	20	5	11
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	14	23		9	14	5	9
Essential serological data missing (code 2100)	3	7		2	4	1	3
ATP immunogenicity cohort	**535**		**68.9**	**308**		**227**	

Vaccine = HPV-16/18 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total cohort
*Elimination code already assigned in study HPV-001 only
Source: STN 125259/0, CSR 007 M36, Table 10, p. 82

Protocol deviations not leading to exclusion of subjects from an analysis: Protocol visit intervals were not used to eliminate subjects from the analyses. One subject had a deviation from the informed consent procedure which occurred during study HPV-007.

Demographic characteristics: The demographic characteristics by region for the ATP cohort for efficacy are presented in Table 63.

Table 63-Study 007: Summary of Demographic Characteristics by Region (ATP Cohort for Efficacy)

		Brazil		North America		Total	
		Vaccine N=214	Control N=196	Vaccine N=135	Control N=144	Vaccine N=349	Control N=340
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)
Age HPV-001 (years)	Mean	19.8	19.8	20.8	20.9	20.2	20.3
	SD	3.2	3.0	2.6	2.5	3.0	2.8
	Median	19.0	19.0	21.0	21.0	20.0	20.0
	Min-Max	15-26	15-26	15-26	15-26	15-26	15-26
Age HPV-007 (years)	Mean	22.9	22.9	23.6	23.6	23.2	23.2
	SD	3.1	2.9	2.6	2.6	3.0	2.8
	Median	23.0	23.0	23.0	24.0	23.0	23.0
	Min-Max	18-29	18-29	17-29	17-28	17-29	17-29
Race	Black	23 (10.7%)	19 (9.7%)	8 (5.9%)	6 (4.2%)	31 (8.9%)	25 (7.4%)
	White/Caucasian	119 (55.6%)	120 (61.2%)	100 (74.1%)	107 (74.3%)	219 (62.8%)	227 (66.8%)
	Oriental	3 (1.4%)	2 (1.0%)	3 (3.0%)	3 (2.1%)	7 (2.0%)	5 (1.5%)
	Other	69 (32.2%)	55 (28.1%)	23 (17.0%)	28 (19.4%)	92 (26.4%)	83 (24.4%)

Vaccine = HPV-16/18 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = standard deviation
Source: STN 125259/0, CSR 007 M36, Table 11, p. 83

The demographic characteristics of the Total cohort were comparable to that of the ATP cohort for efficacy. (Source: STN 125259/0, CSR 007 M36, Table 12, p. 84, not shown here.)

EFFICACY RESULTS

Incident infection: The primary objective of the study was prevention of incident cervical infection with HPV-16 and/or HPV-18 in women who received three doses of vaccine in study HPV-001 and who were considered as uninfected with HPV-16 or HPV-18 at the time of vaccination.

Vaccine efficacy against HPV-16 and/or HPV-18 infection was statistically significant (VE = 96.7% [95% CI: 87.4%, 99.6%]). In addition, there was evidence of protection against HPV-16 infection alone (VE = 97.5% [95% CI: 85.3%, 99.9%]) and HPV-18 infection alone (VE = 96.3% [95% CI: 77.5%, 99.9%]).

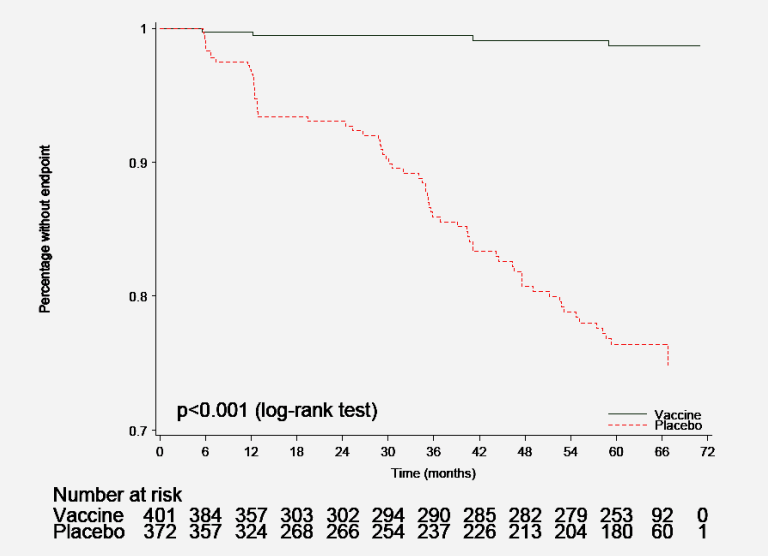
Table 64-Study HPV-007: Incidence Rates and Vaccine Efficacy Against Incident Infection with HPV-16 and/or HPV-18 (by PCR) Using Conditional Exact Method (Cervical Samples only, ATP Cohort for Efficacy) (HPV-007, Cervical Specimens)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI
HPV-16/18	Vaccine	303	2	0.2 (0.0, 0.9)	96.7% (87.4, 99.6%)
	Alum Control	267	47	7.3 (5.4, 9.7)	-
HPV-16	Vaccine	304	1	0.1 (0.0, 0.7)	97.5% (85.3, 99.9%)
	Alum Control	270	33	4.9 (3.4, 6.9)	-
HPV-18	Vaccine	303	1	0.1 (0.0, 0.7)	96.3% (77.5, 99.9%)
	Alum Control	281	24	3.3 (2.1, 4.9)	-

Vaccine = HPV-16/18; Control = Aluminum hydroxide
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for HPV-16 and HPV-18 at Month 0 and Month 6 in HPV-001
Follow-up period starts at Month 0 for HPV-001
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259.0048, CSR 007 M36, Table 13, p. 86

Reviewer's Comment: From Month 24-36, the majority of cases accrued in the control group, and 1 case accrued in the vaccine group for HPV 18. Kaplan-Meier curves are presented for incident HPV 16/18 infection.

Figure 11- Study HPV-007: Kaplan-Meier Curves for Incident Infection with HPV-16 and/or HPV-18 (Combined [pooled] HPV-001/007, Cervical Samples Only, ATP cohort for efficacy)



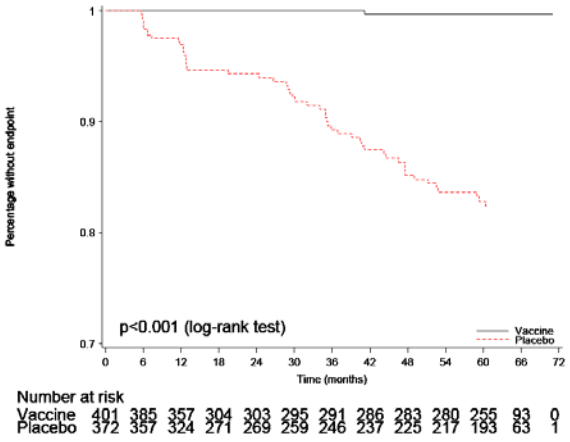
Source: STN 125259/0, CSR 007 M36, Figure 2, p. 86

Vaccine efficacy against incident infection with oncogenic HPV types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 combined) was 9.2% [95% CI: -20.6%, 31.6%].

In a *post-hoc* analysis of vaccine efficacy against incident infection with individual oncogenic HPV type with HPV-31 and HPV-45 was 42.5% [95% CI:-24.8%, 74.5%] and 70.8% [95% CI: 16.6%, 91.6%], respectively. (Source: STN 125259/0, CSR 007 M36, Table 15, p. 88-89, not shown here).

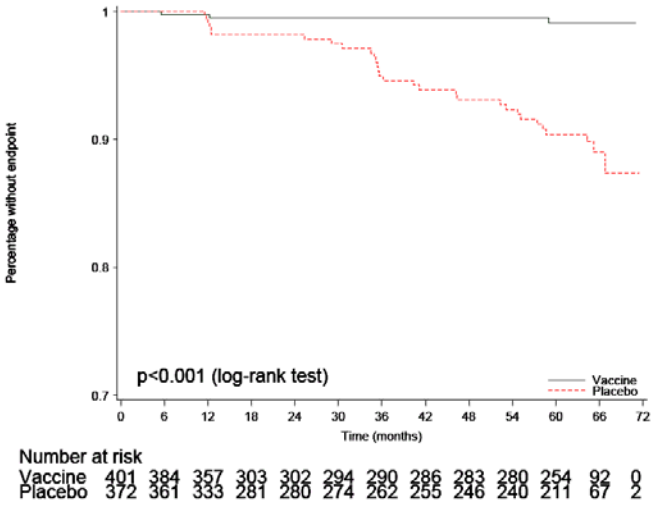
Reviewer's Comment: Kaplan-Meier curves are presented for incident HPV-16 and 18 infection over time.

Figure 12-Study HPV-007: Kaplan-Meier Curves for Incident Infection with HPV-16 (Combined [pooled] HPV-001/007, Cervical Samples Only, ATP Cohort for Efficacy)



Source: STN 125259/0, CSR 007 M36, Figure 3, p. 89

Figure 13-Study HPV-007: Kaplan-Meier Curves for Incident Infection with HPV-18 (Combined [pooled] HPV-001/007, Cervical Samples Only, ATP Cohort for Efficacy)



Source: STN 125259/0, CSR 007 M36, Figure 4, p. 90

Persistent infection (6-month definition), a secondary endpoint**:** Vaccine efficacy against HPV-16 and/or HPV-18 infection was statistically significant (VE = 100% [95% CI: 85.9%, 100%]). Vaccine efficacy against HPV-16 or HPV-18 infection alone was 100% [95% CI: 79.0%, 100%] and 100% [95% CI: 59.4%, 100%], respectively.

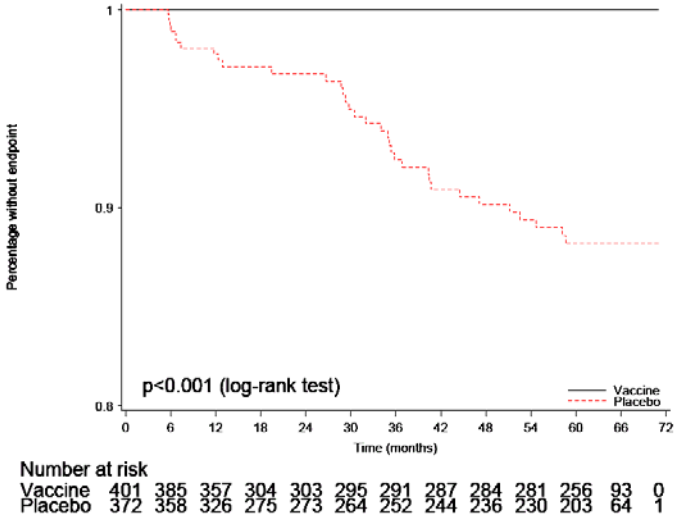
Table 65-Study HPV-007: Incidence rates and vaccine efficacy against persistent infection (6-month) with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (HPV-007, Cervical samples only, ATP cohort for efficacy)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI
HPV-16/18	Vaccine	304	0	0.0 (0.0, 0.4)	100% (85.9, 100%)
	Alum Control	277	24	3.4 (2.2, 5.0)	-
HPV-16	Vaccine	304	0	0.0 (0.0, 0.4)	100% (79.0, 100%)
	Alum Control	277	17	2.4 (1.4, 3.8)	-
HPV18	Vaccine	304	0	0.0 (0.0, 0.4)	100% (59.4, 100%)
	Alum Control	285	10	1.3 (0.6, 2.4)	

Vaccine = HPV-16/18 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for HPV-16 and HPV-18 at Month 0 and Month 6 in HPV-001
T(year) = sum of follow-up period expressed in year censored at the first occurrence of event in each group
Follow-up period starts at Month 0 for HPV-001 and pooled HPV-001/007, interval period between end of HPV-001 and beginning of HPV-007 is censored
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 16, p. 93

Reviewer's Comment: Cases accrued in the control group and not in the vaccine group. 95% Confidence intervals narrowed from Month 24 to Month 36.

Figure 14-Study HPV-007: Kaplan-Meier Curves for Persistent Infection (6-month) with HPV-16 and/or HPV-18
(Combined [pooled] HPV-001/007, Cervical Samples Only, ATP Cohort for Efficacy)



Source: STN 125259/0, CSR 007 M36, Figure 10, p. 94

Vaccine efficacy against persistent infection with oncogenic HPV types was 23.1% [95% CI: -12.9%, 47.8%] but did not reach statistical significance.

Vaccine efficacy against persistent infection (6-month definition) with each individual oncogenic HPV type assessed (i.e. HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 individually) are presented.
Reviewer's Comment: None of the point estimates of efficacy reach statistical significance for 6 month persistent infection for non-vaccine HR HPV types. (Source: STN 125259/0, CSR 007 M36, Table 18, p. 95-96, not shown here).

The analyses for persistent 6 month HPV infection in the Total Cohort are consistent with those in the ATP cohort. (Source: STN 125259/0, CSR 007 M36, Supplement 7-9, p. 206-209, not shown here).

Persistent infection (12-month definition), an exploratory endpoint: Vaccine efficacy against persistent 12-month infection for HPV-16 infection alone was 100% [95% CI: 67.5%, 100%]. For HPV-18, VE = 100% [95% CI: -39.7%, 100%].

Table 66-Study HPV-007: Incidence rates and vaccine efficacy against persistent infection (12-month) with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (HPV-007, Cervical samples only, ATP cohort for efficacy)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI
HPV-16/18	Vaccine	304	0	0.0 (0.0, 0.4)	100% (75, 100%)
	Alum Control	285	15	2.0 (1.1, 3.3)	-
HPV-16	Vaccine	304	0	0.0 (0.0, 0.4)	100% (67.5, 100%)
	Alum Control	285	12	1.6 (0.8, 2.8)	-
HPV 18	Vaccine	304	0	0.0 (0.0, 0.4)	100% (-39.7, 100%)
	Alum Control	285	4	0.5 (0.1, 1.3)	-

Vaccine = HPV-16/18 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for HPV-16 and HPV-18 at Month 0 and Month 6 in HPV-001
Follow-up period starts at Month 0 for HPV-001
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 19, p. 98

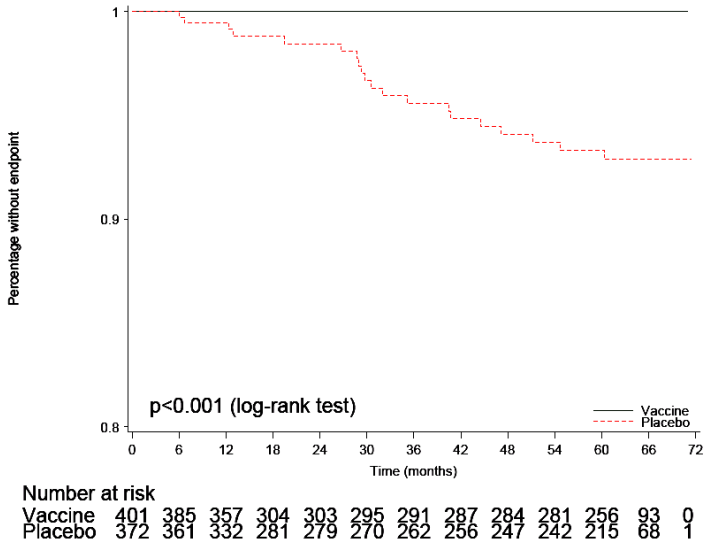
Reviewer's Comment: Cases accrued in the control group and no cases accrued in the vaccine group through Month 36. As noted, the sponsor discussed alpha I adjustment based on their prior look of the data prior to combining the data. The adjustment was agreed upon, and the results of prevention of 6- month and 12-month persistent infection with HPV 16 and/or HPV-18 are shown in Table 67. The conclusions do not change in that point estimates of efficacy remain the same, although LBs of the 98.67% CI are lower as compared to the earlier computation when the alpha adjustment was not taken.

Table 67-Study HPV-001/007: Efficacy of HPV-16/18 L1 AS04 vaccine against persistent infection associated with HPV-16/18 using conditional exact method (According-To-Protocol Cohort)

Combined (pooled HPV-001 and HPV-007) analysis	HPV vaccine		Placebo		% VE (95% CI)	% VE (98.67% CI)
	N	n	N	n		
6-month persistent infection associated with HPV-16/18	401	0	372	34	100 (90.0, 100)	100 (86.2, 100)
12-month persistent infection associated with HPV-16/18	401	0	372	20	100 (81.8, 100)	100 (74.4, 100)

Vaccine = HPV-16/18; Placebo = Aluminum hydroxide
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
Subjects with an event who did not report the same event in HPV-001
Subjects with an event are DNA negative for HPV-16 and HPV-18 at Month 0 and Month 6 in HPV-001
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine Efficacy (Conditional exact method)
6-month persistent infection = Detection of the same HPV type by PCR in cervical specimens at two consecutive evaluations over approximately a 6-month interval (must include at least one evaluation in 580299/007; visits are planned at approximately six-month intervals).
12-month persistent infection = Detection of the same HPV type by PCR in cervical specimens at all consecutive evaluations over approximately a 12-month interval (must include at least one evaluation in 580299/007).
Note: Only cervical samples were included in the combined (pooled HPV-001 and HPV-007) analysis of virological endpoints.
Source: STN 125259.48, study HPV-007 M36, annex 1 report, Table 1, p. 9

Figure 15-Study HPV-007: Kaplan-Meier curves for persistent infection (12-month) with HPV-16 and/or HPV-18 (Combined [pooled] HPV-001/007, Cervical samples only, ATP cohort for efficacy)



Source: STN 125259/0, CSR 007 M36, Figure 11, p. 99

The vaccine efficacy against persistent infection (12-month) with oncogenic HPV types was 21.7% [95% CI:-26.5%, 51.7%]. There was a negative point estimate of efficacy for 12-month persistent infection for high risk types which exclude HPV 16 and/or 18.

Table 68-Study HPV-007: Incidence rates and vaccine efficacy against persistent infection (12-month) with oncogenic HPV types (by PCR) using Conditional exact method (HPV-007, Cervical samples only, ATP cohort for efficacy)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI
HPV-HR	Vaccine	282	35	5.0 (3.5, 6.9)	21.7% (-26.5, 51.7%)
	Alum Control	264	40	6.3 (4.5, 8.6)	-
HPV-HRW	Vaccine	282	35	5.0 (3.5, 6.9)	-16.7% (-99.2, 31.0%)
	Alum Control	264	28	4.3 (2.8, 6.2)	-

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
HPV-HR = High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
HPV-HRW = High-risk (oncogenic) HPV types without HPV-16 or HPV-18: HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 and Month 6 in HPV-001
Follow-up period starts at Month 0 for HPV-001
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 20, p. 100

Reviewer's Comment: In *post-hoc* analyses, none of the point estimates of efficacy reach statistical significance for individual non-vaccine HR HPV types. (Source: STN 125259/0, CSR 007 M36, Table 21, p. 101-102, not shown here). In addition, the analyses of persistent 12 month HPV infection were comparable in the Total Cohort. ((Source: STN 125259/0, CSR 007 M36, Supplements 10-12, p. 210-213, not shown here).

Cytology (Total cohort): A secondary endpoint assessed was prevention of abnormal cytology, i.e. ASC-US, LSIL, HSIL, AGC and ASC-H. No cases of AGC and ASC-H were diagnosed during this study. In addition to the protocol-specified endpoints, a post hoc analysis was performed to evaluate vaccine efficacy against cytological abnormalities ≥ ASC-US and ≥ LSIL.

- **Atypical squamous cells of undetermined significance (ASC-US):**
  - **ASC-US associated with HPV 16/18:** Vaccine efficacy against ASC-US associated with HPV-16 and/or HPV-18 is shown in Table 69.

Table 69-Study HPV-007: Incidence rates and vaccine efficacy against cytological abnormalities (ASC-US) associated with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (Total cohort) (HPV-007)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI
HPV-16/18	Vaccine	357	0	0.0 (0.0, 0.4)	100% (80.5, 100%)
	Alum Control	335	19	2.1 (1.3, 3.3)	-
HPV-16	Vaccine	357	0	0.0 (0.0, 0.4)	100% (69.4, 100%)
	Alum Control	340	13	1.4 (0.8, 2.4)	-
HPV 18	Vaccine	358	0	0.0 (0.0, 0.4)	100% (35.1, 100%)
	Alum Control	339	7	0.8 (0.3, 1.6)	-

N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001
Follow-up period starts at Month 0 for HPV-001
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 22 p. 103

  - **ASC-US associated with High Risk HPV types:** Vaccine efficacy against ASC-US associated with high risk oncogenic HPV types (including HPV 16/18) was 17.2% [95%

CI: -32.8%, 48.6%], and there was a negative point estimate of efficacy when non-vaccine HPV types were considered without HPV 16 or 18. (Source: STN 125259/0, CSR 007 M36, Table 23, p. 104, not shown here).

Reviewer's Comment: None of the point estimates of efficacy reach statistical significance for individual non-vaccine HPV types. (Source: STN 125259/0, CSR 007 M36, Table 24, p. 105-106, not shown here.)

- **Low-grade squamous intraepithelial lesion (LSIL):**
  - **LSIL associated with HPV 16/18:** Vaccine efficacy against LSIL associated with HPV-16 or HPV-18 infection alone was 100% [95% CI: 63.8%, 100%] and 100% [95% CI: 19.8%, 100%], respectively. (Source: STN 125259/0, CSR 007 M36, Table 25, p. 107, not shown here)
  - **LSIL associated with oncogenic HPV types:** VE = 31.5% [95% CI:-9.8%, 57.6%] when including HPV 16/18, and VE=19.4% [95% CI: -31.4, 50.9%] when HPV 16 and 18 were excluded from analyses. (Source: STN 125259/0, CSR 007 M36, Table 26, p. 108, not shown here)
  - **LSIL associated with each individual oncogenic HPV type:** None of the point estimates of efficacy reach statistical significance for the individual non-vaccine HPV types tested. (Source: STN 125259/0, CSR 007 M36, Table 27, p. 108-109, not shown here).
- **High-grade squamous intraepithelial lesion (HSIL):**
  - **HSIL associated with HPV 16/18:** One case of HSIL associated with HPV-16 infection was observed in the control group. (Source: STN 125259/0, CSR 007 M36, Table 28, p. 110, not shown here)
  - **HSIL associated with oncogenic HPV types:** VE = 100% [95% CI: 19.6%, 100%] when including HPV 16 and/or 18. When HPV 16 and/or 18 are included, VE = 100% [95% CI: 19.3%, 100%]. (Source: STN 125259/0, CSR 007 M36, Table 29, p. 111, not shown here)
  - **HSIL associated with each individual oncogenic HPV type**: There were very few cases, and none of the point estimates of efficacy reached statistical significance. (Source: STN 125259/0, CSR 007 M36, Table 30, p. 111-112, not shown here).
- **Cytological abnormalities greater than or equal to ASC-US:**
  - **≥ ASC-US associated with HPV-16 and/or HPV-18:** VE = 100% [95% CI: 87.4%, 100%].

Table 70-Study HPV-007: Incidence rates and vaccine efficacy against cytological abnormalities (greater than or equal to ASC-US) associated with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (Total cohort) (HPV-007)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI
HPV-16/18	Vaccine	357	0	0.0 (0.0, 0.4)	100% (87.4, 100%)
	Alum Control	324	27	3.2 (2.1, 4.7)	-
HPV-16	Vaccine	357	0	0.0 (0.0, 0.4)	100% (82.0, 100%)
	Alum Control	330	20	2.3 (1.4, 3.6)	-
HPV 18	Vaccine	358	0	0.0 (0.0, 0.4)	100% (63.2, 100%)
	Alum Control	337	11	1.2 (0.6, 2.2)	-

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001
Follow-up period starts at Month 0 for HPV-001
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 31, p. 113

Reviewer's Comment: In the above analyses, several additional cases accrued in the control group from Month 24 to Month 36, and none accrued in the vaccine group. Cytology testing is considered a screening test and does not lead directly to definitive treatment.

- **≥ ASC-US) associated with oncogenic HPV types:** VE = 20.1% [95% CI: -15.7%, 44.9%]. The point estimate of efficacy when HPV 16 and/or 18 was excluded did not reach statistical significance. (Source: STN 125259/0, CSR 007 M36, Table 32, p. 114, not shown here)
- **≥ ASC-US associated with each oncogenic HPV type:** None of the point estimates for the individual non-vaccine HR HPV types tested for reach statistical significance. (Source: STN 125259/0, CSR 007 M36, Table 33, p. 115-116, not shown here).

The results of vaccine efficacy against any cytological abnormality (≥ ASC-US) obtained in the ATP cohort for efficacy are also provided, and results are similar to those for the Total Cohort. (Source: STN 125259/0, CSR 007 M36, Supplements 22-24, p. 226-229, not shown here).

- **Cytological abnormalities greater than or equal to LSIL:**
  - **≥ LSIL associated with HPV-16 and/or HPV-18:** VE =100% [95% CI:80.9%, 100%]. The observed vaccine efficacy against cytological abnormalities associated with HPV-16 or HPV-18 alone was also statistically significant (VE = 100% [95% CI: 70.4%, 100%], and VE = 100% [95% CI: 34.5%, 100%], respectively). (Source: STN 125259/0, CSR 007 M36, Table 34, p. 117, not shown here)
  - **≥ LSIL associated with oncogenic HPV types:** VE = 41.7% [95% CI: 8.0%, 63.5%] when HPV 16/18 are included in the analysis, but not without HPV 16 and/or 18. (Source: STN 125259/0, CSR 007 M36, Table 35, p. 118, not shown here).
  - **≥LSIL associated with each oncogenic HPV type assessed**: None of the point estimates of efficacy for the individual non-vaccine HR HPV types reach statistical significance. (Source: STN 125259/0, CSR 007 M36, Table 36, p. 119-120, not shown here).

Reviewer's Comment: The results in the ATP cohort are comparable to those in the Total Cohort. (Source: STN 125259/0, CSR 007 M36, Supplements 25-27, p. 230-233, not shown here).

Histopathology based on protocol-specified analysis (Total cohort): In study HPV-007, association with HPV infection(s) was defined by the HPV DNA type(s) detected by PCR in the cervical biopsy which led to the histopathological diagnosis, while in study HPV-001 association with HPV infection(s) was defined by the HPV DNA type(s) detected by PCR in the cervical or cervicovaginal specimens obtained at the time of diagnosis of the cytological abnormality which led to the biopsy.

Cervical intraepithelial neoplasia (CIN) 1+: Vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 was statistically significant (VE = 100% [95% CI: 52.6%, 100%]). The observed vaccine efficacy against CIN1+ associated with HPV-16 or HPV-18 alone was also statistically significant.

Table 71-Study HPV-007: Incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (Total cohort)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI
HPV-16/18	Vaccine	358	0	0.0 (0.0, 0.4)	100% (52.6, 100%)
	Alum Control	339	9	1.0 (0.5, 1.9)	-
HPV-16	Vaccine	358	0	0.0 (0.0, 0.4)	100% (34.8, 100%)
	Alum Control	339	7	0.8 (0.3, 1.6)	-
HPV-18	Vaccine	358	0	0.0 (0.0, 0.4)	100% (-132.3, 100%)
	Alum Control	345	3	0.3 (0.1, 0.9)	-

Vaccine = HPV-16/18 L1/AS04 (DVLP017A); Placebo = Aluminium hydroxide (DVLP018A)
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001
T(year) = sum of follow-up period expressed in year censored at the first occurrence of event in each group
Follow-up period starts at Month 0 for HPV-001 and pooled HPV-001/007, interval period between end of HPV-001 and beginning of HPV-007 is censored
n/T = person-year rate in each group; LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 37, p. 121

Reviewer's Comment: A comparison was made in the analyses at Month 24 and at Month 36. Several additional cases accrued in the control group from Month 24 to Month 36 and no cases were detected in the vaccine group. Point estimates of efficacy now reach statistical significance for the HPV 16/18 analyses and the HPV 16 analyses as compared to the Month 24 analyses, when these analyses did not reach statistical significance.

Vaccine efficacy against CIN1+ associated with oncogenic HPV types was statistically significant (VE = 57.1% [95% CI: 5.7%, 81.9%]) when HPV 16 and/or 18 were included, but not when HPV 16 and/or 18 are excluded. (Source: STN 125259/0, CSR 007 M36, Table 38, p. 122, not shown here) In an analysis of CIN1+ associated with individual non-vaccine HPV types, very few cases accrued, and none of the point estimates of efficacy reached statistical significance. (Source: STN 125259/0, CSR 007 M36, Table 39, p. 123-124, not shown here).

Reviewer's Comment: The results in the ATP cohort are comparable to those in the Total Cohort. (Source: STN 125259/0, CSR 007 M36, Supplements 28-30, p. 235-237, not shown here).

Cervical intraepithelial neoplasia (CIN) 2+: Vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 was statistically significant (VE = 100% [95% CI: 19.7%, 100%]).

Table 72- Study HPV-007: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (Total cohort) (HPV-007)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI	p-value
HPV-16/18	Vaccine	358	0	0.0 (0.0, 0.4)	100% (19.7, 100%)	0.0133
	Alum Control	342	6	0.7 (0.2, 1.4)	-	-
HPV-16	Vaccine	358	0	0.0 (0.0, 0.4)	100% (-129.7, 100%)	0.1161
	Alum Control	342	3	0.3 (0.1, 0.9)	-	-
HPV -18	Vaccine	358	0	0.0 (0.0, 0.4)	100% (-132.3, 100%)	0.1177
	Alum Control	345	3	0.3 (0.1, 0.9)	-	-

Control = Aluminum hydroxide (DVLP018A)
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001
Follow-up period starts at Month 0 for HPV-001
n/T = person-year rate in each group

LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 40, p. 125

Reviewer's Comment: In comparison, two additional cases accrued in the control group from Month 24 to Month 36: one associated with HPV 16 and one associated with HPV 18, and point estimate of efficacy for the combined analysis reached statistical significance.

Reviewer's Comment: Supplementary analyses considered an adjustment of type I error (alpha) for the efficacy analyses of the main histopathological endpoints associated with HPV-16/18 in the combined analysis of the HPV-001 and HPV-007 studies to account for repeated observations of the data.

Table 73-Study HPV-001/007: Efficacy of HPV-16/18 L1 AS04 vaccine against histopathological lesions associated with HPV-16/18 using conditional exact method (Total Cohort)

Combined (pooled HPV-001 and HPV-007) analysis	HPV vaccine		Placebo		% VE (95% CI)	% VE (98.67% CI)
	N	n	N	n		
CIN1+ associated with HPV-16/18	481	0	470	15	100 (73.4, 100)	100 (62.1, 100)
CIN2+ associated with HPV-16/18	481	0	470	9	100 (51.3, 100)	100 (28.4,100)

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Placebo = Aluminum hydroxide (DVLP018A)
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
Subjects with an event who did not report the same event in HPV-001
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine Efficacy (Conditional exact method)
CIN1+ = cervical intraepithelial neoplasia as CIN1, CIN2, CIN3, adenocarcinoma in situ (AIS), and invasive cervical cancer
CIN2+ = cervical intraepithelial neoplasia as CIN2, CIN3, adenocarcinoma in situ (AIS), and invasive cervical cancer
Source: STN 125259.48, CSR 007 M36 annex 1 report, Table 3, p. 12

Vaccine efficacy against CIN2+ associated with oncogenic HPV types was statistically significant (VE =73.0% [95% CI: 14.0%, 93.5%]) when HPV 16 and/or 18 are included in the analysis, but not when HPV 16 and/or 18 are excluded.

Table 74-Study HPV-007: Incidence rates and vaccine efficacy against CIN2+ associated with oncogenic HPV types (by PCR) using Conditional exact method (Total cohort) (HPV-007)

Event type	Group	N	n	Person-year rate 95% CI	Vaccine efficacy 95% CI	p-value
HPV-HR	Vaccine	358	4	0.4 (0.1, 1.1)	73.0% (14.0, 93.5%)	0.0161
	Alum Control	345	14	1.5 (0.8, 2.6)	-	-
HPV-HRW	Vaccine	358	4	0.4 (0.1, 1.1)	65.5% (-16.5, 92.0%)	0.0692
	Alum Control	345	11	1.2 (0.6, 2.1)	-	-

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
HPV-HR = High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
HPV-HRW = High-risk (oncogenic) HPV types without HPV-16 or HPV-18: HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001

Follow-up period starts at Month 0 for HPV-001
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 41, p. 126

Reviewer's Comment: There are very few cases of CIN2+ associated with individual non-vaccine HPV types in either treatment group, and none of the point estimates of efficacy reach statistical significance. (Source: STN 125259/0, CSR 007 M36, Table 42, p. 126-127, not shown here).

Cytology and histopathology irrespective of HPV DNA status (Total cohort): A post hoc analysis was performed on cytological and histopathological endpoints irrespective of HPV DNA status, to evaluate the overall vaccine benefit against cytological abnormalities and histopathological lesions. The vaccine efficacy against CIN2+ irrespective of HPV DNA status for the combined (pooled) data was 71.9% [95% CI: 20.6%, 91.9%].

Table 75-Study HPV-007: Incidence rates and vaccine efficacy against cytological and histopathological endpoints irrespective of HPV DNA testing (by PCR) using Conditional exact method (Combined [pooled] HPV-001/007 data, Total cohort)

Endpoint	Group	N	n	T (year)	Person-year rate			VE		
					n/T (Per 100)	LL	UL	%	LL	UL
Histopathological endpoints										
CIN1+	Vaccine	505	20	1822.26	1.1	0.7	1.7	50.3	12.5	72.6
	Placebo	497	38	1719.32	2.2	1.6	3.0	-	-	-
CIN2+	Vaccine	505	5	1832.53	0.3	0.1	0.6	71.9	20.6	91.9
	Placebo	497	17	1750.88	1.0	0.6	1.6	-	-	-
CIN1	Vaccine	505	19	1823.01	1.0	0.6	1.6	45.5	1.4	70.7
	Placebo	497	33	1724.64	1.9	1.3	2.7	-	-	-
Cytological endpoints										
ASC-US	Vaccine	505	77	1733.98	4.4	3.5	5.6	38.0	16.4	54.3
	Placebo	497	111	1548.89	7.2	5.9	8.6	-	-	-
LSIL	Vaccine	505	62	1757.22	3.5	2.7	4.5	35.5	9.8	54.2
	Placebo	497	88	1607.95	5.5	4.4	6.7	-	-	-
HSIL	Vaccine	505	0	1843.43	0.0	0.0	0.2	100.0	33.5	100.0
	Placebo	497	7	1766.66	0.4	0.2	0.8	-	-	-
≥ ASC-US	Vaccine	505	118	1699.93	6.9	5.7	8.3	35.4	17.6	49.5
	Placebo	497	162	1506.91	10.8	9.2	12.5	-	-	-
≥ LSIL	Vaccine	505	62	1757.22	3.5	2.7	4.5	39.4	15.6	56.8
	Placebo	497	93	1596.11	5.8	4.7	7.1	-	-	-

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
T(year) = sum of follow-up period expressed in year censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Table 43, p. 130

Reviewer's Comment: These results are of interest, but efficacy endpoints irrespective of HPV type are considered in the pivotal Phase III study HPV-008.

The sponsor also presented analyses of cytological and histopathological endpoints irrespective of HPV DNA status based on the ATP cohort for efficacy. Based on the ATP cohort, vaccine efficacy against CIN2+ irrespective of HPV DNA status for the combined (pooled) data was 71.9% [95% CI:8.9%, 93.3%]. In addition, for cytological abnormalities (ASC-US and ≥ ASC-US), the lower confidence limit for vaccine efficacy was greater than 0 based on the ATP analysis (VE = 33.4% [95% CI: 5.3%, 53.4%] and 27.9% [95% CI:4.0% and 46.0%], respectively).

Reviewer's Comment: Analyses for prevention of other endpoints did not reach statistical significance in the ATP cohort.

Table 76-Study HPV-007: Incidence rates and vaccine efficacy against cytological and histopathological endpoints irrespective of HPV DNA testing (by PCR) using Conditional exact method (Combined [pooled] HPV-001/007 data, All samples combined, ATP cohort for efficacy)

Endpoint	Group	N	n	T (year)	Person-year rate			VE		
					n/T (Per 100)	LL	UL	%	LL	UL
Histopathological endpoints										
CIN1+	Vaccine	375	17	1267.13	1.3	0.8	2.1	45.1	-3.8	71.8
	Placebo	345	28	1144.86	2.4	1.6	3.5	-	-	-
CIN2+	Vaccine	375	4	1272.06	0.3	0.1	0.8	71.9	8.9	93.3
	Placebo	345	13	1163.16	1.1	0.6	1.9	-	-	-
CIN1	Vaccine	375	16	1267.89	1.3	0.7	2.0	44.4	-7.6	72.1
	Placebo	345	26	1145.49	2.3	1.5	3.3	-	-	-
Cytological endpoints										
ASC-US	Vaccine	375	59	1211.44	4.9	3.7	6.3	33.4	5.3	53.4
	Placebo	345	77	1052.99	7.3	5.8	9.1	-	-	-
LSIL	Vaccine	375	49	1217.46	4.0	3.0	5.3	28.7	-5.6	52.1
	Placebo	345	61	1080.46	5.6	4.3	7.3	-	-	-
HSIL	Vaccine	375	0	1280.33	0.0	0.0	0.3	100.0	-39.4	100.0
	Placebo	345	4	1177.78	0.3	0.1	0.9	-	-	-
≥ ASC-US	Vaccine	375	91	1182.51	7.7	6.2	9.4	27.9	4.0	46.0
	Placebo	345	110	1029.96	10.7	8.8	12.9	-	-	-
≥ LSIL	Vaccine	375	49	1217.46	4.0	3.0	5.3	31.3	-1.4	53.7
	Placebo	345	63	1075.07	5.9	4.5	7.5	-	-	-

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
T(year) = sum of follow-up period expressed in year censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE(%) = Vaccine Efficacy (Conditional exact method)
Source: STN 125259/0, CSR 007 M36, Supplement 40, p. 250

Efficacy results using Cox regression model: In addition to the primary efficacy analysis using the Conditional exact method, vaccine efficacy was calculated using a Cox regression model. The results obtained with the Cox regression model were consistent with those obtained with the Conditional exact method.
Reviewer's Comment: These analyses were reviewed for the ATP cohort and Total Cohort, and results were comparable to those noted above. (Source: STN 125259/0, CSR 007 M36, Supplements 41-108, p. 251-340, not shown here).

Exploratory covariate analyses were conducted.
Efficacy analysis by region: Exploratory analyses were performed for the virological and histopathological endpoints for both HPV-007 and combined (pooled) HPV-001/007 data to evaluate the effect of geographical region (North America and Brazil) on the vaccine efficacy. The results of the combined (pooled) analysis of vaccine efficacy endpoints associated with HPV-16 and/or HPV-18 by region were presented. Vaccine efficacy against each endpoint was similar in both regions. (Source: STN 125259/0, CSR 007 M36, Table 44, p. 131, not shown here)

Reviewer's Comment: Results were also presented for the Total Cohort in North America and Brazil separately. Point estimates were similar in both groups, although with smaller numbers of events in each analyses, not all reached statistical significance. (Source: STN 125259/0, CSR 007 M36, Supplements 109-138, p. 341-380, not shown here). In addition, results were presented individually for North America and Brazil for the ATP cohort, and results are comparable to

those in the ATP cohort. (Source: STN 125259/0, CSR 007 M36, Supplements 139-168, p. 381-420, not shown here).

Other covariate analyses: No other covariates were analyzed. An overview of the number of subjects in the vaccine and control groups for the covariates smoking status and contraception status demonstrated that the proportions of subjects who smoked or took contraceptives were similar in both treatment groups.

Vulval intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN): As part of the other endpoints defined in the protocol, occurrence of histopathologically confirmed VIN or VaIN associated with oncogenic HPV types was to be evaluated. For the combined (pooled) HPV-001/HPV-007 analysis, two cases of VaIN associated with oncogenic HPV types were reported, i.e. a VaIN1 case in one subject who had a CIN1 lesion at a different time point and a VaIN2+ case in another subject who had a CIN2+ lesion at the same time point.

SAFETY RESULTS

Data sets analyzed: Analysis of safety was performed on the ATP cohort for safety (primary analysis) and the Total cohort with data collected from the end of study HPV-001 throughout the entire HPV-007 study period. The sponsor had presented safety data from the Brazil site in a partially blinded manner, but unsolicited adverse events were provided in the wunsol.xpt dataset.

According-To-Protocol analysis

Adverse events: According to the protocol, medically significant conditions defined as "Conditions prompting either emergency room visits that are not related to common diseases or physician visits that are not related to common diseases" were to be collected. The sponsor notes that since no specific records of medically attended visits were included in the non-serious adverse events sections of the eCRFs for study HPV-007, an analysis of all AEs recorded by the investigator was performed in place of an analysis limited to medically significant conditions.

A global summary of all AEs observed from the end of study HPV-001 throughout the entire HPV-007 study period is provided in Table 77. Overall, the number of subjects with an AE reported was slightly lower in the vaccine group (106 subjects, 28.4%) compared to the control group (123 subjects, 33.3%).

Table 77-Study HPV-007: Global Summary of AEs (ATP cohort for safety)

	Group		
	Vaccine	Placebo	Total
Number of subjects with at least one AE reported	106	123	229
Number of AEs classified by MedDRA Preferred Term*	136	192	328
Number of AEs reported	141	199	340

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
* Symptoms reported by a subject and classified by the same Preferred Term are counted once
Source: STN 125259/0, CSR 007 M36, Table 54, 153

Table 78-Study HPV-007: Global Summary of AEs (Total cohort)

	Group		
	Vaccine	Placebo	Total
Number of subjects with at least one unsolicited symptom reported	110	126	236
Number of unsolicited symptoms classified by MedDRA Preferred Term*	143	195	338
Number of unsolicited symptoms reported	149	202	351

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
* Symptoms reported by a subject and classified by the same Preferred Term are counted once
Source: STN 125259/0, CSR 007 M36, Supplement 197, p. 449

Reviewer's Comment: The results were reviewed from the wunsol.xpt dataset from the Month 36 report for CSR 007. The results are comparable to those included in the ATP cohort. In the vaccine group, there was 1 additional subject with dengue fever, 1 additional subject with vaginitis, 1 additional subject with depression, and 1 additional subject with asthma (exercise induced). In the control group, there was 1 additional subject with pulmonary TB, one additional subject with a UTI and 1 additional subject with a spontaneous abortion. Supplements 197-204 were reviewed to compare results between ATP cohort and total cohort. (p. 449-460, not shown here).

Table 79-Study HPV-007: Percentage of subjects reporting the occurrence of AEs subjects classified by MedDRA Primary System Organ Class and Preferred Term (ATP cohort) [Total cohort]

	Preferred Term	Vaccine N=373	Control N=369
Primary System Organ Class		**n (%) [total cohort]**	**n (%) [total cohort]**
At least one symptom		**106 (28.4%) [110/28%]**	**123 (33.3%) [26/32.9%]**
Blood and lymphatic system disorders	Anemia	2 (0.5%)	2 (0.5%)
	Lymphadenopathy	2 (0.5%)	1 (0.3%)
	Splenomegaly	0 (0.0%)	1 (0.3%)
Cardiac disorders	Angina Pectoris	0 (0.0%)	1 (0.3%)
	Mitral valave incompetence	0 (0.0%)	1 (0.3%)
Ear and labyrinth disorders	Ear Pain	0 (0.0%)	1 (0.3%)
	Inner ear disorder	0 (0.0%)	1 (0.3%)
Endocrine disorders	Autoimmune thyroiditis	0 (0.0%)	1 (0.3%)
	Hyperandrogenism	0 (0.0%)	1 (0.3%)
	Hyperprolactinemia	1 (0.3%)	1 (0.3%)
	Hypothyroidism	3 (0.8%)	4 (1.1%)
Eye disorders	Conjunctivitis	1(0.3%)	0 (0.0%)
Gatrointestinal disorders	Abdominal pain	0 (0.0%)	1 (0.3%)
	Abdominal pain lower	1 (0.3%)	0 (0.0%)
	Colitis	1 (0.3%)	1 (0.3%)
	Colitis ulcerative	1 (0.3%)	0 (0.0%)
	Constipation	1 (0.3%)	0 (0.0%)
	Gastritis	2 (0.5%)	3 (0.8%)
	GERD	2 (0.5%)	0 (0.0%)
	Hemorrhoids	2 (0.5%)	2 (0.5%)
	Irritable bowel syndrome	0 (0.0%)	1 (0.3%)
	Esophagitis	0 (0.0%)	1 (0.3%)
	Rectal hemorrhage	1 (0.3%)	0 (0.0%)
	Tooth disorder	0 (0.0%)	1 (0.3%)
	Umbilical hernia	0 (0.0%)	1 (0.3%)
General disorders and administration site conditions	Fatigue	0 (0.0%)	1 (0.3%)
	Malaise	0 (0.0%)	1 (0.3%)
	Pyrexia	1 (0.3%)	0 (0.0%)
Hepatobiliary disorders	Cholecystitis acute	1 (0.3%)	0 (0.0%)
	Cholelithiasis	0 (0.0%)	3 (0.8%)
	Hepatomegaly	0 (0.0%)	1 (0.3%)
Immune system disorders	Drug hypersensitivity	1 (0.3%)	0 (0.0%)
	Hypersensitivity	0 (0.0%)	1 (0.3%)
	Latex allergy	0 (0.0%)	1 (0.3%)

Table 79-Study HPV-007: Percentage of subjects reporting the occurrence of AEs classified by MedDRA Primary System Organ Class and Preferred Term (ATP cohort) [Total cohort] [CONT]

	Preferred Term	Vaccine N=373	Control N=369
Primary System Organ Class		**n (%)**	**n (%)**
Infections and infestations	Abscess limb	1 (0.3%)	0 (0.0%)
	Acarodermatitis	0 (0.0%)	2 (0.5%)
	Anigenital warts	2 (0.5%)	5 (1.4%)
	Appenidicitis	0 (0.0%)	1 (0.3%)
	Brain abscess	0 (0.0%)	1 (0.3%)
	Bronchitis	1 (0.3%)	0 (0.0%)
	Bronchopneumonia	2 (0.5%)	1 (0.3%)
	Candidiasis	0 (0.0%)	3 (0.8%)
	Cellulitis	1 (0.3%)	0 (0.0%)
	Cervicitis	0 (0.0%)	1 (0.3%)
	Chlamydial infection	0 (0.0%)	1 (0.3%)
	Cystitis	0 (0.0%)	1 (0.3%)
	Dengue fever	1 (0.3%)	1 (0.3%)
	Ear infection	0 (0.0%)	1 (0.3%)
	Endometritis	1 (0.3%)	0 (0.0%)
	Eye infection bacterial	1 (0.3%)	0 (0.0%)
	Follicultis	0 (0.0%)	2 (0.5%)
	Fungal infection	1 (0.3%)	0 (0.0%)
	Gastroenteritis	0 (0.0%)	1 (0.3%)
	Gastroenteritis shigella	0 (0.0%)	1 (0.3%)
	Groin abscess	0 (0.0%)	1 (0.3%)
	Gyn chlamydia infection	2 (0.5%)	1 (0.3%)
	Hepatitis C	1(0.3%)	0 (0.0%)
	Herpes simplex	5 (1.3%)	5 (1.3%)
	Impetigo	0 (0.0%)	1 (0.3%)
	Infectious mononucleosis	1 (0.3%)	0 (0.0%)
	Labyrinthitis	1 (0.3%)	0 (0.0%)
	Mastitis	0 (0.0%)	1 (0.3%)
	Neurocysticercosis	1 (0.3%)	0 (0.0%)
	PID	1 (0.3%)	1 (0.3%)
	Pharyngitis streptococcal	1 (0.3%)	1 (0.3%)
	Pilonidal cyst	0 (0.0%)	2 (0.5%)
	Pneumonia	1 (0.3%)	1 (0.3%)
	Pneumonia mycoplasma	0 (0.0%)	1 (0.3%)
	Postoperative wound infection	1 (0.3%)	0 (0.0%)
	Pulmonary TB	3 (0.8%)	1 (0.3%)
	Pyelonephritis	1 0.3%)	2 (0.5%)
	Pyelonephritis acute	0 (0.0%)	1 (0.3%)
	Sinusitis	1 (0.3%)	1 (0.3%)
	Tonsillitis	0 (0.0%)	3 (0.8%)
	Trichomoniasis	0 (0.0%)	2 (0.5%)
	Tubo-ovarian abscess	1 (0.3%)	0 (0.0%)
	UTI	1 (0.3%)	6 (1.6%)
	Vaginitis bacterial	1 (0.3%)	1 (0.3%)
	Varicella	1 (0.3%)	0 (0.0%)
	Vulvitis	0 (0.0%)	1 (0.3%)
	Vulvovaginitis trichomonal	1 (0.3%)	0 (0.0%)

Table 79-Study HPV-007: Percentage of subjects reporting the occurrence of AEs classified by MedDRA Primary System Organ Class and Preferred Term (ATP cohort) [Total cohort] [CONT]

	Preferred Term	Vaccine N=373	Control N=369
Primary System Organ Class		**n (%)**	**n (%)**
Injury, poisoning and procedural complications1	Anesthetic complication	1 (0.3%)	0 (0.0%)
	Electric shock	0 (0.0%)	1 (0.3%)
	Failed forceps delivery	1 (0.3%)	0 (0.0%)
	Foot fracture	1 (0.3%)	0 (0.0%)
	Head injury	1 (0.3%)	0 (0.0%)
	Hip fracture	1 (0.3%)	0 (0.0%)
	Human bite	0 (0.0%)	1 (0.3%)
	Incisional hernia	1 (0.3%)	0 (0.0%)
	Joint injury	0 (0.0%)	1 (0.3%)
	Joint sprain	1 (0.3%)	0 (0.0%)
	Multiple fractures	0 (0.0%)	1 (0.3%)
	Neck injury	0 (0.0%)	1 (0.3%)
	Nerve injury	0 (0.0%)	1 (0.3%)
	Post-procedural hemorrhage	0 (0.0%)	2 (0.5%)
	Wrist fracture	0 (0.0%)	1 (0.3%)
Investigations	Hepatic enzyme increased	0 (0.0%)	1 (0.3%)
Metbaolism and nutrition disorders	Dehydration	1 (0.3%)	0 (0.0%)
	Diabetes mellitus, non-insulin dependent	2 (0.5%)	0 (0.0%)
	Dyslipidemia	0 (0.0%)	1 (0.3%)
	Hypercholesterolemia	0 (0.0%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	Arthralgia	0 (0.0%)	2 (0.5%)
	Arthropathy	0 (0.0%)	1 (0.3%)
	Back pain	1 (0.3%)	1 (0.3%)
	Intervertebral disc disorder	0 (0.0%)	1 (0.3%)
	Muscle spasms		
	Neck pain	0 (0.0%)	2 (0.5%)
	Osteoarthritis	0 (0.0%)	1 (0.3%)
	RA	1 (0.3%)	0 (0.0%)
	TMJ	0 (0.0%)	1 (0.3%)
	Tendonitis	0 (0.0%)	1 (0.3%)
	Tenosynovitis	0 (0.0%)	2 (0.5%)
		1 (0.3%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Benign ovarian tumor	0 (0.0%)	1 (0.3%)
	Fibroadenoma breast	0 (0.0%)	3 (0.8%)
	Melanocytic nevus	0 (0.0%)	1 (0.3%)
	Uterine leiomyoma	1 (0.3%)	1 (0.3%)
Nervous system disorders	Convulsion	1 (0.3%)	0 (0.0%)
	Facial palsy	1 (0.3%)	0 (0.0%)
	Headache	1 (0.3%)	2 (0.5%)
	Migraine	1 (0.3%)	0 (0.0%)
	Paresthesia	0 (0.0%)	1 (0.3%)

Table 79-Study HPV-007: Percentage of subjects reporting the occurrence of AEs classified by MedDRA Primary System Organ Class and Preferred Term (ATP cohort) [Total cohort][CONT]

	Preferred Term	Vaccine N=373	Control N=369
Primary System Organ Class		**n (%)**	**n (%)**
Pregnancy, puerperium and perinatal conditions	Abortion complete	0 (0.0%)	1 (0.3%)
	Abortion missed	1 (0.3%)	2 (0.5%)
	Abortion spontaneous	6 (1.6%)	9 (2.4%)
	Abortion spontaneous complete	2 (0.5%)	0 (0.0%)
	Abortion spontaneous incomplete	1 (0.3%)	2 (0.5%)
	Abortion threatened	1 (0.3%)	2 (0.5%)
	Blighted ovum	1 (0.3%)	0 (0.0%)
	Chorioamnionitis	0 (0.0%)	1 (0.3%)
	Eclampsia	1 (0.3%)	0 (0.0%)
	Ectopic pregnancy	0 (0.0%)	1 (0.3%)
	Fetal distress syndrome	1 (0.3%)	0 (0.0%)
	Intra-uterine death	0 (0.0%)	1 (0.3%)
	Placenta previa	0 (0.0%)	1 (0.3%)
	Pre-eclampsia	2 (0.5%)	2 (0.5%)
	Premature baby	0 (0.0%)	1 (0.3%)
	Premature labor	0 (0.0%)	1 (0.3%)
	Stillbirth	1 (0.3%)	0 (0.0%)
Psychistric disorders	Anxiety	0 (0.0%)	2 (0.5%)
	Attention deficit/hyperactivity disorder	1 (0.3%)	0 (0.0%)
	Bipolar disorder	0 (0.0%)	2 (0.5%)
	Depression	9 (2.4%)	9 (2.4%)
	Insomnia	1 (0.3%)	0 (0.0%)
	Panic reaction	1 (0.3%)	2 (0.5%)
	Suicidal ideation	1 (0.3%)	0 (0.0%)
	Suicide attempt	0 (0.0%)	2 (0.5%)
Renal and urinary disorders	Hypertonic bladder	0 (0.0%)	1 (0.3%)
	Nephritis	1 (0.3%)	0 (0.0%)
	Nephrolithiasis	5 (1.3%)	0 (0.0%)
	Renal colic	0 (0.0%)	1 (0.3%)
Reproductive system and breast disorders	Adenomyosis	1 (0.3%)	0 (0.0%)
	Bartholinitis	0 (0.0%)	1 (0.3%)
	Breast mass	2 (0.5%)	0 (0.0%)
	Cervical dysplasia	1 (0.3%)	0 (0.0%)
	Dysfunctional uterine bleeding	1 (0.3%)	1 (0.3%)
	Fallopian tube obstruction	1 (0.3%)	0 (0.0%)
	Menstruation irregular	1 (0.3%)	1 (0.3%)
	Ovarian cyst	3 (0.8%)	8 (2.2%)
	Ovarian cyst ruptured	0 (0.0%)	1 (0.3%)

Table 79-Study HPV-007: Percentage of subjects reporting the occurrence of AEs classified by MedDRA Primary System Organ Class and Preferred Term (ATP cohort) [Total cohort] [CONT]

	Preferred Term	Vaccine N=373	Control N=369
Primary System Organ Class		**n (%)**	**n (%)**
Respiratory, thoracic and medistinal disorders	Asthma	0 (0.0%)	1 (0.3%)
	Epistaxis	1 (0.3%)	0 (0.0%)
	Pharyngolaryngeal pain	0 (0.0%)	1 (0.3%)
	Pneumonia aspiration	1 (0.3%)	0 (0.0%)
	Pneumonitis	0 (0.0%)	1 (0.3%)
	Rhinitis allergic	1 (0.3%)	0 (0.0%)
Skin and subcutaneous tisse disorders	Acne	1 (0.3%)	1 (0.3%)
	Dernatitis allergic	1 (0.3%)	0 (0.0%)
	Dermatitis contact	1 (0.3%)	0 (0.0%)
	Rash	2 (0.5%)	0 (0.0%)
	Urticaria	1 (0.3%)	1 (0.3%)
Surgical and medical procedures	Abortion induced	3 (0.8%)	4 (1.1%)
	Wisdom tooth removed	0 (0.0%)	1 (0.3%)
Vascular disorders	Hypertension	1 (0.3%)	3 (0.8%)
	Thrombophlebitis	0 (0.0%)	1 (0.3%)

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminium hydroxide (DVLP018A)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 007 M36, Table 55, p. 154-158, Supplement 198, p.450-454, and dataset WUNSOL 007 M36
[]number of events in the total vaccinated cohort

Reviewer's Comment: The number of cases for each event was located by search of the WUNSOL.xpt dataset from CSR 007 Month 36 report. In a few instances, some of the events were present prior to vaccination and were not included in the totals. Nephrolithiasis was noted to occur in a higher number of subjects in the vaccine group (5) as compared to the control group (0). These events occurred 444-1658 days after the receipt of dose 3, and do not appear to be related to vaccine.

New onset chronic diseases: Global summaries of NOCDs (as assessed by GSK and by investigators) reported from the end of study HPV-001 throughout the entire HPV-007 study period were provided.

Reviewer's Comment: The results of the investigator assessment were used to compare the events in the wunsol.xpt dataset, because most of the **chronic** events located in the datasets were reported in the investigator's assessment. One case of ulcerative colitis developed at 1554 days after dose 3, remote from the time of vaccination. The case of drug hypersensitivity is a sulfa allergy. For the cases of herpes simplex, 4 were considered chronic in the vaccine group and 0 in the control group, although 5 cases occurred in each treatment group. The two cases of diabetes mellitus non-insulin dependent occurred 545-1026 days after receipt of dose 3. The one case of osteoarthritis in the vaccine group occurred at 1596 days after dose 3. The one case of rheumatoid arthritis in the control group occurred at 1145 days after dose 3. There were two subjects with migraines in the vaccine group, but one of these subjects suffered from migraines since 1992 and therefore this was not a new onset chronic disease. The one subject with ADHD developed this at1571 days after dose 3. Four subjects in the control group were diagnosed with bipolar disorder, but 3 were already present prior to vaccination, and one was considered a new onset chronic disease. This event developed at 1271 days after dose 3. The vaccine recipient with insomnia developed at 1711 days after dose 3. Two subjects with asthma were identified in the wunsol dataset, but one in the vaccine group was diagnosed as exercise induced and not assessed as chronic (developed at 1691 days after dose 3).

Table 80-Study HPV-007: Percentage of subjects reporting the occurrence of NOCDs classified by MedDRA Primary System Organ Class and Preferred Term (ATP cohort for safety, Investigator assessment)

	Preferred Term	Vaccine N=373	Control N=369
Primary System Organ Class		**n (%)**	**n (%)**
At least one symptom		**18 (4.8%)**	**21 (5.7%)**
Blood and lymohatic system disorders	Anemia	0 (0.0%)	2 (0.5%)
Cardiac disorders	Angina pectoris	0 (0.0%)	1 (0.3%)
Endocrine disorders	Autoimmune thyroiditis	1 (0.3%)	3 (0.8%)
	Hyperprolactinemia	1 (0.3%)	1 (0.3%)
	Hypothyroidism	3 (0.8%)	4 (1.1%)
Gastrointestinal disorders	Colitis ulcerative	1 (0.3%)	0 (0.0%)
	Gastritis	1 (0.3%)	0 (0.0%)
	Hemorrhoids	1 (0.3%)	2 (0.5%)
	Irritable bowel syndrome	0 (0.0%)	1 (0.3%)
Immune system disorders	Drug hypersensitivity	1 (0.3%)	0 (0.0%)
Infections and Infestations	Herpes simplex	4 (1.1%)	0 (0.0%)
	Vaginitis bacterial	1 (0.3%)	0 (0.0%)
Metabolism and nutrition disorders	Diabetes mellitus non-insulin dependent	2 (0.5%)	0 (0.0%)
	Hypercholesterolemia	0 (0.0%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	Back pain	0 (0.0%)	1 (0.3%)
	Osteoarthritis	1 (0.3%)	0 (0.0%)
	Rheumatoid arthritis	0 (0.0%)	1 (0.3%)
Nervous system disorder	Migraine	1 (0.3%)	0 (0.0%)
Psychiatric disorders	Anxiety	0 (0.0%)	2 (0.5%)
	Attention deficit/hyperactivity disorder	1 (0.3%)	0 (0.0%)
	Bipolar disorder	0 (0.0%)	1 (0.3%)
	Depression	1 (0.3%)	2 (0.5%)
	Insomnia	1 (0.3%)	0 (0.0%)
	Panic reaction	0 (0.0%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	Asthma	0 (0.0%)	1 (0.3%)
Skin and subcutaneous tissue disorders	Acne	1 (0.3%)	0 (0.0%)
Vascular disorders	Hypertension	0 (0.0%)	1 (0.3%)

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 007 M36, Table 59, p. 161 and dataset WUNSOL 007 M36

New onset autoimmune diseases: Based on a pre-defined list of potential autoimmune events, a GSK Biologicals physician reviewed the AEs identified as NOCDs and classified as NOADs. As shown in Table 81, NOADs were reported for a total of six subjects during the entire study period - two subjects (0.5%) in the vaccine group and four subjects (1.1%) in the control group.

Table 81-Study HPV-007: Global Summary of NOADs
(ATP cohort for safety, GSK assessment)

	Group		
	Vaccine	Placebo	Total
Number of subjects with at least one NOAD reported	2	4	6
Number of NOADs classified by MedDRA Preferred Term*	2	5	7
Number of NOADs reported	2	5	7

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminium hydroxide (DVLP018A)
* Symptoms reported by a subject and classified by the same Preferred Term are counted once
Source: STN 125259/0, CSR 007 M36, Table 60, p. 162

Serious adverse events: The analysis of SAEs was performed on both the ATP cohort for safety and the Total cohort. Results from the Total cohort are presented. It should be noted that the clinical database used for statistical analysis only contains SAEs that are directly related to study participants and does not include SAEs related to offspring.

Fatal events: None of the study participants died during this study.

Non-fatal events: A global summary of the SAEs reported from the end of study HPV-001 throughout the entire HPV-007 study period is provided in Table 82. Overall, the number of subjects who experienced an SAE was slightly lower in the vaccine group (31 subjects, 7.9%) compared to the control group (39 subjects, 10.2%).

Table 82-Study HPV-007: Global summary of SAEs (Total cohort)

	Group		
	Vaccine	Placebo	Total
Number of subjects with at least one SAE reported	31	39	70
Number of SAEs classified by MedDRA Preferred Term*	34	41	75
Number of SAEs reported	36	46	82

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
* Symptoms reported by a subject and classified by the same Preferred Term are counted once
Source: STN 125259/0, CSR 007 M36, Table 62, p. 163

The most frequently reported SAE was spontaneous abortion, reported for 6 subjects (1.5%) in the vaccine group and 10 subjects (2.6%) in the control group. SAEs were reported for at most 2 subjects (≤ 0.5%) in either vaccine or control groups. None of the SAEs were considered related to vaccination according to the investigators. Apart from 2 events which were still ongoing (depression and pneumonitis), all SAEs were resolved at the end of the study.

Table 83-Study 007: Percentage of subjects reporting the occurrence of SAEs classified by MedDRA Primary System Organ Class and Preferred Term (Total cohort)

	Preferred Term	Vaccine N=373	Days after dose 3	Control N=369	Days after dose 3
Primary System Organ Class		**n (%)**		**n (%)**	
At least one symptom		**31 (7.9%)**		**39 (10.2%)**	
Gastrointestinal disorders	Colitis	1 (0.3%)	438	1 (0.3%)	1499
	GERD	1 (0.3%)	1600	0 (0.0%)	NA
Hepatobiliary disorders	Cholecystitis acute	1 (0.3%)	1765	0 (0.0%)	NA
	Cholelithiasis	0 (0.0%)	NA	2 (0.5%)	1563, 1065
Infections and Infestations	Abscess limb	1 (0.3%)	1878	0 (0.0%)	NA
	Appendicitis	0 (0.0%)	NA	1 (0.3%)	1112
	Bronchopneumonia	1 (0.3%)	1326	0 (0.0%)	NA
	Groin abscess	0 (0.0%)	NA	1 (0.3%)	1153
	Neurocysticercosis	1 (0.3%)	1092	0 (0.0%)	NA
	Pulmonary TB	2 (0.5%)	1730, 1375	1 (0.3%)	915
	Pyelonephritis	0 (0.0%)	NA	2 (0.5%)	1165, 1879
	Tubo-ovarian abscess	1 (0.3%)	818	0 (0.0%)	NA
Injury, poisoning and procedural complications	Anasethetic complication	1 (0.3%)	1148	0 (0.0%)	NA
	Failed forceps delivery	1 (0.3%)	1866	0 (0.0%)	NA
	Head injury	1 (0.3%)	534	0 (0.0%)	NA
	Hip fracture	1 (0.3%)	835& 1064	0 (0.0%)	NA
	Incisional hernia	1 (0.3%)	1627	0 (0.0%)	NA
	Multiple fractures	0 (0.0%)	NA	1 (0.3%)	1845
	Post procedural hemorrhage	0 (0.0%)	NA	1 (0.3%)	1264
Musculoskeletal and connective tissue disorders	Muscle spasms	0 (0.0%)	NA	1 (0.3%)	1641
	Pathological fracture	1 (0.3%)	1044	0 (0.0%)	NA
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine leiomyoma	0 (0.0%)	NA	1 (0.3%)	941
Nervous system disorder	Convulsion	1 (0.3%)	534	0 (0.0%)	NA
Pregnancy, puerperium and perinatal conditions	Abortion complete	0 (0.0%)	NA	1 (0.3%)	499
	Abortion missed	1 (0.3%)	848	2 (0.5%)	1468, 1365
	Abortion spontaneous	6 (1.5%)	1680, 1574, 1187, 756 & 1247, 850, 1069	10 (2.6%)	1303, 1540, 1346, 1265, 2096, 1788, 522, 966, 1135, 1465, 1183, 945
	Abortion spontaneous complete	2 (0.5%)	1467, 1591	0 (0.0%)	NA
	Abortion spontaneous incomplete	1 (0.3%)	1762	2 (0.5%)	1696, 1742
	Chorioamnionitis	0 (0.0%)	NA	1 (0.3%)	2123
	Eclampsia	1 (0.3%)	1279	0 (0.0%)	NA
	Ectopic pregnancy	0 (0.0%)	NA	1 (0.3%)	1721
	Foetal distress syndrome	1 (0.3%)	840	0 (0.0%)	NA
	Intrauterine death	0 (0.0%)	NA	1 (0.3%)	1143
	Placenta praevia	0 (0.0%)	NA	1 (0.3%)	648
	Pre-eclampsia	2 (0.5%)	757, 1936	2 (0.5%)	1630, 2016
	Premature baby	0 (0.0%)	NA	1 (0.3%)	2016
	Premature labor	0 (0.0%)	NA	1 (0.3%)	1732
	Stillbirth	1 (0.3%)	907	0 (0.0%)	NA
Psychiatric disorders	Bipolar disorder	0 (0.0%)	NA	1 (0.3%)	1942&1608& 2015
	Depression	1 (0.3%)	940	1 (0.3%)	808
	Suicidal ideation	1 (0.3%)	1022	0 (0.0%)	NA
	Suicide attempt	0 (0.0%)	NA	2 (0.5%)	1809, 2024
Renal and urinary disorders	Renal colic	0 (0.0%)	NA	1 (0.3%)	737
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	0 (0.0%)	NA	1 (0.3%)	732
	Pneumonia aspiration	1 (0.3%)	1149	0 (0.0%)	NA
	Pneumonitis	0 (0.0%)	NA	1 (0.3%)	1130

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminum hydroxide (DVLP018A)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom

95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 007 M36, Table 63, p. 164-165 and wunsol.xpt dataset

Reviewer's Comment: Similar results were obtained for the ATP cohort for safety. (Source: STN 125259/0, CSR 007 M36, Supplements 215-216, p. 482-484, not shown here).

Pregnancy: During the entire study period, a total of 261 pregnancies (130 in the vaccine group and 131 in the control group) were reported for 217 subjects. The outcomes of these pregnancies are detailed in Table 84. The number of pregnancies not resulting in delivery of a normal, healthy infant was similar or lower in the vaccine compared to the control group. A total of 19 cases of spontaneous abortion, abnormal infant, elective termination, missed abortion or still birth were observed in the vaccine group compared to 29 cases in the control group. None of the abnormal pregnancy outcomes reported as SAE were considered to be related to vaccination by the investigator.

Table 84-Study HPV-007: Outcome of reported pregnancies (Total cohort)

	Vaccine N=130	Control N=131	Total N=261
Pregnancy outcomes	**n (%)**	**n (%)**	**n (%)**
Normal infant	**104 (80.0%)**	**90 (68.7%)**	**194 (74.3%)**
Premature birth	**2 (1.5%)**	**2 (1.5%)**	**4 (1.5%)**
Abnormal infant	**1 (0.8%)**	**5 (3.8%)**	**11 (4.2%)**
Elective termination	**6 (4.6%)**	**5 (3.8%)**	**11 (4.2%)**
Ectopic pregnancies	**0 (0.0%)**	**1 (0.8%)**	**1 (0.4%)**
Spontaneous abortion	**10 (7.7%)**	**15 (11.5%)**	**25 (9.6%)**
Still birth	**1 (0.8%)**	**1 (0.8%)**	**2 (0.8%)**
Lost to follow-up	*	*	**1 (0.4%)**
Pregnancy ongoing	**4 (3.1%)**	**9 (6.9%)**	**13 (5.0%)**
Missed abortion	**1 (0.8%)**	**3 (2.3%)**	**4 (1.5%)**

Control = Aluminium hydroxide (DVLP018A)
N = number of pregnancies
n = number of pregnancies in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
Spontaneous abortion includes missed abortion
*blinded
Source: STN 125259/0, CSR 007 M36, Table 64, p. 166 and wunsol.xpt

The six abnormal pregnancy outcomes (one in the vaccine group and five in the control group) reported during study HPV-007 are as follows:

- Mother's PID 6282 (case ID B0426754B): male neonate was born prematurely at 25 weeks of gestation and developed a respiratory distress. The infant subsequently died. Vaccination of the mother occurred approximately six years before. (Aluminum hydroxide control)
- Mother's PID 6087 (case ID A0506536B): neonate reported with atrial septal defect, patent ductus arteriosus and ventricular septal defect. Vaccination of the mother occurred approximately three years before. (Aluminum hydroxide control)
- Mother's PID 6246 (case ID A0573003B): premature infant (29 weeks of gestation) reported with cardiac murmur and hypoacusis. Vaccination of the mother occurred approximately three years before. (Aluminum hydroxide control)
- Mother's PID 7064 (case ID B0337332B): male premature infant (24 weeks of gestation) reported with congenital foot malformation. Vaccination of the mother occurred approximately 2.5 years before. (Aluminum hydroxide control)
- Mother's PID 7392 (case ID B0448422B): male neonate developed a congenital bacterial infection. Of note, the mother had a clinical diagnosis of chorioamnionitis due to rupture of the amniotic membranes, suspected to have occurred four days before delivery. Vaccination of the mother occurred approximately six years before. (Aluminum hydroxide control)

- Mother's PID 7650 (case ID B0402771B): male fetus having presented an atrial flutter was born by cesarian section after 36 weeks of pregnancy. Neither structural cardiac anomalies nor other anomalies were found. Vaccination of the mother occurred approximately five years before. (HPV 16/18 vaccine)

All the mothers (study subjects) of the above abnormal infants were exposed to vaccine or aluminum control long before conception.

Safety analysis by region: The results of the analysis of AEs, NOCDs, NOADs and SAEs by region (North America and Brazil) are provided. No apparent differences in the incidence of AEs, NOCDs, NOADs and SAEs were observed between study groups in the analysis by regions. (Source: STN 125259/0, CSR 007 M36, Supplements 205-226, p. 461-505, not shown here).

Safety conclusions: Overall, the safety profile of the vaccine group was similar to that of the control group, with, in fact, fewer events reported in the vaccine group for most analyses from the end of study HPV-001 throughout the entire HPV-007 study period.

IMMUNOGENICITY RESULTS

Data sets analyzed: Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and the Total cohort.

Subjects were enrolled into study HPV-007 on dates that were independent from the date of first vaccination in study HPV-001. As a result, the time points for immunogenicity measurement in study HPV-007 differed between subjects, in reference to vaccine administration. Actual dates of samples collection were used for each subject, and time periods for analysis were defined as 6-month intervals indicating the number of months between the first vaccination visit in study HPV-001 and the blood sampling visit in study HPV-007.

In study HPV-007, ELISA version 2 was used.

Anti-HPV-16/18 antibodies measured by ELISA

An overview of the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies at each time point is shown in Tables 85and 86, respectively. Only a limited number of subjects had results allocated to the last time interval (Month 75-76).

Up to 76 months following first vaccination in study HPV-001 (up to 70 months following completion of the full vaccination course), 98.6% or more of the vaccinees remained seropositive for both HPV-16 and HPV-18 as measured by ELISA. GMT levels for both HPV-16 and HPV-18 reached a plateau during study HPV-007 at approximately one log below the peak response level observed at Month 7 (in study HPV-001) without substantial evidence of further decline between Month 18 and the last time intervals evaluated (Months 69-74 and 75-76).

At the two last intervals (Month 69-74 and Month 75-76), vaccine-induced GMTs were higher than those elicited by natural infection for anti HPV-16 antibodies and for anti HPV-18 antibodies. GMT values for natural infection were obtained from subjects evaluated in a phase III study (HPV-008) who had developed a natural infection and cleared it prior to enrolment, i.e., subjects who were DNA negative and seropositive for the respective HPV type at enrolment (GMT levels corresponding to natural infection in study HPV-008 were 29.8 EL.U/mL (95% CI: [95% CI:28.5; 31.0]) for HPV-16 and 22.6 EL.U/mL (95% CI: [95% CI:21.6; 23.6]) for HPV-18). The sponsor selected this population because it was considered to be the most relevant to indicate GMTs that may reflect protective immune responses against natural infection.

Table 85-Study HPV-007: Seropositivity rates and GMTs for anti-HPV-16 IgG antibodies (ATP cohort for immunogenicity)

				≥ 8 EL. U/mL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-16 IgG	Vaccine	PRE	301	18	6.0	3.6	9.3	4.3	4.2	4.4	<8.0	30.0
		PIII(M7)	301	301	100	98.8	100	4197.5	3766.1	4678.3	65.0	34561.0
		PIII(M12)	302	302	100	98.8	100	1241.0	1094.7	1406.8	70.0	25655.0
		PIII(M18)	300	299	99.7	98.2	100	737.8	651.0	836.2	<8.0	10228.0
		[M25-M32]	71	70	98.6	92.4	100	670.4	489.2	918.8	<8.0	9900.0
		[M33-M38]	172	171	99.4	96.8	100	454.7	381.7	541.6	<8.0	4974.0
		[M39-M44]	126	126	100	97.1	100	567.8	475.9	677.4	46.0	5264.0
		[M45-M50]	190	190	100	98.1	100	399.4	340.6	468.5	29.0	4562.0
		[M51-M56]	100	100	100	96.4	100	622.8	506.1	766.5	74.0	6137.0
		[M57-M62]	179	179	100	98.0	100	426.7	362.0	503.0	29.0	5479.0
		[M63-M68]	103	103	100	96.5	100	542.3	439.7	668.7	64.0	5659.0
		[M69-M74]	178	177	99.4	96.9	100	394.3	332.0	468.4	<8.0	4233.0
		[M75-M76]	52	52	100	93.2	100	463.6	360.8	595.5	89.0	4707.0

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
Source: STN 125259/0, CSR 007 M36, Table 46, p. 139

Table 86-Study HPV-007: Seropositivity rates and GMTs for anti-HPV-18 IgG antibodies (ATP cohort for immunogenicity)

				≥ 7 EL. U/mL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-18 IgG	Vaccine	PRE	301	30	10.0	6.8	13.9	3.9	3.8	4.1	<7.0	33.0
		PIII(M7)	300	300	100	98.8	100	3358.0	3041.8	3707.0	107.0	45888.0
		PIII(M12)	302	302	100	98.8	100	995.3	888.5	1115.0	91.0	30401.0
		PIII(M18)	300	299	99.7	98.2	100	591.9	524.7	667.8	<7.0	7518.0
		[M25-M32]	71	70	98.6	92.4	100	596.9	439.6	810.5	<7.0	12988.0
		[M33-M38]	172	171	99.4	96.8	100	378.6	320.0	447.9	<7.0	3711.0
		[M39-M44]	127	126	99.2	95.7	100	435.1	351.1	539.0	<7.0	11173.0
		[M45-M50]	190	190	100	98.1	100	297.5	254.4	348.0	22.0	5649.0
		[M51-M56]	100	100	100	96.4	100	454.9	370.8	558.1	23.0	8272.0
		[M57-M62]	179	179	100	98.0	100	322.5	274.9	378.4	23.0	4775.0
		[M63-M68]	103	103	100	96.5	100	359.9	295.0	439.2	24.0	6130.0
		[M69-M74]	178	177	99.4	96.9	100	305.3	258.1	361.1	<7.0	3415.0
		[M75-M76]	52	52	100	93.2	100	279.8	218.0	359.1	55.0	2408.0

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
Source: STN 125259/0, CSR 007 M36, Table 47 p. 140

Reviewer's Comment: For anti-HPV 16 antibodies, a smaller number of subjects was tested at M75-76, but 100% of tested subjects were seropositive, with a mean GMT of 360.8. 100% seropositivity was also noted for testing of anti-HPV 18 antibodies. For the control recipients, the proportion of subjects who were seropositive for anti-HPV 16 anytime during the study was as high as 20%, although the GMTs were much lower in those with natural infection. At the last time point, 11.4% were seropositive and the maximum GMT was 17.0. For control subjects, the

proportion of subjects who were seropositive for anti-HPV 18 anytime during the study was as high as 20%. At the last time point, 14.3% were seropositive and the maximum GMT was 27.0.

Reverse cumulative distribution curves are very similar for anti-HPV 16 for Months 33-38, 45-50, and 69-74. Similarly, reverse cumulative distribution curves are very similar for anti-HPV 18 at these same time points. (Source: STN 125259/0, CSR 007 M36, Figures 16 and 17, p. 142).

Reviewer's Comment: The sponsor also presented separate RCDCs for Month 18, 25-32 and 33-38; for Month 39-44, 45-50 and 51-56; and for Month 57-62, 63- 68, 69-74 and 75-76. The curves are similar to each other when the time periods are broken down into smaller time periods. (Source: STN 125259/0, CSR 007, Month 36, Supplements 171-176, p. 425-427, not shown here).

As no breakthrough cases of persistent HPV-16/18 infection (6-month and 12-month definition) were observed in the vaccine group during studies HPV-001 and HPV-007, and as only three cases of breakthrough HPV 16/18 incident infection were reported in the vaccine group, the sponsor was not able to calculate an immune correlate of protection. The ELISA titers obtained for these subjects with breakthrough infection were provided in Table 87.

Table 87-Study HPV-007: GMTs for anti-HPV-16 and anti-HPV-18 IgG antibodies (by ELISA) for vaccine subjects with breakthrough incident infection

	Timing							
	PRE	PIII(M7)	PIII(M12)	PIII(M18)	[M39-M44]	[M45-M50]	[M57-M62]	[M75-M76]
Subject with breakthrough HPV-16 incident infection (Month 35)								
HPV-16 GMT	<8	982	145	197	139	102	123	145
HPV-18 GMT	<7	1110	158	190	97	73	53	48
Subject with breakthrough HPV-16 incident infection (Month 35)								
	PRE	PIII(M7)	PIII(M12)	PIII(M18)	[M33-M38]	[M45-M50]	[M57-M62]	[M69-M74]
HPV-16 GMT	<8	1438	504	350	180	167	152	149
HPV-18 GMT	<7	968	325	136	85	74	81	95
Subject with breakthrough HPV-18 incident infection (Month 35)								
	PRE	PIII(M7)	PIII(M12)	PIII(M18)	[M33-M38]	[M45-M50]	[M57-M62]	[M69-M74]
HPV-16 GMT	<8	689	223	168	123	79	468	674
HPV-18 GMT	<7	2214	801	673	545	401	417	482

GMT = geometric mean antibody titre (EL. U/mL; assay cut-off for HPV-16: ≥ 8 EL.U/mL; assay cut-off for HPV-18: ≥ 7 EL.U/mL)
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7)
PIII(M12) = Post Dose III (Month 12)
PIII(M18) = Post Dose III (Month 18)
Source: STN 125259/0, CSR 007 M36, Supplement 177, p. 428

V5/J4 monoclonal antibodies measured by inhibition enzyme immunoassay: Similar to the results with ELISA, GMT levels for both HPV-16 and HPV-18 by inhibition tests showed a plateau that began approximately at Month 18 post vaccination and was sustained over time. Seropositivity rates (range: 56.7% to 98.5% for HPV-16 and 26.7% to 98.5% for HPV-18) were lower than observed by ELISA (≥ 98.6% for both antigens), were assessed by the sponsor as probably a consequence of the lower sensitivity of the monoclonal antibody inhibition enzyme immunoassay.

Anti-HPV-16/18 neutralizing antibodies measured by pseudovirion neutralization assay: The seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 pseudovirion neutralizing antibodies in a subset of subjects were presented. Similar to the results with ELISA, GMT levels for both HPV-16 and HPV-18 by assays for pseudovirion neutralizing antibodies showed a plateau that began approximately at Month 18 post vaccination and was maintained for up to 76

months of follow-up. Seropositivity rates for both HPV-16 and HPV-18 (≥ 98.0%) were similar to those observed with ELISA (≥ 98.6%).

Table 88-Study HPV-007: Seropositivity rates and GMTs for anti-HPV-16 pseudovirion neutralizing antibodies (ATP cohort for immunogenicity; subset)

				≥ 40 ED50				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-16 PSV AB	HPV	PRE	87	2	2.3	0.3	8.1	21.0	19.6	22.4	<40.0	174.0
		PIII(M7)	87	87	100	95.8	100	23579.4	18473.6	30096.4	499.0	655360.0
		PIII(M12)	21	21	100	83.9	100	9668.0	5024.0	18604.7	321.0	178449.0
		PIII(M18)	85	85	100	95.8	100	4060.9	3207.4	5141.7	317.0	90626.0
		[M25-M32]	29	29	100	88.1	100	3404.5	2160.3	5365.4	606.0	52711.0
		[M33-M38]	49	49	100	92.7	100	2222.3	1496.6	3300.0	51.0	25327.0
		[M39-M44]	49	48	98.0	89.1	99.9	2925.4	1979.1	4324.2	<40.0	51984.0
		[M45-M50]	55	54	98.2	90.3	100	2124.9	1434.0	3148.7	<40.0	28728.0
		[M51-M56]	41	41	100	91.4	100	3220.9	2056.8	5043.9	232.0	441024.0
		[M57-M62]	50	49	98.0	89.4	99.9	2038.0	1303.1	3187.4	<40.0	41919.0
		[M63-M68]	39	39	100	91.0	100	2846.4	1933.7	4190.1	423.0	77872.0
		[M69-M74]	53	53	100	93.3	100	1963.1	1382.0	2788.5	82.0	26112.0
		[M75-M76]	18	18	100	81.5	100	4695.6	2623.4	8404.6	625.0	94179.0

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
PSV AB = pseudovirion neutralizing antibodies
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
Source: STN 125259/0, CSR 007 M36, Table 50, 146

Table 89-Study HPV-007: Seropositivity rates and GMTs for anti-HPV-18 pseudovirion neutralizing antibodies (ATP cohort for immunogenicity; subset)

				≥ 40 ED50				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-18 PSV AB	HPV	PRE	87	0	0.0	0.0	4.2	20.0	20.0	20.0	<40.0	<40.0
		PIII(M7)	87	87	100	95.8	100	13941.6	11025.2	17629.4	273.0	227155.0
		PIII(M12)	21	21	100	83.9	100	3823.4	2347.3	6227.7	377.0	26373.0
		PIII(M18)	85	85	100	95.8	100	1870.9	1428.5	2450.3	123.0	42975.0
		[M25-M32]	30	30	100	88.4	100	1234.6	760.8	2003.4	90.0	7925.0
		[M33-M38]	49	49	100	92.7	100	1059.4	744.6	1507.3	75.0	13592.0
		[M39-M44]	49	48	98.0	89.1	99.9	959.9	659.1	1397.9	<40.0	11101.0
		[M45-M50]	55	54	98.2	90.3	100	718.0	514.3	1002.4	<40.0	10690.0
		[M51-M56]	41	41	100	91.4	100	926.7	611.2	1404.9	66.0	14885.0
		[M57-M62]	50	50	100	92.9	100	804.6	542.7	1193.0	67.0	18407.0
		[M63-M68]	39	39	100	91.0	100	802.0	549.3	1171.0	103.0	7348.0
		[M69-M74]	53	53	100	93.3	100	955.0	670.0	1361.0	58.0	9519.0
		[M75-M76]	18	18	100	81.5	100	652.9	356.0	1197.6	105.0	4411.0

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
PSV AB = pseudovirion neutralizing antibodies
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
Source: STN 125259/0, CSR 007 M36, Table 51, 147

Reviewer's Comment: In the control group for HPV 16, there was 1 subject who developed pseudovirion neutralizing antibodies at M7 (GMT 291), and 1 subject who developed pseudovirion neutralizing antibodies at M45-40 (GMT 70). In the control group for HPV 18, there was 1 subject who developed pseudovirion neutralizing antibodies to HPV 18 at M69-74 (GMT 43.0).

Immunogenicity analysis by region: Although the GMTs for HPV 16 and 18 were numerically higher for both HPV 16 and 18 in North America as compared to Brazil, the 95% CIs around the GMTs were overlapping, and no difference in efficacy was noted. (Source: STN 125259/0, CSR 007, M36, Supplement 182-185, p. 431-434, not shown here).

ATP kinetic cohort analysis: To better assess the immune response over time, a post-hoc analysis of the ATP kinetic cohort was performed with data collected from subjects in both studies HPV-001 and HPV-007 who had blood samples available for all time points or time intervals. Only subjects from the vaccine group were evaluated in the kinetic cohort. The ATP kinetic cohort included all subjects from the ATP cohort for immunogenicity who had an ELISA result at all time points in study HPV-001 and at the Months 33-38, 45-50, 57-62 and 69-74 intervals in study HPV-007. The seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies for the ATP kinetic cohort are presented. GMT levels for this cohort showed a plateau that began approximately 18 months after first vaccination and was sustained over time (up to Months 69-74 of follow up). Seropositivity rates for both antibodies remained close to 100% up to 6 years post vaccination. The results are similar to those obtained for the ATP cohort for immunogenicity (primary analysis).

Table 90- Study HPV-007: Seropositivity rates and GMTs for anti-HPV-16 IgG antibodies (Vaccine group, ATP kinetic cohort for immunogenicity)

				≥ 8 EL. U/mL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-16 IgG	Vaccine	PRE	136	10	7.4	3.6	13.1	4.4	4.1	4.6	<8.0	28.0
		PIII(M7)	136	136	100	97.3	100	3819.4	3200.9	4557.4	65.0	34561.0
		PIII(M12)	136	136	100	97.3	100	991.2	828.0	1186.6	99.0	9795.0
		PIII(M18)	136	136	100	97.3	100	633.5	532.5	753.7	49.0	4510.0
		[M33-M38]	136	136	100	97.3	100	437.0	363.1	526.0	39.0	3648.0
		[M45-M50]	136	136	100	97.3	100	382.9	316.5	463.2	29.0	3971.0
		[M57-M62]	136	136	100	97.3	100	388.1	321.5	468.6	29.0	4252.0
		[M69-M74]	136	136	100	97.3	100	351.1	290.2	424.8	27.0	3927.0

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
Source: STN 125259/0, CSR 007 M36, Table 52, 150

Table 91-Study HPV-007: Seropositivity rates and GMTs for anti-HPV-18 IgG antibodies (Vaccine group, ATP kinetic cohort for immunogenicity)

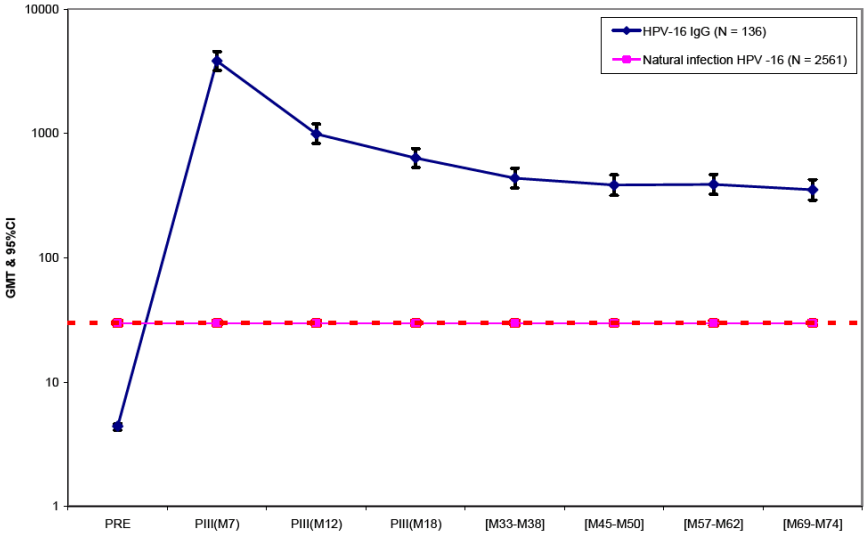
				≥ 7 EL. U/mL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-18 IgG	Vaccine	PRE	135	12	8.9	4.7	15.0	3.9	3.7	4.2	<7.0	33.0
		PIII(M7)	135	135	100	97.3	100	3197.1	2740.0	3730.4	107.0	25776.0
		PIII(M12)	135	135	100	97.3	100	807.4	681.2	957.0	91.0	15304.0
		PIII(M18)	135	135	100	97.3	100	502.7	423.7	596.5	46.0	7518.0
		[M33-M38]	135	135	100	97.3	100	355.4	295.8	427.1	36.0	3711.0
		[M45-M50]	135	135	100	97.3	100	289.0	238.5	350.2	22.0	5649.0
		[M57-M62]	135	135	100	97.3	100	288.6	239.9	347.3	23.0	4775.0
		[M69-M74]	135	134	99.3	95.9	100	260.2	213.8	316.7	<7.0	3415.0

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Prevaccination

PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
Source: STN 125259/0, CSR 007 M36, Table 53, 150

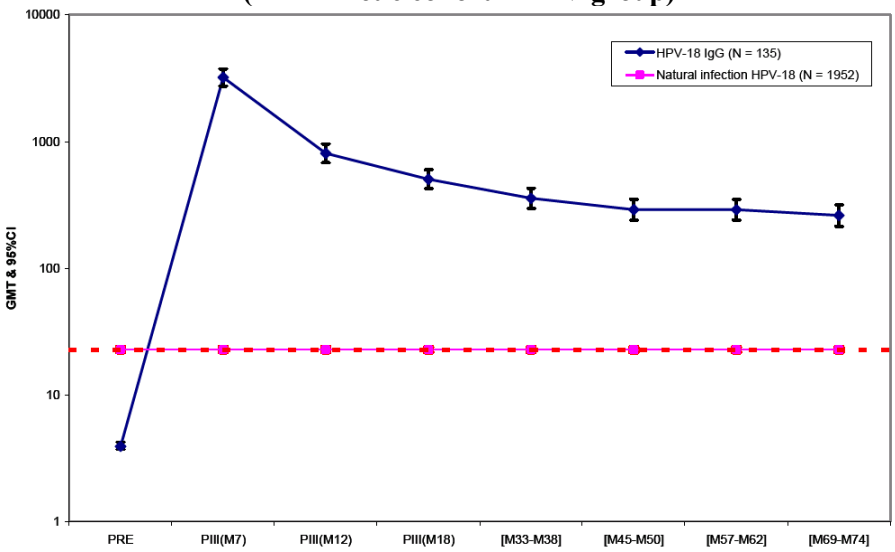
The kinetics of anti-HPV-16 and anti-HPV-18 antibody responses are shown in Figures 16 and 17, respectively. The antibody titers were well above those elicited by naturally acquired infection at each time point post vaccination. Peak antibody levels at Month 7 followed by gradual decline of antibodies until Month 18) are noted. Similar to other studies, the decrease of the antibody levels from Month 18 onwards is less pronounced than the decrease observed at earlier time points.

Figure 16-Study HPV-007: Kinetics for anti-HPV-16 IgG antibodies (ATP kinetic cohort – HPV group)



Note: antibody levels associated with naturally-acquired HPV-16/18 infection are shown by a horizontal line; GMT values for natural infection were obtained from baseline sera samples of subjects in the phase III study HPV-008 who were seropositive and HPV DNA negative for the respective HPV type.
Source: STN 125259/0, CSR 007 M36, Figure 20, 151

Figure 17-Study HPV-007: Kinetics for anti-HPV-18 IgG antibodies (ATP kinetic cohort – HPV group)



Note: antibody levels associated with naturally-acquired HPV-16/18 infection are shown by a horizontal line; GMT values for natural infection were obtained from baseline sera samples of subjects in the phase III study HPV-008 who were seropositive and HPV DNA negative for the respective HPV type.
Source: STN 125259/0, CSR 007 M36, Figure 21, 151

Analysis of total cohort: The data for the Total cohort were reviewed and were consistent with those in the ATP cohort. (Source: STN 125259/0, CSR 007 M36, Supplements 186-195, p. 435-442, not shown here).

HPV-007, Annex 1: This report summarizes the evaluation of the immune response against nonvaccine oncogenic HPV types (HPV-31 and HPV-45) in terms of binding ELISA a and neutralizing antibodies (pseudovirion assay) in studies HPV-001 and HPV-007. Data are presented for binding ELISA up to 56 months of follow-up post dose 1 (studies HPV-001 and HPV-007) and for neutralizing antibodies (pseudovirion assay) up to 50 months of follow-up post dose 1 (studies HPV-001 and HPV-007), in subjects that participated in study HPV-001 and received all three doses of vaccine/control.

Study time points and laboratory assays: The outline of the study time points for the serum samples that were tested using the anti-HPV-31 and anti-HPV-45 binding ELISA and neutralization assay are presented in Table 92. The laboratory assays used are shown in Table 93. All assays were performed at GSK Biologicals laboratories.

Table 92-Study HPV-007, Annex 1: Outline of study time points for anti-HPV-31 and anti-HPV-45 binding ELISA and neutralization assay

Timing	Study	
	HPV-001	HPV-007†
Day 0	●	●
Month 7	●	
Month 12	●	●
Month 24		●

†Subjects were enrolled into study HPV-007 independently from the date of first vaccination in study HPV-001. As a result, the time points planned according to the protocol for immunogenicity measurement in study HPV-007 (Months 0, 12, 24 and 36, where Month 0 was defined as the start of HPV-007) differ between subjects. Therefore, each subject was allocated to a time point in study HPV-007 at approximately 6-month intervals based on the length of time since first vaccine administration in study HPV-001 (i.e months 25-32; 33-38; 39-44; 45-50; 51-56 post Dose 1 in study HPV-001) and not according to protocol-defined sampling time points.
Source: STN 125259/0, CSR 007 M24 Annex 1, Table 1, p. 8

Table 93-Study HPV-007, Annex 1: Immunological assays for HPV-31 and HPV-45

Antigen	Assay method	Assay unit	Assay cut-off
HPV-31	Binding ELISA	EL.U/mL	(b)(4)
HPV-45	Binding ELISA	EL.U/mL	
HPV-31	Neutralizing	ED 50	40
HPV-45	Neutralizing	ED 50	40

ED 50 = Estimate Dose 50 % (the estimated serum dilution reducing the signal generated by viral infection by 50 %).
Source: STN 125259/0, CSR 007 M24 Annex 1, Table 2, p. 9

Statistical evaluation: Subjects were enrolled into study HPV-007 independently from the date of first vaccination in study HPV-001. As a result, the time points planned according to the protocol for immunogenicity measurement in study HPV-007 (Months 0, 12, 24 and 36, where Month 0 was defined as the start of study HPV-007) differ between subjects. Because these time points differ between subjects, each subject was allocated to a time point in study HPV-007 at approximately 6-month intervals based on the length of time since first vaccine administration in study HPV-001 (i.e. Months 25-32; 33-38; 39-44; 45-50 and 51-56 post Dose 1 in study HPV-001) and not according to protocol-defined sampling time points. Seropositivity rates and geometric mean titers (GMTs) with 95% CIs were calculated for each interval, starting from the minimum time point to the maximum time point available.

The primary analysis was based on the ATP cohort for analysis of immunogenicity. A second analysis based on the Total cohort was performed to complement the ATP analysis.

The level of antibodies for both HPV-31 and HPV-45 was evaluated by computing the Geometric Mean Titers (GMTs) for each blood sampling time point:

- The GMT calculations were performed by taking the anti-log of the mean of the log titer transformations. Antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation.
- A seronegative subject was a subject whose antibody concentration/titer was below the cut-off value.
- A seropositive subject was a subject whose antibody concentration/titer was greater than or equal to the cut-off value.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

For each treatment group, at each time point that a blood sample result was available:

- seropositivity rates for both HPV-31 and HPV-45 ELISA titers, and pseudovirion neutralizing antibody assay (subset of subjects) (with exact 95% CI) were calculated by group,
- GMTs with 95% CI were tabulated for antibodies for each antigen and each test.

Statistical analyses were performed using Statistical Analysis System (SAS) 8.2. For the anti-HPV-31 and anti-HPV-45 binding ELISA and neutralization assay, a subset of 80 subjects (consisting of 40 subjects in the HPV group and 40 subjects in the control group) selected by laboratory personnel based on Month 7 immunogenicity results were used to evaluate the cross-reactivity by binding ELISA and neutralization assay (anti-HPV-31 and anti-HPV-45) for serological sampling timepoints in study HPV-001 (Day 0, Month 7 and Month 12). For the serological sampling timepoints in study HPV-007 (Day 0, Month 12 and Month 24), this subset was supplemented by subjects from the protocol-specified subset of 150 subjects (100 subjects in the HPV group and 50 subjects in the control group). This combined subset was also used for the neutralization assay for anti-HPV-16 and anti-HPV-18. If there was an insufficient blood sample volume to perform immunogenicity testing, testing was first performed for HPV-16 and HPV-18 and thereafter the ranking was first HPV-31 and then HPV-45 testing.

Immunogenicity results

HPV-31 and HPV-45 binding ELISA results: All subjects were seropositive for both antigens at Month 7, with GMTs of 1150.5 EL.U/mL [95% CI: 790.3; 1674.9] for HPV-31 and 1292.1 ELU/mL [95% CI: 948.1; 1760.9] for HPV-45. After, titers for both HPV-31 and HPV-45 reached a plateau at Months [95% CI: 25-32] that persisted until the last time-point evaluated (Months [95% CI: 51-56]), or 56 months following first vaccination. 69.2% of subjects were seropositive for anti- HPV-31 antibodies and 92.3% of subjects seropositive for anti- HPV-45 at Months [51-56].

Table 94-Study HPV-007, Annex 1: Seropositivity rates and GMTs for anti-HPV-31 VLP IgG antibodies following vaccination with HPV-16/18 VLPs (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	(b)(4) EL.U/mL				GMT			Min	Max
				n	%	95% CI			95% CI			
						LL	UL	value	LL	UL		
HPV 31.VLP IgG	Vaccine	PRE	34	2	5.9	0.7	19.7	32.6	28.3	37.5	<59.0	199.0
		PIII(M7)	33	33	100	89.4	100	1150.5	790.3	1674.9	180.0	28230.0
		PIII(M12)	34	32	94.1	80.3	99.3	274.6	189.2	398.7	<59.0	7024.0
		[M25-M32]	24	20	83.3	62.6	95.3	160.1	104.2	246.1	<59.0	647.0
		[M33-M38]	35	28	80.0	63.1	91.6	139.0	97.7	197.6	<59.0	717.0
		[M39-M44]	40	35	87.5	73.2	95.8	178.3	128.0	248.4	<59.0	2613.0
		[M45-M50]	43	38	88.4	74.9	96.1	184.4	129.0	263.4	<59.0	2719.0
		[M51-M56]	13	9	69.2	38.6	90.9	152.9	63.9	366.1	<59.0	3157.0
	Placebo	PRE	28	2	7.1	0.9	23.5	32.3	28.2	37.0	<59.0	160.0
		PIII(M7)	28	3	10.7	2.3	28.2	33.0	28.9	37.7	<59.0	117.0
		PIII(M12)	28	2	7.1	0.9	23.5	31.7	28.6	35.1	<59.0	89.0
		[M25-M32]	9	0	0.0	0.0	33.6	29.5	29.5	29.5	<59.0	<59.0
		[M33-M38]	15	3	20.0	4.3	48.1	36.8	28.5	47.4	<59.0	100.0
		[M39-M44]	11	2	18.2	2.3	51.8	38.0	26.0	55.4	<59.0	126.0
		[M45-M50]	16	3	18.8	4.0	45.6	35.0	28.7	42.8	<59.0	87.0
		[M51-M56]	3	0	0.0	0.0	70.8	29.5	29.5	29.5	<59.0	<59.0

Vaccine = HPV-16/18 L1 VLP AS04 vaccine (DVLP017A)
Control = Control (DVLP018A)
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7)
PIII(M12) = Post Dose III (Month 12)
Source: STN 125259/0, CSR 007 M24 Annex 1, Table 3, p. 11

Table 95-Study HPV-007, Annex 1Seropositivity rates and GMTs for anti-HPV 45 VLP IgG antibodies following vaccination with HPV-16/18 VLPs (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	(b)(4) EL. U/mL				GMT			Min	Max
				n	%	95% CI			95% CI			
						LL	UL	value	LL	UL		
HPV 45.VLP IgG	Vaccine	PRE	34	3	8.8	1.9	23.7	33.0	28.9	37.6	<59.0	149.0
		PIII(M7)	33	33	100	89.4	100	1292.1	948.1	1760.9	156.0	10498.0
		PIII(M12)	34	34	100	89.7	100	336.9	240.9	471.3	77.0	2389.0
		[M25-M32]	24	22	91.7	73.0	99.0	209.3	136.0	322.2	<59.0	836.0
		[M33-M38]	35	30	85.7	69.7	95.2	180.4	120.9	269.3	<59.0	1781.0
		[M39-M44]	40	36	90.0	76.3	97.2	195.8	140.1	273.6	<59.0	3064.0
		[M45-M50]	43	36	83.7	69.3	93.2	168.0	112.7	250.4	<59.0	7068.0
		[M51-M56]	13	12	92.3	64.0	99.8	143.8	84.7	244.1	<59.0	658.0
	Placebo	PRE	28	1	3.6	0.1	18.3	30.6	28.4	32.8	<59.0	79.0
		PIII(M7)	28	2	7.1	0.9	23.5	31.7	28.6	35.1	<59.0	85.0
		PIII(M12)	28	2	7.1	0.9	23.5	31.6	28.6	35.0	<59.0	91.0
		[M25-M32]	9	0	0.0	0.0	33.6	29.5	29.5	29.5	<59.0	<59.0
		[M33-M38]	15	1	6.7	0.2	31.9	35.1	24.2	50.7	<59.0	392.0
		[M39-M44]	11	2	18.2	2.3	51.8	41.9	24.8	70.9	<59.0	214.0
		[M45-M50]	16	3	18.8	4.0	45.6	38.8	27.7	54.5	<59.0	217.0
		[M51-M56]	3	2	66.7	9.4	99.2	69.1	9.9	484.0	<59.0	138.0

Vaccine = HPV-16/18 L1 VLP AS04 vaccine (DVLP017A)
Control = Control (DVLP018A)
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Prevaccination; PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12)
Source: STN 125259/0, CSR 007 M24 Annex 1, Table 4, p. 12

HPV-31 and HPV-45 neutralizing assay results: The analysis of neutralizing antibodies to HPV-31 and HPV-45 revealed very low levels of titers induced following HPV-16/18 vaccination, with detectable antibodies at the peak response at Month 7 observed in 47.6% and 9.5% of subjects for HPV-31 and HPV-45, respectively and then, at Month 12, in 9.5% and 0% of the subjects for HPV-31 and HPV-45, respectively.

Reveiwer's Comment: Very few subjects seroconverted for anti-HPV 31 PSV antibodies and only 9.5% seroconverted for anti-HPV 45 PSV at Month 7, then none thereafter. It is acknowledged that antibodies to both HPV 31 HPV 45 as measured by ELISA were higher than those who received control material. It is possible that a higher level of antibodies to phylogenetically related HPV types (HPV 31 for HPV 16 and HPV 45 for HPV 18) may be required, but it is not clear as to how long the antibodies will last. Antibodies as measured by PSV for HPV 16 and HPV 18 were much higher than those noted for HPV-31 and HPV-45, and nearly all subjects who received vaccine seroconverted. Results are similar for the Total Cohort. (Source: STN 125259/0, CSR 007 M24 Annex 1, Supplements 1-4, p. 16-19, not shown here).

Extension study HPV-023 and fourth dose study HPV-024: GSK indicates they are extending the assessment of Cervarix in part of the cohort (study sites in Brazil). This extension of the long-term follow-up is being conducted under a separate study protocol (study number 109616 / 109624 / 109625 [HPV-023 Ext 001]) and will evaluate the long-term efficacy in the prevention of cervical infection with HPV-16 and/or HPV-18, persistence of vaccine-induced immune responses and safety of the vaccine administered in study HPV-001 with a similar study design to study HPV-007.

HPV-007 study participants from the North American cohort have been invited to participate in a fourth dose study (study number 109628 [HPV-024 BST 001]) to evaluate the safety and immunogenicity of a fourth dose of HPV-16/18 L1/AS04 vaccine administered approximately seven years post vaccination. Subjects who received control in study HPV-001 are offered cross-over vaccination with the HPV-16/18 L1/AS04 vaccine.

CONCLUSIONS FOR STUDY HPV-007: This study demonstrated longer term efficacy in prevention of HPV 16 and/or 18 incident infection as well as 6- and 12-month persistent infection out to 6.4 years after dose 1 in subjects naïve for the corresponding vaccine HPV type. In addition, there was evidence of prevention of HPV 16 and/or 18 related CIN2+ in subjects naïve for the corresponding vaccine HPV type at this time point as well. Efficacy for non-vaccine HPV types is discussed in study HPV-008 which has a larger sample size. There were no identified safety issues. The immune responses as measured by ELISA (anti-HPV-16 and anti-HPV-18 IgG) were detected out to Month 76. The antibody response to anti-HPV-31 and anti-HPV-45 (IgG by ELISA) were >80% out to Month 50, although the antibody response as tested by pseudovirion neutralization was not detected at Month 50.

PIVOTAL EFFICACY STUDY

8.6: Trial #6: HPV-008: A phase III, double-blind, randomized, controlled, multi-center study to evaluate the efficacy of GlaxoSmithKline Biologicals' HPV-16/18 VLP/AS04 vaccine compared to hepatitis A vaccine as control in prevention of persistent HPV-16 or HPV-18 cervical infection and cervical neoplasia, administered intramuscularly according to a 0, 1, 6 month schedule in healthy females 15-25 years of age.

Study Dates: 5/6/04-8/31/08 (data lock point); database freeze for final analysis 10/24/08

Study Site: This study was being conducted by 131 principal investigators (135 centers) in 14 countries (Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK and USA) at the time of the final analysis.

This study report is the final efficacy analysis for the pivotal efficacy trial for Cervarix. In 2007, the sponsor submitted an interim analysis of the HPV-008 study assessing vaccine efficacy against CIN2+, CIN1+ and persistent infection (6-month and 12-month definition) associated with HPV-16 and/or HPV-18, as well as efficacy against 6-month persistent infection with HPV types 45, 31 and 52.

However, CBER had several concerns regarding the results of the efficacy and safety results presented in this study. A complete response letter was sent to the sponsor in 12/07 with the following issues:

- CBER was unable to assess the benefits and risk of the product because both safety and efficacy data were deficient. CBER stated that the final efficacy data from study HPV-008 and unblinded safety data were needed for complete assessment of the application.
- The product contains both HPV Virus Like Particles (VLPs) with AS04 adjuvant added to enhance the immune response to the HPV vaccine antigens. CBER determined that there were numerical imbalances for neuroinflammatory adverse events and musculoskeletal events of potential autoimmune etiology in the two treatment groups (vaccine vs. control). Given the imbalances observed in subjects who received Cervarix compared to those receiving controls, CBER was concerned about the possibility that these imbalances may be due to AS04 adjuvant. Given this concern, and in light of the relevant regulation (21 CFR 61 0.15(a), an adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety of the product), CBER required additional efficacy and safety data to make this assessment.
- At the time of the interim efficacy analysis, the study was unblinded to a firewall group in order to maintain integrity of the trial as it proceeded. Due to this situation, presentation of safety data was still partially blinded and incomplete in some instances (although the sponsor did provide requested data throughout the review). CBER requested more comprehensive, cohesive presentations of deaths, pregnancy outcomes, neuroinflammatory events and expert analysis, autoimmune events and expert analysis.
- Results of the interim analysis demonstrated that vaccine efficacy against CIN2+ associated with HPV-18 did not reach statistical significance (VE = 83.3% [-78.8%, 99.9%], p=0.1249).
- The primary efficacy population analyzed at the time of the interim analysis (Total Vaccinated Cohort) was different from the primary efficacy population to be used at the time of the final analysis (According to Protocol Cohort, ATP cohort). For the interim analysis, efficacy objectives were asssessed post dose 1 in adolescent and young adult women who were DNA negative for the corresponding HPV type at Month 0 with normal or low-grade cytology at baseline. At the final analysis, efficacy objectives were to include subjects who were seronegative at baseline and PCR negative through Month 6. Because of this difference, it was noted that of the 23 cases of CIN 2+ used to provide demonstration of efficacy at the time of the interim analysis, 14 subjects became PCR positive for the relevant vaccine HPV type by Month 6 and would not be included at the time of the final efficacy analysis in the primary efficacy population, while the recommended vaccine course would include 3 doses of vaccine. It was unclear how this difference could be reconciled in the labeling instructions.
- In the prevention of persistent infection (6-month definition) with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 (by PCR), there were 14 different secondary analyses, yet no adjustment for alpha was considered. The

interim data were not considered definitively indicative of clinical impact on non-vaccine oncogenic HPV types. CBER also noted that the interim analyses related to persistent and incident infections lacked adjustment and introduced considerable Type I error probability. The same comment applied to the evaluation of histopathologically-confirmed CIN1 + (or CIN2+) associated with the oncogenic HPV types detected within the lesional component of the cervical tissue specimen.

- CBER did not agree with the sponsor conclusion that interim safety data and immune responses in women> 26 years of age provided evidence that Cervarix protects against CIN 2+ associated with HPV 16 or 18 in this older age group. Given the absence of efficacy data in this population against development of CIN 2+, the likelihood that older women are sexually experienced, the type-specific lack of efficacy in females with pre-existing HPV infections, and the incomplete information at the time of interim analysis from Study HPV-015 regarding the proportion of women who were non naive at baseline, CBER could not definitively conclude if Cervarix would prevent HPV 16 or 18 related CIN 2+ in this older age group.
- CBER noted that there was no correlation between immunogenicity and vaccine efficacy identified in Studies HPV-008 and HPV-001/007. CBER felt it was important to investigate the immunogenicity information of those CIN2+ cases associated with HPV-16/18, and requested immunological data for CIN 2+ cases in the study group that received Cervarix.

Because of these issues, further discussions were held between CBER and GSK. It was decided that study HPV-008 would be completed to provide the final efficacy analysis, and then the final response to the Complete Response would be completed. GSK notes that the first major market in which the HPV vaccine under evaluation in this study was licensed is Australia in May 2007 for use in 10 to 45 year old females. The vaccine is marketed under the trade name Cervarix. In September 2007, the vaccine was licensed in the European Union for the prevention of premalignant cervical lesions and cervical cancer causally related to HPV types 16 and 18. The vaccine is currently licensed in more than 90 countries worldwide.

The event-driven final analysis presented in this review was conducted when at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the according-to-protocol (ATP) cohort for efficacy. In addition, a criterion for the number of HPV-18 CIN2+ cases was considered before triggering the final analysis (at least 15 cases) and described in the Report Analysis Plan (RAP). The primary analysis of efficacy objectives was performed on the ATP cohort for efficacy post Dose 3 in women who were DNA negative for the corresponding HPV type at Months 0 and 6. The final analysis was also performed by an external statistician in order to maintain the study blind for individuals involved in the interpretation of the data. It was documented in a separate charter prior to the final analysis that certain data may be unblinded for core members of the clinical team to facilitate the reporting of final data. As a result, individual data (for specific safety events) were unblinded in this final clinical study report. GSK has stated that precautions have been taken to maintain the study blind for the investigators and subjects who are still active in the study.

Objectives

Primary objective: Demonstrate efficacy of the candidate vaccine compared with control in the prevention of histopathologically-confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR). This objective was assessed post Dose 3 in adolescent and young adult women who were

negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA). The principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample.
Reviewer's Comment: The sponsor also assessed efficacy for all histopathological outcomes (primary and secondary endpoints) using an exploratory "HPV type assignment algorithm". In this analysis, for cases with more than one HPV type detected in the lesion the association between the cervical lesion and the HPV type was based not only on the detection of HPV DNA in the lesion, but also evaluated the presence of HPV types in the two immediately preceding cytology samples. CBER acknowledged the rationale for using this algorithm. However, the algorithm was proposed well into the course of the study, and CBER considered these as exploratory analyses. This review includes analyses of endpoints as originally defined for the study. CBER notes that point estimates of efficacy were generally higher when the HPV type assignment algorithm was used.

Secondary objectives: For all serostratified secondary and exploratory efficacy analyses, the principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample. Secondary objectives are presented in the order defined in the protocol.

Secondary Safety Objective: Evaluate the safety of the candidate vaccine in adolescent and young adult women, overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and HPV-16/18 antibody status (by ELISA) throughout the entire study period.

Secondary Virological Objectives:

- Demonstrate efficacy of the candidate vaccine compared with control in the prevention of **persistent infection (12-month definition) with HPV-16 or HPV-18** (by PCR) post Dose 3 in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- Evaluate efficacy of the candidate vaccine compared with control in the prevention of **persistent infection (6-month definition) with HPV-16 or 18** (PCR) post Dose 3 in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- Evaluate efficacy of the candidate vaccine compared with control in the prevention of **persistent infection (6-month definition) with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR).** This objective was assessed post Dose 3 in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type.

Secondary Histopathological Objectives:

- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with the following oncogenic HPV types** (or combination of types) detected within the lesional component of the cervical tissue specimen (by PCR): **HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.**
- Evaluate efficacy of the candidate vaccine compared with control in the prevention of histopathologically-confirmed **CIN1+ associated with HPV-16 or HPV-18** detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).

- Evaluate efficacy of the candidate vaccine compared with control in the prevention of **histopathologically-confirmed CIN1+ associated with the following oncogenic HPV types** (or combination of types) detected within the lesional component of the cervical tissue specimen (by PCR): **HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.**

These objectives were assessed post Dose 3 in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type.

Secondary Immunogenicity Objectives:

- Evaluate **vaccine immunogenicity in a subset of subjects** from selected study sites (immunogenicity subset: N ≥ 2000, at least 500 per region), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus.
- Evaluate **immune correlates of protection** against persistent infections (6- and 12-month definition) with HPV-16 or 18 and CIN2+ associated with HPV-16 or 18 cervical infection (by PCR) post Dose 3 using Month 7 and Month 24 immunogenicity evaluations.

Exploratory objectives described in the protocol:

- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with HPV-16 or HPV-18 detected in the preceding cytological specimen (by PCR) post Dose 3** in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ or any grade CIN associated with HPV-16 or HPV-18 cervical infection, post Dose 1 in adolescent and young adult women infected prior to vaccination with the corresponding HPV type,** i.e. positive for HPV DNA (by PCR) at Month 0 and with a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with cervical infection by HPV-16 only, HPV-18 only or HPV-16 and HPV-18 only defined by PCR post Dose 3** in adolescent and young adult women, who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).
- Evaluate efficacy of the candidate vaccine compared with control in the prevention of **any cytological abnormality associated with HPV-16/18 or with the following oncogenic HPV types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (by PCR), post Dose 3** in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type.
- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of persistent infection (12-month definition) with the following oncogenic HPV types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, by PCR), post Dose 3** in adolescent and young adult women who were negative for HPV DNA by PCR) at Months 0 and 6 for the corresponding HPV type.
- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed VIN1+ or VaIN1+ (combined endpoint) associated with HPV-16 and/or HPV-18** detected within the lesional component of the tissue specimen (by PCR), post Dose 3 in adolescent and young adult women who were negative for HPV DNA

(by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).

- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed VIN1+ or VaIN1+ (combined endpoint) associated with the following oncogenic HPV types detected within the lesional component of the tissue specimen (by PCR): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, post Dose 3** in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type.
- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed VIN1+ or VaIN1+ (combined endpoint), irrespective of HPV DNA** results found in the lesional component of the tissue specimen, post Dose 3 in adolescent and young adult women (1) who were negative for HPV DNA (by PCR) at Months 0 and 6 for all HPV types (high-risk and non-high-risk types), (2) who were negative for HPV DNA (by PCR) at Months 0 and 6 for all high-risk HPV types (i.e. HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), (3) irrespective of their baseline HPV DNA status.
- Evaluate the efficacy of the candidate vaccine compared with control in the **reduction of local cervical therapy (LEEP, CONE, KNIFE or LASER), post Dose 1** in adolescent and young adult women with a normal cytology or low-grade cytology (negative or ASC-US or LSIL) at Month 0, irrespective of their baseline HPV DNA status.

Exploratory objectives described in the RAP

- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of incident infection with HPV-16 or HPV-18 (PCR) post Dose 3** in adolescent and young adult women who are negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of incident infection with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR) post Dose 3** in adolescent and young adult women who are negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type.
- Evaluate the efficacy of the candidate vaccine compared with control in the **clearance of HPV-16 or HPV-18 cervical infection, post Dose 1** in adolescent and young adult women infected prior to vaccination with the corresponding HPV type, i.e. positive for HPV DNA (by PCR) at Month 0, and with a normal or low-grade cytology at Month 0, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- Evaluate the efficacy of the candidate vaccine compared with control in the prevention of any cytological abnormality and in the **prevention of histopathologically-confirmed CIN1+ and CIN2+, irrespective of HPV DNA results,** (1) post Dose 3 in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for all the HPV types (high-risk and non high-risk types), (2) post Dose 3 in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the high-risk HPV types (i.e. HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), and (3) post Dose 1 in adolescent and young adult women irrespective of their baseline HPV DNA status.
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR), post Dose 1** in adolescent and young adult women with a normal or low-grade cytology at Month 0, irrespective of their baseline HPV DNA status.
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of persistent infection (6-month definition) associated with HPV-16 and/or HPV-18 (PCR)**

post Dose 1 in adult women with a history of infection with the other vaccine type (HPV DNA positive and/or seropositive) prior to vaccination and with a normal or low-grade cytology at Month 0, e.g. efficacy against HPV-16 infection in women who were seropositive and/or DNA positive for HPV-18 at Month 0 and seronegative and DNA negative for HPV-16 at Months 0 and 6.

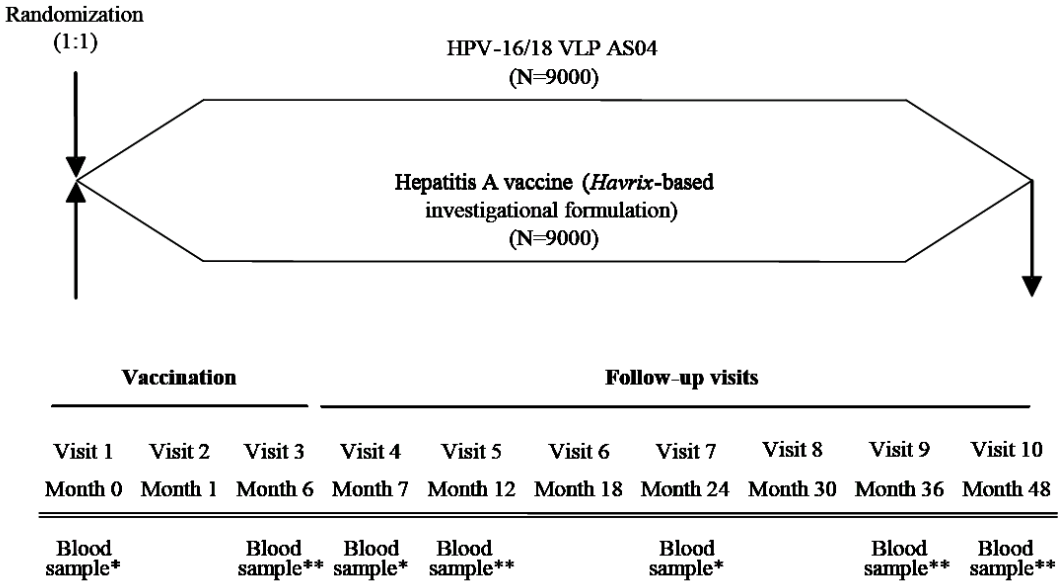
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of incident infection with HPV-16 or HPV-18 (PCR) post Dose 2** in adolescent and young adult women who received only two doses of the study vaccine and who were negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR) post Dose 2 in adolescent and young adult women who received only two doses of the study vaccine** and who were negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).
- Evaluate the **immune response at Month 7 after a 0, 2, 6-month schedule compared to a 0, 1, 6-month schedule.**
- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of any abnormal cytology and histopathologically-confirmed CIN1+ and CIN2+ associated with the following combination of oncogenic HPV types detected in the cytology sample** (for the cytology endpoint) or within the lesional component of the cervical tissue specimen (by PCR) (for the histopathologically endpoints): The next two most common types: HPV-31/45; The next five most common types: HPV-31/45/33/52/58; A7 clade (HPV-39/45/59/68), A7 clade extended (HPV-39/45/59/68/51/56) and A9 clade (HPV-31/33/35/52/58); The next ten most common types: HPV-31/45/33/52/58/35/39/51/56/59.
- Evaluate efficacy of the candidate vaccine compared with control in the **prevention of persistent infection (6-month or 12-month definition) associated with the following combination of oncogenic HPV types in adolescent and young adult women who are negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type:** The next two most common types: HPV-31/45; The next five most common types: HPV-31/45/33/52/58; A7 clade (HPV-39/45/59/68), A7 clade extended (HPV-39/45/59/68/51/56) and A9 clade (HPV- 31/33/35/52/58); The next ten most common types: HPV-31/45/33/52/58/35/39/51/56/59.
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18 cervical infection, post Dose 1** in adolescent and young adult women with a history of infection (HPV DNA positive and/or seropositive) prior to vaccination with the corresponding HPV type, i.e. positive for HPV DNA (by PCR) and/or seropositive (by ELISA) at Month 0 and with a normal or low-grade cytology (i.e. negative, ASC-US or LSIL) at Month 0.
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18 cervical infection, post Dose 1** in adolescent and young adult women who were DNA negative for HPV-16 and HPV-18 and had a negative cytology at Month 0.
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with the following oncogenic HPV types detected within the lesional component of the tissue specimen (by PCR): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, post Dose 1** in adolescent and young adult women who were DNA negative for HPV-16 and HPV-18 and had a negative cytology at Month 0.

- Evaluate in both treatment groups the **proportion of subjects with a CIN2+ diagnosed (by the routine panel) as a result of an abnormal cytology (ASC-US or higher) at baseline.**
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18 cervical infection irrespective of baseline HPV DNA status.**
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with HRW-HPV (i.e., high-risk (oncogenic) HPV types without HPV-16 or HPV-18: HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) cervical infection irrespective of baseline HPV DNA status.**
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ associated with HR-HPV cervical infection irrespective of baseline HPV DNA status.**
- Evaluate the efficacy of the candidate vaccine compared with control in the **prevention of histopathologically-confirmed CIN2+ irrespective of HPV cervical infection irrespective of baseline HPV DNA status.**

Reviewer's Comment: The primary efficacy endpoint, CIN 2/3 or worse associated with virology, was the endpoint considered by the Vaccine and Related Biological Products Advisory Committee (VRBPAC) in November 2001to represent the most appropriate surrogate in prevention of cervical cancer. Accordingly, this review will focus on the data addressing this endpoint. Although many of the secondary and exploratory endpoints are of interest, only selected endpoints relevant to considerations of the information ultimately included in the package insert for Cervarix will be addressed in this review.

Study design: A phase III, double-blind, controlled, multi-center and multicountry study with two parallel groups.

Figure 18-Study HPV-008: Overall study design HPV-008



N= planned number of subjects
* All subjects had blood drawn at these time points.
** A subset of subjects from selected study sites (immunogenicity subset) had additional blood samples taken at these time points.
Source: STN 125259.0048, CSR 008, Figure 1, p. 124

- Treatment groups: HPV group: HPV-16/18 L1 VLP AS04 vaccine and HAV group: Hepatitis A vaccine (Havrix-based investigational formulation).
- Treatment allocation: Randomized (1:1); randomization method: --b(4)-- (internet randomization).
- Vaccination schedule: Three doses of vaccine or control (active) according to a 0, 1, 6-month schedule.
- Target enrolment: 18,000 women aged 15 to 25 years.
- Study regions: Asia Pacific, Europe, Latin America and North America.
- Type of study: IND study. The study is being conducted under the supervision of an Independent Data Monitoring Committee (IDMC).
- Duration of the study: Approximately 48 months of follow-up was planned for all subjects.

Study Procedures (some subjects had not yet completed their 48 month visit at the time of this report)

- Ten scheduled visits per subject at Months 0, 1, 6, 7, 12, 18, 24, 30, 36 and 48.
- A subset of subjects from selected study sites (i.e. safety diary card subset: N ≥ 4000, at least 1000 per region) completed safety diary cards to record solicited (days 0-6) and unsolicited symptoms (days 0-29) after each vaccination.
- Serious adverse events (SAEs), pregnancies and their outcomes, new onset chronic diseases (NOCD), medically significant conditions and sexually transmitted diseases were collected throughout the trial in all subjects.
- Blood samples were drawn from all subjects at Months 0, 7 and 24. In a subset of subjects from selected study sites (i.e. immunogenicity subset: N ≥ 2000, at least 500 per region), additional blood samples were taken at Months 6, 12, 36 and 48.
- Gynecological examination was performed in all subjects at Months 0, 12, 24, 36 and 48.
- Cervical liquid-based cytology (LBC) samples were collected in all subjects at Months 0, 6, 12, 18, 24, 30, 36 and 48* for: HPV DNA typing by PCR, performed on LBC samples collected at Months 0, 6, 12, 18, 24, 30, 36 and 48. HPV DNA testing was done at DDL Diagnostic Laboratory (Voorburg, Netherlands). ; Cytopathological examination, performed on LBC samples collected at Months 0, 12, 24, 36 and 48 using the Bethesda system of cervical cytology reporting.; *Chlamydia trachomatis* and *Neisseria gonorrhea* testing, performed on LBC samples collected at Months 0, 12, 24, 36 and 48. (Note: screening for *Neisseria gonorrhea* was done only if considered appropriate by the investigator.) Colposcopic referral and/or repeat cytology were performed according to appropriate clinical management algorithms. A central laboratory (Quest Diagnostics Clinical Trials, Teterboro, NJ, USA) processed and interpreted results from liquid-based cytology and histology samples. All CIN endpoints were confirmed by an expert histopathology review panel that was blinded to vaccine status, HPV DNA status before biopsy, and cytology reports.
- Behavioural questionnaires were completed by interview of all subjects at Months 1, 12, 24, 36 and 48.

Study Analyses*:*

- An event-driven interim analysis was performed when at least 23 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the Total Vaccinated cohort for efficacy 1 (TVC-1). The efficacy objectives were assessed at the interim analysis post Dose 1 in adolescent and young adult women who were DNA negative for the corresponding HPV type at Month 0. Data from this interim analysis were reported in a separate interim clinical study report dated March 2007.
- An event-driven final analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the ATP cohort for efficacy, including at least

15 cases of CIN2+ associated with HPV-18 infection. The efficacy objectives were assessed at the final analysis post Dose 3 in women who were DNA negative for the corresponding HPV type at Months 0 and 6. These data are presented in this final clinical study report. The sponsor notes that the endpoints assessed at the interim analysis were assessed again at the final analysis with higher power to evaluate the endpoints and adjustment of the alpha for the two analyses. The blinding was maintained for all subjects and investigators until the subject has completed the study.

Management of women with abnormal cytology: Guidance for the management of women with cervical cytological abnormalities was based on standards of care accepted for women undergoing screening within a range of national screening programs Table 96).

Table 96-Study HPV-008: Management of women with abnormal cytology

Cytology	Medical management
Normal or ASC-US/HCII negative	Yearly Pap smear as scheduled (Months 0, 12, 24, 36, and 48)
ASC-US/HCII positive, ASC-US/HCII QNS, LSIL or non-evaluable	For a single observation, cytology was to be repeated at next scheduled study visit (6 months later) or subject could be referred immediately for colposcopy. Two observations (consecutive or intermittent): referral for colposcopy
ASC-H, AGC, or ≥HSIL	For a single observation: immediate referral for colposcopy

ASC-US: Atypical Squamous Cells of Undetermined Significance
AGC: Atypical Glandular Cells
ASC-H: Atypical squamous cells/high-grade ASC-US; does not exclude HSIL
HSIL: High-grade Squamous Intraepithelial Lesions
LSIL: Low-grade Squamous Intraepithelial Lesions
QNS: Quantity not sufficient (insufficient sample volume to perform HCII test), considered equivalent to a positive HCII test result in cytology management algorithm
HCII: Hybrid Capture II (HR-HPV types)
Source: STN 125259.0048, CSR 008, Table 1, p. 128

Table 97-Study HPV-008: Outline of study procedures

Visit Timing Sampling timepoint	Visit 1 Month 0 Pre-vacc I	Visit 2 Month 1 Post vacc I	Visit 3 Month 6 Post vacc II	Visit 4 Month 7 Post vacc III	Visit 5 Month 12 Post vacc III	Visit 6 Month 18 Post vacc III	Visit 7 Month 24 Post vacc III	Visit 8 Month 30 Post vacc III	Visit 9* Month 36 Post vacc III	Visit 10 Month 48 Post vacc III
Informed consent†	●									
Check inclusion criteria	●									
Check exclusion criteria	●									
Check elimination criteria		●	●	●	●	●	●	●	●	●
Check contraindications		●	●							
Collect demographic data (age, ethnicity, weight, height)	●									
General Medical History	●									
Gynaecological History	●		●		●	●	●	●	●	●
Pregnancy test (urine sample 10 ml)	●	●	●							
History-directed medical examination	●									
Pre-vaccination body temperature	●	●	●							
Gynaecological examination according to local practice (may include breast exam)[1, 2]	●				●		●		●	●
Collection of cervical samples[1-2, 4]	●		●		●	●	●	●	●	●
Randomization	●									
Blood sampling: (10 ml)[5,6]	●		●	●	●		●		●	●
Vaccination	●	●	●							
Distribution of diary cards for post-vaccination recording of solicited symptoms (days 0-6) and unsolicited symptoms (days 0-29)[7]	○	○	○							
Return of diary cards[7]		○	○	○						
Diary card transcription[7]		●	●	●						
Record concomitant medication/vaccination	●	●	●	●	●	●	●	●	●	●
Reporting of all pregnancies and pregnancy outcomes		●	●	●	●	●	●	●	●	●
Reporting of Adverse Events[8]	●	●	●	●	●	●	●	●	●	●
Reporting of Serious Adverse Events	●	●	●	●	●	●	●	●	●	●
Administration of questionnaire		●			●		●		●	●
Referral for Colposcopy[3]		○	○	○	○	○	○	○	○	○
Reporting of all colposcopy results[9]		●	●	●	●	●	●	●	●	●
Exit Colposcopy[10]										●
Study Conclusion										●

† For subjects below the legal age of consent, consent was obtained from the legally acceptable representative and assent from the subject.

1. Study related gynaecological examinations including collection of cervical specimens (cervical cytology, HPV PCR, *Chlamydia trachomatis*/*Neisseria gonorrhea*) were suspended in women known to be pregnant, and resumed three months after resolution of pregnancy. Missing procedures were not rescheduled.
2. Subjects withdrawn because of the administration of an HPV vaccine other than that foreseen by the study protocol or following a request for unblinding to obtain a licensed HPV vaccine, were to be offered an exit gynaecological examination, including collection of cervical samples for cytology and *Chlamydia trachomatis*/*Neisseria gonorrhea* or HPV PCR testing.
3. Women with abnormal cervical cytologies were evaluated according to the cytology and colposcopy clinical management algorithm.
4. Cervical samples were used for cervical cytology, HPV DNA PCR and *Chlamydia trachomatis*/*Neisseria gonorrhea* testing. All samples collected were according to protocol specified schedule. Sexually Transmitted Disease(s) (STDs) were recorded in the Adverse Events section of the eCRF in all subjects. Management of STDs followed routine local medical practice.
5. All subjects had blood drawn at Month 0, 7 and 24. Subjects from a subset of selected study sites (N ≥ 2000) had blood samples collected at specific timepoints (immunogenicity subset).
6. Control vaccine recipients may have hepatitis A testing on blood samples at Month 0 and 7 at study conclusion.
7. All subjects/subjects parents from a subset of selected study sites (N = ≥4000) received diary cards to record solicited adverse events within 7 days (day 0-6) of vaccination dose and any unsolicited adverse events within 30 days of vaccination. Subjects were instructed to return the diary cards distributed at Visits 1, 2 and 3 at the next study visit or by mail.
8. All subjects were asked whether they experienced new onset chronic diseases, medically significant conditions, STDs were recorded in the Adverse Events section of the eCRF in all subjects.
9. All colposcopy results, including any results obtained from outside of the study, were reported in the eCRF.
10. Exit colposcopy should be performed within 30 days after cytology results have been communicated to the study site in all women who meet cytology management algorithm criteria for colposcopic referral.

In addition, exit colposcopy should be performed in all women who have had cytologically evident abnormalities (ASC-US/oncogenic HPV positive by HCII or LSIL) present in the 12 months preceding, and including, the Month 48 visit. Subjects in whom exit colposcopy is performed will have their study conclusion page completed in the eCRF at Visit 10. Study blind will be maintained until exit colposcopy data are entered into the study database and at least until the database is frozen for final analysis. Subjects with normal cytology but who are high-risk HPV DNA positive at study end will be offered participation to a gynaecological follow-up study.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
***** An additional Visit 9 will only be performed in case a cytological sample has to be taken according to the cytology management and colposcopy management.
Note: An interim analysis was performed when at least 23 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in TVC-1. The final event-driven analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the ATP cohort for efficacy.
Source: STN 125259.0048, CSR 008, Table 2, p. 130-131

Selection of study population: Subjects were recruited in 135 centers in 14 countries spread across four study regions: Asia Pacific, Europe, Latin America and North America. The target was to enroll approximately 18 000 unscreened women aged 15 to 25 years. The inclusion and exclusion criteria were selected to allow enrolment of a broad population of women, including both those previously not infected with HPV (HPV naïve) and those previously or currently infected with HPV (HPV non-naïve).

Inclusion criteria:
- A healthy female 15-25 years of age at the time of the first vaccination
- Written informed consent from subjects and parents/guardians (with assent from minors)
- Subject had to have a negative urine pregnancy test
- Subject had to be of non-childbearing potential (surgically sterilized) and using appropriate contraception for 30 days prior to the first vaccination and had to agree to continue such precautions for two months after completion of the vaccination series.
- Subject with no more than 6 lifetime sexual partners prior to enrolment. According to local regulatory/ethical requirements, this criterion may not have been applicable in subjects less than 18 years of age.
- Subject had to have intact cervix

Exclusion criteria:
- Pregnant or breastfeeding. Women had to be at least three months post-pregnancy and not breastfeeding to enter the study.
- A woman planning to become pregnant or planning to discontinue contraceptive precautions during approximately the first nine months of the study (Months 0-8).
- Previous administration of MPL or AS04 adjuvant.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days) of immune-modifying drugs within six months prior to the first vaccine dose.
- Planned administration/administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after (days 0-29) each dose of vaccine. Administration of routine meningococcal, hepatitis B, inactivated influenza, diphtheria/tetanus and/or diphtheria/tetanus-containing vaccine up to eight days before each dose of study vaccine was allowed. Enrolment was deferred until the subject was outside of specified window.
- Previous vaccination against HPV
- History of vaccination against Hepatitis A or a known clinical history of Hepatitis A disease

- History of having had colposcopy or planned colposcopy to evaluate an abnormal cervical cytology (Pap smear) test
- Any medically diagnosed or suspected immunodeficient condition
- History of allergic disease, suspected allergy or reactions likely to be exacerbated by any component of the study vaccines, e.g. MPL, AS04, Hepatitis A antigen, 2-phenoxyethanol or neomycin
- Hypersensitivity to latex (found in syringe-tip cap and plunger)
- Known acute or chronic, clinically significant pulmonary, cardiovascular, neurologic, hepatic or renal functional abnormality, as determined by previous physical examination or laboratory tests.
- History of chronic condition(s) requiring treatment such as cancer, chronic hepatic or kidney disease(s), diabetes, or autoimmune disease
- Received immunoglobulins and/or blood product within 90 days preceding enrolment.
- Acute disease at the time of enrolment. Acute disease was defined as the presence of a moderate or severe illness with or without fever. Enrolment was deferred until condition was resolved. All vaccines could be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e. oral/axillary temperature <37.5°C (99.5°F).
- Heavy bleeding (menstruation or other) or heavy vaginal discharge in which a pelvic exam could not be performed.

Elimination criteria: The following criteria were to be checked at each visit subsequent to the first visit. If any become applicable during the study, it did not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analyses.

- Pregnancy after administration of first vaccine dose and within two months after completion of vaccination.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs occurring less than three months prior to study visit.
- Administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before and ending 30 days after (i.e. days 0-29) each dose of study vaccine. Administration of routine meningococcal, hepatitis B, inactivated influenza, diphtheria/tetanus and/or diphtheria/tetanus-containing vaccine up to eight days before each dose of study vaccine was allowed if the subject was outside of the 30-day follow-up period of the previous dose.
- Administration of any HPV vaccine other than that foreseen by the study protocol during the study period. (Administration of any HPV vaccine other than that foreseen by the study protocol also resulted in withdrawal from the study.)
- Received immunoglobulins and/or blood product within 90 days preceding a vaccination visit or blood sampling.
- Subjects who have had a colposcopy completed outside the study, but biopsy sample was not available for study purposes.

Contraindications to subsequent doses of vaccine: The following adverse events (AEs) constituted absolute contraindications to further administration of any study vaccine; if any of these AEs occurred during the study, the subject was not to receive additional doses of vaccine but was allowed to continue other study procedures at the discretion of the investigator. The subject had to be followed until resolution of the event, as with any AE:

- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).
- Pregnancy.
- Hypersensitivity reaction following vaccine administration (including urticaria within 30 minutes of vaccine administration).
- Anaphylactic reaction following the administration of vaccine(s).
- Any serious adverse event (SAE) judged to be related to study vaccine.
- Other significant reactions, which in the opinion of the investigator precluded further administration of the study vaccine (could include severe pain, severe swelling, severe limitation of motion, persistent high fever, severe headache or other systemic or local reactions).
- Any acute or newly acquired chronic condition at the time of scheduled vaccination, which in the opinion of the investigator precluded further administration of the study vaccine.

The vaccine was not to be administered if the subject had a moderate or severe illness with or without fever, but at the resolution of such an illness, vaccinations could resume. All vaccines could be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e. oral /axillary temperature <37.5°C (99.5°F).

Subject completion: For the final analysis, a subject who returned for the concluding visit (Visit 10, Month 48) and who completed all study related activities for Visit 10 per protocol, e.g. gynecological follow-up or treatment, was considered to have completed the study.

Subject withdrawal from the study: For the final analysis, a withdrawal from the study was defined as any subject who did not come back for the concluding visit foreseen in the protocol. The reason for withdrawal from the study was to be indicated.

Subject withdrawal from administration of the investigational product: A withdrawal from the investigational product was any subject who did not receive the complete treatment, i.e. when no further planned dose was administered from the date of withdrawal, and the reason would need to be recorded.

Description of vaccines: The candidate HPV vaccine and the hepatitis A control vaccine were provided as 0.6 ml liquid in pre-filled syringes for single use.

A total number of six different vaccine lots were used in this study: three lots of the HPV vaccine and three lots of the hepatitis A control vaccine.

Table 98-Study HPV-008: Vaccines, formulation, lot numbers and allocation

Group	Vaccine/ Control	Formulation	Presentation	Volume	Lot numbers
Vaccine	HPV-16/18 L1 VLP AS04	Each 0.5 ml dose contains: - 20 µg HPV-16 L1 protein, - 20 µg HPV-18 L1 protein, - 50 µg MPL , - 0.5 mg aluminium as $Al(OH)_3$ - 4.4 mg sodium chloride, - 0.624 mg NaH_2PO_4 $2H_2O$ - water for injection	Liquid in pre-filled syringes	0.6 ml	- DHPV005A9 - DHPV006A9 - DHPV007A9 (expiry date: 30/09/2006)
Control	Hepatitis A vaccine (*Havrix*-based investigational formulation)	Each 0.5 ml dose contains: - 720 EL.U of inactivated HAV antigen, - 0.5 mg aluminium as $Al(OH)_3$ - 0.5% (w/v) 2-phenoxyethanol, - 0.3% (w/v) amino acid supplement, - 25 µg polysorbate 20, - 2.246 mg NaCl, - 0.056 mg KCl, - 0.323 mg Na_2HPO_4, - 0.056 mg KH_2PO_4, - water for injection, - trace amounts neomycin sulphate (<20 ng/dose)	Liquid in pre-filled syringes	0.6 ml	- DVHA817A9 - DVHA817B9 - DVHA819B9 (expiry date: 31/05/2006)†

w/v = weight/volume
Note: The vaccine release protocols for GSK formulated vaccines were archived in the study file and are available upon request.
† The expiry date of the control Hepatitis A vaccine lots was extended to December 2006 based on additional stability data.
Source: STN 125259.0048, CSR 008, Table 4, p. 138

Dosage and administration: The HPV vaccine and the hepatitis A control vaccine were administered (0.5 ml dose) intramuscularly into the deltoid of the non-dominant arm according to a 0, 1, 6-month schedule.

Subsets of subjects

- **Safety diary card subset:** All subjects from a subset of selected study sites were to complete safety diary cards (safety diary card subset: $N \geq 4000$, at least 1000 per region) to record solicited (days 0-6) and unsolicited symptoms (days 0-29) following each vaccine dose.
- **Immunogenicity subset:** Blood samples were to be drawn from all subjects at Months 0, 7 and 24 for HPV-16/18 serology testing by ELISA. All subjects from a subset of selected study sites were to have additional blood samples taken at Months 6, 12, 36 and 48 (immunogenicity subset: $N \geq 2000$, at least 500 per region) for HPV-16/18 serology testing by ELISA and possibly by HPV pseudovirion based neutralization assays (PBNA) and/or monoclonal antibody inhibition enzyme immunoassay.
- **Hepatitis A immunogenicity subset:** At the end of the study (Month 48), a subset of subjects in the hepatitis A vaccine group will be randomly selected within the immunogenicity subset (to provide about 400 subjects who were anti-HAV negative pre-vaccination; approximately 100 per region) for hepatitis A antibody assessment (by ELISA) on Months 0 and 7 sera samples.
- **Exit colposcopy subset:** Exit colposcopy is planned to be performed within 30 days after cytology results of the Month 48 visit are communicated to the study site for: all women who have had cytologically evident abnormalities (ASC-US/ oncogenic HPV positive by HCII or LSIL) present in the 12 months preceding, and including, the Month 48 visit. Women with normal cytology but who are high-risk HPV positive will be offered participation in a four year gynecological follow-up study under a separate protocol.

Reviewer's Comment: At the time of submission of this clinical study report (given the event driven endpoint) not all subjects had completed their Month 48 visit.

Randomization: At first vaccination (Day 0), the treatment allocation was performed at the investigator sites using a central randomization system on Internet -b(4)--

Blinding: This study was performed in a double-blinded manner. Blinding will be maintained for all subjects and investigators and their study staff participating in this study with regard to the individual subject treatment assignments allocated in this study (vaccine or control) and the HPV DNA PCR results until the subject has completed the study, except for the subjects who may have requested the non-emergency unblinding (see below). GSK personnel directly involved in the conduct of this study (site monitors, medical monitors, laboratory personnel, etc.) are also to remain blinded to the subjects' treatment assignments until the subject has completed the study. Since another HPV vaccine became licensed in 2006, the sponsor instituted a procedure to cover situations in which women participating in study HPV-008 requested unblinding in order to receive the other HPV vaccine.

The study IDMC recommended that unblinding and cross-over immunization of both treatment and control recipients with the HPV vaccine or licensed Havrix, as appropriate, be offered to subjects after completion of their end of study activities (Visit 10, Month 48). This was described in amendment 5 of the protocol dated 3/17/08, and precautions were made to only unblind subjects who had completed all study related activities prior to the final analysis. For subjects who had completed the study and requested unblinding before the final analysis, data cleaning, assignment of elimination codes and freezing of the data were to be completed before unblinding. At the time of final analysis no subjects that have completed the study (Month 48) have been unblinded according to this procedure. The first subjects that have completed the study will be unblinded after the final analysis. Therefore, the study blind will be maintained for all subjects still active in the study until their (individual) completion of the four-year follow-up (study end).

The current final event-driven analysis was performed by an external statistician to maintain the study blind. A limited group of pre-specified individuals within GSK, who were involved in the preparation of the final clinical study report (clinical, statistical, data management and safety teams) were allowed to request access to unblinded data on individual subjects (e.g. for specific safety events). The composition of this group and their operating principles was defined in the *Charter of the Group of Unblinded Individuals for the Event-Triggered Final Analysis of Study HPV-008*, dated 11/21/08 (data on file). Requests for unblinding were sent to the head of Medical Governance with the following information: 1) information for which unblinding was requested, 2) rationale for the unblinding 3) individuals who were to be given access to unblinded data. Upon approval of the request, the unblinded information was requested from the external statistician by a GSK statistician and subsequently provided to the group of unblinded individuals only.

The group of unblinded individuals is made of individuals who are internal to GSK Biologicals and individuals who are external to GSK Biologicals (principle investigator reviewing the final clinical study report, individuals involved in publication of study data, IDMC members). Agreement was obtained from all individuals to comply with the charter and to ensure that unblinded data would not be further distributed.

For the final clinical study report (final event-driven analysis prior to completion of the Month 48 visit for all subjects), the external statistician provided blinded and censored safety tables (without study group distribution detail for events that had no cases reported in one of the

groups). GSK clinical and safety personnel belonging to the group described above could request unblinding of individual adverse events according to the charter, so that safety tables could be presented with complete information regarding study group distribution of adverse events. This group could also request inclusion of safety tables with study group distribution detail in the final clinical study report for events that had no cases reported in one of the groups, potentially allowing identification of the treatment group for some subjects. The sponsor notes that tables included in this final clinical study report present information that has the potential to allow identification of treatment group assignments for a limited group of subjects. To avoid compromising the study blind at the individual subject level where possible, unblinded subject data listings were not included in this report but will be provided to regulatory authorities by the external statistician upon request.
Reviewer's Comment: Information was previously requested from the sponsor, and safety datasets searched by diagnosis in order to complete safety tables within this review.

The laboratories involved in the testing of clinical samples remained blinded for all testing included in the final analysis and will remain blinded to treatment group assignment for those subjects who have not yet completed the study until the end of 48-month follow-up for all subjects. Any additional testing (for example, on the biopsies that constitute primary efficacy endpoints) was done by external laboratories without knowledge of the subject's HPV PCR results.

Prior and concomitant medication /vaccinations: At each study visit/contact, the investigator questioned the subject and/or the subject's parent/guiardian about the medication(s) taken. The subject and/or the subject's parent/guardian in the safety diary card subset were also questioned about any medication(s) taken during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after each dose of study vaccine.

- **In all subjects:** In all subjects, any treatments and/or medications and/or vaccines specifically contraindicated (-30 to +30 days around vaccination). Concomitant medication administered for the treatment of an SAE within the follow-up period for serious adverse events was recorded as specified for SAEs on the SAE Report Form.
- **In the safety diary card subset:** In the safety diary card subset, all concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after each dose of study vaccine were to be recorded. A prophylactic medication was a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic was considered to be prophylactic when it was given in the absence of fever and any other symptom, to prevent fever from occurring).

Assessment of efficacy variables
The laboratory assays performed in this study, and the laboratories at which they were performed, are summarized in Table 99. Details of laboratory procedures have been provided earlier in this review (give page numbers) and are described in detail in the product reviewer's review

Table 99-Study HPV-008: Laboratory assays

Assay type	Marker	Assay method	Test kit	Assay unit	Assay cut-off	Laboratory
Qualitative Cervical cytology	Bethesda 2001 System for cervical cytology diagnoses	Microscopy of cervical cytology	ThinPrep® PapTest™ (Cytyc Corp., Boxborough, MA, USA)	Qualitative	Qualitative	Quest Diagnostics Clinical Trials (Teterboro, NJ, USA)
Qualitative Histopathology	CIN, VaIN and VIN classification	Microscopy of tissue sections	Not applicable	Qualitative	Qualitative	Quest Diagnostics Clinical Trials (Teterboro, NJ, USA)
Qualitative "generic" PCR for HPV DNA (using SPF_{10} primers) + LiPA	HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74	PCR + nucleic acid hybridization	HPV SPF_{10} LiPA kit / DDL Diagnostic Laboratory (DDL)	Qualitative	Qualitative	GSK Biologicals (cytology samples); DDL (histopathology samples)
Qualitative (type-specific) PCR for HPV DNA	HPV-16 and 18	PCR	DDL methodology	Qualitative	Qualitative	GSK Biologicals (cytology samples); DDL (histopathology samples)
Qualitative	HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 (oncogenic probe; cocktail B)	Nucleic acid hybridization	Hybrid Capture II HPV DNA Test (Digene Corporation)	Qualitative	Qualitative	Quest Diagnostics Clinical Trials (Teterboro, NJ, USA)
Qualitative	*Chlamydia trachomatis* DNA, *Neisseria gonorrhea* DNA	PCR	(b)(4)	Qualitative	Qualitative	Quest Diagnostics Clinical Trials Center(b)(4) (b)(4)
Qualitative	*Chlamydia trachomatis* rRNA, *Neisseria gonorrhea* rRNA	(b)(4)		Qualitative	Qualitative	Quest Diagnostics (b)(4)
Quantitative	anti-HPV-16 and anti-HPV-18	ELISA	(b)(4) methodology, modified by GSK Biologicals	EL.U/ml	8 EL.U/ml for anti-HPV-16; 7 EL.U/ml for anti-HPV-18	GSK Biologicals or designated laboratory
Quantitative	anti-HPV-16 and anti-HPV-18	Pseudovirion based neutralization assay (PBNA)	NCI methodology adapted by GSK	ED50	40	GSK Biologicals
Quantitative	anti-HPV-16 and anti-HPV-18	V5/J4 monoclonal antibody inhibition enzyme immunoassay	GSK Biologicals	EL.U/ml	(b)(4) EL.U/ml for J4; (b)(4) EL.U/ml for V5	GSK Biologicals
Quantitative	Anti-hepatitis A	ELISA	(b)(4)	mIU/ml	(b)(4) mIU/ml	GSK Biologicals (or designated laboratory)

PCR = Polymerase chain reaction, ED50 = Estimated Dose 50% (the estimated serum dilution reducing the signal generated by viral infection by 50%), ELISA = Enzyme-linked immunosorbent assay, EL.U = ELISA units
NCI = National Cancer Institute
Source: STN 125259.0048, CSR 008, Table 6, p. 145-146

Histology

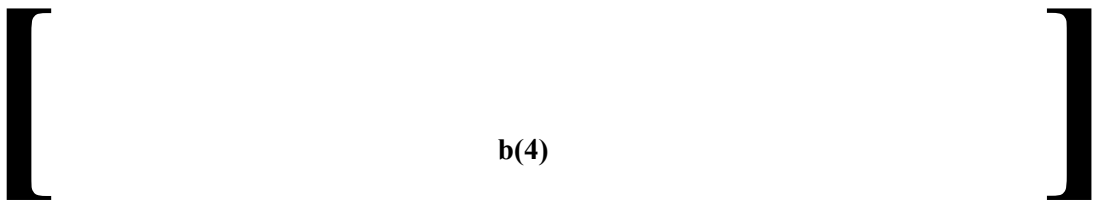
Histopathological analysis: Biopsy and excisional treatment (e.g., loop electrosurgical excisional procedure [LEEP] or cone biopsy) specimens obtained during the trial were fixed in buffered formalin (provided by Quest Diagnostics) and shipped to Quest Laboratories Clinical

Trials Center in ----------b(4)---------- depending on geographical location of study site. All specimens were then transferred to Quest Diagnostics Clinical Trials in Teterboro (NJ, USA) for evaluation.

All specimens were evaluated by two panels of histopathologists.

- First, the specimens were examined by a routine panel of histopathologists, who provided the histopathological diagnosis used for clinical management of the subject. The routine panel consisted of two designated, expert pathologists who independently evaluated the study specimens. In case of disagreement in diagnosis between the two pathologists, a third expert panel member examined the specimen and a consensus diagnosis was reached. The consensus diagnoses were placed in the results reporting system and made available electronically at each site within a designated timeframe of receipt at Quest. Quest expedited reports on specimens marked urgent, engaged in telephone consultation with clinicians and sent slides to sites for review by local pathologists on request.
- Following the review by the routine panel, tissue samples and slides with a diagnosis of CIN1, VIN1, VaIN1 or higher were sent to a second panel of histopathologists (the study panel) for the purpose of endpoint determination. This second histopathological review process was performed in a blinded way, without knowledge of the diagnosis previously made by the routine panel. The study panel consisted of three expert gynecological pathologists under the supervision of a fourth pathologist. This fourth pathologist coordinated the independent and blind review process, and ensured that agreement on the grade level and location of the lesion in the tissue was obtained between at least two members of the study panel. When multiple areas of abnormality were present in a single tissue specimen, the most severe area constituted the study endpoint. The histopathological endpoint determination process summarized here was described in detail in a separate guidance document. The sequence of slides produced per tissue block at Quest (and at DDL). For each relevant specimen, material to be reviewed by the study panel consists of all ------b(4)---------- stained sections plus any additional slides with biomarkers (e.g. ---b(4)-------) that were produced during the routine histopathology review process. In addition, each member of the study panel has a color-paper copy of the digital image of the deepest -b(4)- slide of the block made at low magnification level, to allow location of all observed lesions.

Figure 19-Study HPV-008: Sequence of slides produced per tissue block at Quest and DDL
Quest DDL



----------b(4)----------
BU = Back-up slide, Bef = Before, Aft = After
Source: STN 125259.0048, CSR 008, Figure 2, p. 149

Efforts were made to retrieve specimens from women who had biopsies performed outside the study (e.g. very urgent clinical need – such as suspected invasive cancer) so that the results from these specimens could be reviewed with data from the study.

HPV DNA PCR testing in tissue: Following the histopathological endpoint determination at Quest Diagnostics Clinical Trials, the blocks and slides and images from cases identified as CIN1, VIN1, VaIN1 or higher by the study panel were sent to DDL for HPV DNA PCR testing of lesional tissue at all endpoint locations identified on the digital images. The process of histopathological review at DDL involved examination of additional sections produced at DDL (Figure 19 above) to attempt to associate histopathological lesions with specific HPV types identified by HPV PCR on biopsy sections. If the pathologist at DDL identified any lesion of potentially different grade than the endpoint diagnosis during the examination of the additional sections, these sections were returned to Quest immediately after evaluation by DDL for targeted review by the study panel. The members of the panel independently examined all additional sections from DDL according to the same process defined for the study endpoint definition. The study panel review of slides sent back by DDL was focused on specific questions and/or areas of the slide, which had been highlighted by the DDL pathologist. A final diagnosis for the histopathological lesion was then established by the study panel. The lesional PCR result matched to the highest grade of histopathological abnormality reported by the study panel constituted the study endpoint. For PCR examination, the -----b(4)---------- tissue blocks used for histopathological endpoint analysis were sectioned using an appropriate clean technique. Samples of lesions were selected for further analysis using micro-dissection as appropriate.

In some cases where multiple HPV types have been detected in the samples, additional exploratory assays, such as laser capture microdissection or E4 immunostaining, have been performed to investigate the causal role of individual HPV types.

Assessment of safety variables

Adverse Events: In all subjects throughout the entire study period, AEs related to new onset chronic diseases (NOCD), medically significant conditions and sexually transmitted diseases (STDs) were recorded, irrespective of severity or whether they were considered vaccination-related. In addition, in a subset of subjects from selected study sites (safety diary card subset) diary cards were distributed to record solicited (days 0-6) and unsolicited (days 0-29) adverse events after each vaccination. For each AE the subject experienced, the subject/subject's parent or guradian was asked (1) if she received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason, and (2) whether it resulted in school or work absenteeism. Serious adverse events were recorded throughout the entire study period in all subjects.

The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination had to be established for each adverse event.

Solicited local and general adverse events: These are as described for study HPV-001.

Grading of Adverse Events: This is as presented for study HPV-001.

Relationship of adverse events to vaccination was assessed by the investigator.

Outcome of adverse events were to be assessed as in study HPV-001.

Pregnancy was to followed as noted in study HPV-001.

Assessment of immunogenicity variables

Laboratory assays and time points: Serological assays were performed at GSK Biologicals laboratories (Rixensart) or designated laboratory using standardized validated procedures with

adequate controls. Blood samples were drawn from all subjects at Months 0, 7 and 24. In a subset of subjects (immunogenicity subset), additional blood samples were taken at Months 6, 12, 36 and 48.

Anti-HPV-16 and anti-HPV-18 ELISA: Anti-HPV-16 and anti-HPV-18 ELISA testing was performed on all blood samples at Months 0, 7 and 24. Subjects in the immunogenicity subset were also assessed for anti-HPV-16 and anti-HPV-18 antibodies (by ELISA) at Months 6, 12, 36 and 48. In addition, women with breakthrough infection or neoplasia at final analysis and a matched set of women without breakthrough infection or neoplasia were to be tested for anti-HPV-16 and anti-HPV-18 antibodies by ELISA at Months 7 and 24.

HPV-16 and HPV-18 pseudovirion based neutralization assay: Anti-HPV-16 and anti-HPV-18 PBNA was performed on serum samples from a subset of 100 subjects at Months 0, 7, 12 and 24. The subjects were randomly selected from subjects in the immunogenicity subset included in the ATP cohort for immunogenicity, who were DNA negative for HPV-16, 18, 31, 33 and 45 at Month 0 and seronegative (by ELISA) for HPV-16 and HPV-18 at Month 0. In addition, subjects identified with breakthrough infections could be further analysed using this assay. The sponsor reports that a high correlation in antibody titers between ELISA and PBNA assays has been demonstrated for both HPV-16 and HPV-18, up to 6.4 years after primary vaccination (study HPV-007).

Anti-hepatitis A ELISA: At the end of the study (when all subjects have completed Month 48), Month 0 and 7 sera samples from a subset of the hepatitis A vaccine recipients and hepatitis A vaccine lots (to provide about 400 subjects who were anti-HAV negative pre-vaccination; approximately 100 subjects per region) will be tested by ELISA (------b(4)----------) to detect seroconversion to hepatitis A. If seroconversion is not demonstrated in all initially seronegative subjects in the subset, all control vaccine recipients will have Month 7 sera tested. Licensed Havrix will be offered to any control recipients not demonstrating hepatitis A antibody seropositivity at this timepoint. Seroconversion is defined as the appearance of anti-HAV concentrations ≥15 milli international units per millilitre (mIU/ml) in subjects seronegative for anti-HAV antibodies before vaccination.

STATISTICAL CONSIDERATIONS

Statistical methods: The analyses were performed as specified in protocol amendment 5 (dated 3/17/08, amendment 2 of the RAP for Efficacy and amendment 1 of the RAP for Demographics, Safety and Immunogenicity (dated 8/8/08 and 10/25/06, respectively). See statistical review for further details.

Primary endpoint: Histopathologically-confirmed **CIN2+ associated with HPV-16 or HPV-18** cervical infection detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA). CIN2+ was defined as CIN2, CIN3, adenocarcinoma in-situ (AIS) or invasive cervical cancer.

Secondary endpoints: Secondary endpoints are presented in the order defined in the protocol.

Secondary Safety endpoints:

- Occurrence, intensity, relationship to vaccination and resulting school or work absenteeism (as applicable) of any **solicited local or general symptoms within 7 days** (days 0-6) after each vaccination dose, and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA) in a subset of subjects from selected study sites (safety diary card subset: N = ≥4000, at least 1000 per region).

- Occurrence, intensity, relationship to vaccination and resulting school or work absenteeism (as applicable) of any **unsolicited symptoms within 30 days** (days 0-29) after any vaccination and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA) in a subset of subjects from selected study sites (safety diary card subset, N = ≥4000, at least 1000 per region).
- Occurrence of **SAEs throughout the entire study period** (Month 0 to Month 48) and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA) in all subjects.
- Occurrence of **new onset chronic disease throughout the entire study** (Month 0 to 48) in all subjects and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA).
- Occurrence of **medically significant conditions throughout entire study period** (Month 0 to Month 48) and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or18 serostatus (by ELISA). Medically significant conditions are defined as: adverse events prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that are not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities, and injury.
- **Outcome of all pregnancies throughout the entire study period (**Month 0 to Month 48), overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or -18 serostatus (by ELISA).

The sponsor notes that the first two safety endpoints (symptoms within 7 days and 30 days of vaccination) were exclusively assessed at the interim analysis. These results were not repeated at this final analysis, but are presented in this final clinical study report for completeness.

Secondary Virological endpoints:

- **Persistent infection (12-month definition) with HPV-16 or HPV-18** (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA). Persistent cervical HPV infection (12-month definition) was defined as the detection of the same HPV type (by PCR) at all available timepoints over approximately a 12 month interval (evaluations are planned at approximately 6-month intervals).
- **Persistent infection (6-month definition) with HPV-16 or HPV-18** (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA). Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type (by PCR) in cervical samples at two consecutive evaluations over approximately a 6-month interval.
- **Persistent infection (6-month definition)** with the following **oncogenic HPV types:** HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR).

Secondary Histopathological endpoints:

- Histopathologically-confirmed **CIN2+** associated with the following **oncogenic HPV types** (or combination of types): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR) detected within the lesional component of the cervical tissue specimen (by PCR).
- Histopathologically-confirmed **CIN1+ associated with HPV-16 or HPV-18** detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA). CIN1+ was defined as CIN1, CIN2, CIN3, adenocarcinoma in-situ (AIS) or invasive cervical.

- Histopathologically-confirmed **CIN1+ associated with** the following **oncogenic HPV types** (or combination of types): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR) detected within the lesional component of the cervical tissue specimen.

Secondary Immunogenicity endpoints:

- **HPV-16 and HPV-18 ELISA titers and seroconversion at Month 6, 7, 12, 24, 36, and 48** (in the immunogenicity subset). These analyses were stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus. Antibody titers and seroconversion for V5/J4 monoclonal antibody inhibition testing and viral neutralization may be assessed in a selected subset of subjects.
- **HPV-16 and HPV-18 ELISA titers and seroconversion assessed in vaccine recipients with breakthrough HPV-16 and/or HPV-18 infections and HPV-16 and/or HPV-18 associated neoplasias, compared with selected non-cases (**vaccine recipients without persistent infection or neoplasia matched for age, ethnicity and clinic site). Antibody titers and seroconversion for V5/J4 monoclonal antibody inhibition testing and/or viral neutralization may also be assessed on these samples. These analyses are restricted to subjects who are seronegative for the corresponding HPV type prior to vaccination.

Exploratory endpoints described in the protocol and RAP: Please see objectives section for these endpoints.

Pending analyses: As this final analysis was event-driven not all subjects had completed the study at the time of the analyses. When all subjects have completed the study, all data up to Month 48 will be analyzed and presented in a separate annex report.

Determination of sample size: The target enrolment of 18,000 unscreened subjects was to provide 17100 evaluable women negative for HPV-16 or HPV-18 DNA (by PCR) at Months 0 and 6. Assuming that the drop-out rate at Month 12 was no greater than 15%, the estimated sample size was to provide approximately 14534 women at Month 12 for primary and secondary endpoint assessment (at interim analysis) in women negative for HPV-16 or HPV-18 DNA (by PCR) at Months 0 and 6. Assuming that the drop-out rate at Month 48 is no greater than 35%, it should provide at least 11114 women at Month 48 who were negative for HPV-16 or HPV-18 DNA (by PCR) at Months 0 and 6 for the final primary and secondary histopathological and virological endpoint assessment. The following statistical hypothesis and assumptions were taken into account to calculate the sample size for this study.

The final analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 and/or HPV-18 cervical infection were detected in the ATP cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection. Type I error rate for CIN2+ associated with HPV-16 and/or HPV-18 cervical infection was 0.021 (interim analysis) and 0.039 (final analysis), both alpha are two-sided.

Adjustment plan for interim and final analyses: The following plan was used to adjust the alpha for the interim and final analyses.
(1) For the primary endpoint and each secondary endpoint, a global alpha of 0.05 was used.
(2) For the interim and final analyses, alpha was adjusted similar to the O'Brien-Fleming adjustment:

- For the primary histopathological endpoint, the overall alpha of 0.05 was split into 0.021 for the interim analysis and 0.039 for the final analysis.

- For all secondary endpoints, the overall alpha of 0.05 was split into 0.021 for the interim analysis and 0.039 for the final analysis.

(3) At the interim analysis, a sequential approach was applied to control the Type I error. First, vaccine efficacy against the primary histopathological endpoint was evaluated. If this objective was met, secondary endpoints were evaluated sequentially until an objective was not met. At this point, descriptive analyses of the remaining endpoints were performed. The ranking was established on the basis of clinical needs and on the power to demonstrate the objectives.
Reviewer's Comment: Please see statistical review for full comments and review re: methodology.

Study cohorts /data sets analyzed: At the final analysis:

- Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis, except for endpoints evaluated in HPV DNA positive women at Month 0), and on the Total Vaccinated cohort for efficacy 1 (TVC-1). In addition, exploratory analyses using HPV type assignment algorithm were performed for the ATP cohort for efficacy and the TVC-1 for primary and secondary histopathological endpoints. Analyses on the TVC-2, TVC naïve and ATP naïve cohorts included primary and secondary endpoints associated with HPV-16 and/or HPV-18 and oncogenic HPV types and some exploratory endpoints were also assessed. Additional analyses were performed in the Total Vaccinated cohort for efficacy.
- Analysis of safety was performed on the Total Vaccinated cohort (primary analysis) and on the ATP cohort for safety.
- Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and on the Total Vaccinated cohort.
- Subjects were classified according to the randomized treatment assignment.

Study cohorts considered for analyses of efficacy

- **According-to-protocol (ATP) cohort for analysis of efficacy:** The ATP cohort for analysis of efficacy included all evaluable subjects (those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning efficacy endpoint measures were available and who had a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0. In addition, subjects had to be negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type considered in the analysis (HPV type associated with the efficacy endpoint), except for the endpoints evaluated in HPV DNA positive women at Month 0. For this cohort, the follow-up time for subjects started at the day after Dose 3. For all stratified efficacy endpoints, the principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type considered in the analysis. At the final analysis, the ATP cohort for efficacy was the primary cohort for all endpoints, except for endpoints evaluated in HPV DNA positive women at Month 0.
- **Total Vaccinated cohort for efficacy 1 (TVC-1):** The Total Vaccinated cohort for efficacy 1 (TVC-1) included all vaccinated subjects (i.e., who received at least one dose) for whom data concerning efficacy endpoint measures were available and who had a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0. In addition, subjects had to be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type considered in the analysis (HPV type associated with the efficacy endpoint), except for the endpoints evaluated in HPV DNA positive women at Month 0. For this cohort, the follow-up time for subjects started at the day after Dose 1. For all stratified efficacy endpoints, the principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type considered in the analysis.

- **Total Vaccinated cohort for efficacy 2 (TVC-2):** The Total Vaccinated cohort for efficacy 2 (TVC-2) included all vaccinated subjects (who received at least one dose) for whom data concerning efficacy endpoint measures were available and who had a normal cytology (negative or ASC-US/oncogenic HPV negative by HCII) at Month 0. In addition, subjects had to be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type considered in the analysis (i.e. HPV type associated with the efficacy endpoint), except for the endpoints evaluated in HPV DNA positive women at Month 0. For this cohort, the follow-up time for subjects started at the day after Dose 1. For all stratified efficacy endpoints, the principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type considered in the analysis. Analysis on TVC-2 complemented the analysis on TVC-1 and was only performed on primary and secondary endpoints and selected exploratory endpoints.
- **Total Vaccinated cohort for efficacy (TVC):** The Total Vaccinated cohort for efficacy included all vaccinated subjects for whom data were available for analysis of the efficacy endpoints. Thus, the Total Vaccinated cohort analysis included all subjects with at least one vaccine dose administration documented.
- **ATP cohort of HPV "naïve" women for analysis of efficacy (ATP-naïve):** The ATP cohort for analysis of efficacy in oncogenic HPV naïve women included all evaluable subjects (those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study), for whom data concerning efficacy endpoint measures were available and who had a normal (negative or ASC-US/oncogenic HPV negative by HCII) cytology at Month 0. In addition, subjects were to be HPV DNA negative for all high risk HPV types (by PCR) at Month 0, seronegative (by ELISA) at Month 0 for both HPV-16 and HPV-18 and HPV DNA negative (by PCR) at Month 6 for the corresponding HPV type considered in the analysis (HPV type associated with the efficacy endpoint). For this cohort, the follow-up time for subjects started at the day after Dose 3. This analysis supplemented the overall ATP analysis and was only performed on primary, secondary and selected exploratory endpoints.
- **TVC of HPV "naïve" women for analysis of efficacy (TVC-naïve):** The Total Vaccinated cohort for efficacy in oncogenic HPV naïve women at the final analysis included all vaccinated subjects (i.e., who received at least one dose) for whom data concerning efficacy endpoint measures were available and who had a normal cytology (negative or ASC-US/oncogenic HPV negative by HCII) at Month 0. In addition, subjects were to be HPV DNA negative for all high risk HPV types (by PCR) at Month 0 and seronegative (by ELISA) at Month 0 for both HPV-16 and HPV-18. For this cohort, the follow-up time for subjects started at the day after Dose 1. This analysis supplemented the analysis of the overall TVC-1 and TVC-2 cohorts and was only performed on primary, secondary and selected exploratory endpoints.

Reviewer's Comment: A summary of the analysis populations is presented in Table 100.

Table 100-Study HPV-008: Efficacy Populations [CBER Generated]

Population	Protocol deviations	Pap Test Baseline	Serostatus D0	PCR status	Doses/cases counted when
ATP Cohort	No	Normal or low-grade(a)	Neg. relevant HPV	Neg. through M6 for relevant HPV type	3 doses/1 day after dose 3
TVC-1	Yes	Normal or low-grade (a)	Neg, relevant HPV	Neg. for relevant HPV type D0	1 dose/1 days after dose 1
TVC-2	Yes	Normal	Neg, relevant HPV	Neg. for relevant HPV type D0	1 dose/1 days after dose 1
TVC	Yes	All	All	All	1 dose/1 day after dose 1
ATP naive	No	Normal (b)	Neg. for HPV 16 and 18	Neg. through M6 for relevant HPV type Neg. baseline all oncogenic HPV types M0	3 dose/1 day after dose 3
TVC naive	Yes	Normal (b)	Neg. for HPV 16 and 18	Neg. for all oncogenic HPV types M0	1 dose/1 day after dose 1

(a) normal or low-grade cytology = negative or ASC-US or LSIL
(b) Normal cytology=negative or ASC-US HCII negative

Study cohorts considered for analyses of safety: Part of the safety analyses presented in this final clinical study report was performed at the interim analysis, but were included for completeness. As a result, the safety analyses presented in this report are based on different cohorts depending on the endpoint analyzed: The analysis of solicited symptoms (days 0-6), unsolicited symptoms (days 0-29) and concomitant medication and vaccination (days 0-29) is based on the ATP cohort and Total Vaccinated cohort for safety defined at the interim analysis, referred as "Interim ATP cohort for safety" and "Interim Total Vaccinated cohort for safety" throughout this report.; The analysis of SAEs, pregnancies, pregnancy outcomes and AEs related to NOCDs and medically significant conditions is based on the ATP cohort and Total Vaccinated cohort for safety defined at the current final analysis, as the follow-up time for these endpoints was much longer. These cohorts are referred to as "Final ATP cohort for safety" and "Final Total Vaccinated cohort for safety" throughout this report.

- **Total Vaccinated cohort for safety:** The Total Vaccinated cohort for safety included all vaccinated subjects for whom data were available for analysis of the safety endpoints. The Total Vaccinated cohort analysis included all subjects with at least one vaccine administration documented. The Total Vaccinated cohort for the analysis of solicited symptoms included the subset of subjects from selected study sites (safety diary card subset) who completed and returned a safety diary card. The Total Vaccinated cohort for the analysis of unsolicited symptoms included the safety diary card subset for solicited (days 0-6) and unsolicited (days 0-29) symptoms after vaccination, and all subjects for SAEs, NOCD and medically significant conditions during the entire study period. The safety analyses were also stratified according to baseline HPV DNA and/or seropositivity status using the following cohorts:
  - **Vaccinated HPV-16 and HPV-18 seronegative and DNA negative cohort:** The vaccinated seronegative and DNA negative cohort included subjects that belonged to the Total Vaccinated cohort and who were seronegative and DNA negative at baseline (Month 0) for both HPV-16 and HPV-18. This cohort was only used for analysis of safety.
  - **Vaccinated HPV-16 or HPV-18 seropositive and/or DNA positive cohort:** The vaccinated seropositive and/or DNA positive cohort included subjects that belonged to the Total Vaccinated cohort and who were seropositive and/or DNA positive at baseline (Month 0) for either HPV-16 or HPV-18. This cohort was only used for analysis of safety.
  - **Vaccinated HPV-16 or HPV-18 DNA positive cohort:** The vaccinated DNA positive cohort included subjects that belonged to the Total Vaccinated cohort and who were DNA positive at baseline (Month 0) for either HPV-16 or HPV-18. This cohort was only used for analysis of safety.

- **ATP cohort for analysis of safety:** The ATP cohort for safety was based on the Total Vaccinated cohort and included all subjects: who had received three doses of study vaccine/control according to their random assignment; with sufficient data to perform an analysis of safety (at least one dose with safety follow-up); for whom administration site of study vaccine/control was known; who had not received a vaccine not specified or forbidden in the protocol; for whom the randomization code had not been broken.

Study cohorts considered for analyses of immunogenicity

- **ATP cohort for analysis of immunogenicity:** The ATP cohort for immunogenicity was based on the Total Vaccinated cohort for immunogenicity. The ATP cohort for analysis of immunogenicity included all evaluable subjects (those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available. These included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination. **Subjects who acquired either HPV-16 or HPV-18 infection during the trial were excluded from the ATP cohort for immunogenicity.** The analysis of antibody kinetics for a given read-out was performed on a sub-cohort of subjects included in the ATP cohort for immunogenicity who had results available at all timepoints.
- **Total Vaccinated cohort for immunogenicity:** The Total Vaccinated cohort for immunogenicity was a subset of subjects from selected study sites (immunogenicity subset: N $\geq$ 2000, at least 500 per region).

Reviewer's Comment: Results of the Total Vaccinated Cohort was compared to the analysis in the ATP chohrt for immunogenicity. In all cases throughout this study, analyses for the two analysis cohorts were comparable.

Derived and transformed data:

- The assay cut-off value was defined by the laboratory before the analysis.
- A seronegative subject was a subject whose titer was below the cut-off value.
- A seropositive subject was a subject whose titer was greater than or equal to the cutoff value.
- Seroconversion was defined as the appearance of antibodies (i.e. titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.
- The Geometric Mean Titer (GMT) calculations were performed by taking the anti-log of the mean of the log titer transformations. Antibody titers below the cutoff of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation.
- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.
- For the analysis of solicited symptoms, missing or non-evaluable measurements were not replaced. Therefore, the analysis of solicited symptoms based on the Total Vaccinated cohort included only subjects/doses with documented safety data (i.e. symptom screen/sheet completed).
- For the analysis of unsolicited adverse events/serious adverse event/concomitant medication, all vaccinated subjects were considered and subjects who did not report an event were considered as subjects without an event.

Analysis of demographics: For the final analysis, the following analyses were performed:

- Demographic characteristics (age, region, ethnicity) of each study cohort were tabulated.
- The mean age (plus range and standard deviation) by country of the enrolled subjects, as a whole and per group, were calculated.

- The distribution of subjects enrolled among the study sites was tabulated, as a whole and per group.

Analysis of efficacy

- An interim analysis was performed by an external statistician when at least 23 cases of CIN2+ associated with HPV-16 or HPV-18 cervical infection were detected in TVC-1.
- The final analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 cervical infection were detected in the ATP cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection. This additional criterion provided at least 80% power to demonstrate efficacy against CIN2+ associated with HPV-18 individually, with a lower limit of the 96.1% CI above 0. The final analysis was done by an external statistician to maintain the blinding. No stopping rules were included in the interim and final analyses plan. Therefore, the study blind will be maintained for subjects still active in the study until completion of the four year follow-up (study end).
- An additional descriptive analysis will be performed at the end of the trial, after all subjects have completed the Month 48 visit and study related activities, and will be reported in a separate annex report.
- The vaccine efficacy for all endpoints was calculated using a conditional exact method (primary analysis). In addition, p-values were calculated using the Fisher's exact test to compare the attack rates between both groups. At final analysis, VE for primary and secondary efficacy endpoints was also calculated using additional confirmatory analyses such as Cox regression model and adjust vaccine efficacy method.
- At the end of the study (Month 48) additional confirmatory analysis will be performed including the unconditional asymptotic method.
- For CIN2+ associated with HPV-16 or HPV-18 cervical infection, statistical significance at the interim analysis was reached if the lower limit of the 97.9% CI for the conditional exact method was above 0. At the final analysis, statistical significance of this endpoint was reached if the lower limit of the 96.1% CI using the conditional exact method was above the specified limit. Results at the final analysis were considered statistically significant if the lower limit of the 96.1% CI was above 0.
- For all serostratified efficacy analyses, the principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type considered in the analysis. In addition, analyses were performed overall (i.e., regardless of initial serostatus) and on subjects who were seropositive (by ELISA) prior to vaccination for the corresponding HPV type considered in the analysis.

Case definitions for efficacy: For all subjects assumed to meet criteria for primary or secondary efficacy endpoints (virological or histopathological), all available clinical and laboratory data were reviewed by a case assessment and endpoints committee prior to study unblinding by the external statistician to make final case assignments. This review included any laboratory data and clinical evaluations performed outside the protocol specified procedures. This review was done before the interim and final analyses were performed. The endpoints committee was blinded with respect to PCR results for subjects who achieved histopathological endpoints.

Histopathological endpoints using the primary case definition: The case definition for CIN2+ is summarized in Table 101 below.

Table 101-Study HPV-008: Case definition for CIN2+

Result of (b)(4) slide at Quest[1]	Result of (b)(4) slide before PCR[2]	Result of (b)(4) slide after PCR[2,3]	Case CIN2+ irrespective of HPV DNA result	Case CIN2+ associated with specific virus type[4]
CIN2+	CIN2+	CIN2+	Yes	Yes
CIN2+	CIN2+	< CIN2+	Yes	Yes
CIN2+	< CIN2+	CIN2+	Yes	Yes
CIN2+	< CIN2+	< CIN2+	Yes	No
< CIN2+	CIN2+	CIN2+	Yes	Yes
< CIN2+	CIN2+	< CIN2+	Yes	Yes
< CIN2+	< CIN2+	CIN2+	Yes	No
< CIN2+	< CIN2+	< CIN2+	No	No

1. This is the result of the deepest ----b(4)---------- slide. If there is another slide with a more severe diagnosis than the deepest slide, this is indicated on the listing of the endpoint committee. The more severe diagnosis is only used for the evaluation of CIN2+ cases irrespective of HPV DNA results.
2. If there is disagreement between the results of the -b(4)-slide at Quest and the -b(4)-slides at DDL, the latter will be re-diagnosed by the study panel at Quest (the results shown here are the final diagnoses of the study panel).
3. If the -b(4)-slide after PCR is negative or not available, a -b(4)- slide can also be used to provide this result.
4. "Yes" if (1) CIN2+ on (b)(4) slide at Quest or on slide before PCR, and CIN2+ on slide after PCR (i.e. PCR is sandwiched between two CIN2+ results), or (2) CIN2+ on (b)(4) slide adjacent to the PCR slide.
Source: STN 125259.0048, CSR 008, Table 10, p. 175

For the endpoints irrespective of HPV DNA result, an endpoint (for example CIN2+) had to be detected on the -b(4)- slide at Quest or on the slide before or after PCR. For all other histopathological endpoints associated with specific virus types (e.g. HPV-16 and/or HPV-18), an endpoint (e.g. CIN2+) had to appear on the -b(4)- slide at Quest or on the -b(4)- slide before PCR, and the endpoint had to appear on the -b(4)- slide after PCR (i.e. PCR had to be "sandwiched" between two CIN2+ evaluations), or the endpoint (e.g. CIN2+) had to appear on the -b(4)- slide adjacent to the PCR slide.

Persistent infection

- **Protocol definition of 12-month persistent infection:** Persistent cervical HPV infection (12-month definition) was defined as the detection of the same HPV type (by PCR) at all available timepoints over approximately a 12-month interval (evaluations planned at approximately 6-month intervals). At the final analysis, a subject had a 12-month persistent infection for a specified HPV type if there existed a sequence of at least two positive samples (difference larger than 300 days) and no negative samples in between. No maximal range was defined for consecutive positive samples.
- **Protocol definition of 6-month persistent infection:** Persistent cervical HPV infection (6-month definition) was defined as detection of the same HPV type (by PCR) in cervical samples at two consecutive evaluations over approximately a 6-month interval (evaluations are planned at approximately 6-month intervals). There was a sequence of positive samples not interrupted by negative samples, such that the total range was more than five months (> 150 days) and each consecutive positive sample was no more than 10 months apart (≤ 300 days). In addition, all 12-month persistent infections were also considered as 6-month persistent infections.

Primary analysis: vaccine efficacy using Conditional exact method

This method computes an exact confidence interval (CI) around the rate ratio (ratio of the event rates in the HPV group versus the HAV group) and takes into account the follow-up time of the subjects within each group. VE is then defined as 1 minus the rate ratio. For the clearance endpoints, the ratio of event rates was based on the rate of subjects not cleared (obtained by [N-n] divided by N).

The follow-up time for each subject starts:

- at the day after first vaccination (Month 0), if analyses were done on the Total Vaccinated cohort for efficacy, or
- at the day after third vaccination (Month 6), if analyses were done on the ATP cohort for efficacy.

The follow-up time for each subject ends:

- at the time of the event (e.g. the start of persistent infection or the time of the histopathological endpoint),
- at Month 48 for subjects who completed the study and did not have an event, or
- at the latest visit for which data was available for subjects who had not yet completed the study at the time of the interim analysis or final analysis (if 36 CIN2+ cases were reached before all subjects completed their Month 48 visit) and did not have an event:
  - For histopathological endpoints, the date of the last biopsy or last cytology (result satisfactory or satisfactory without endocervical component), whichever comes latest, was taken.
  - For cytological endpoints, the date of the last cytology (result satisfactory or satisfactory without endocervical component) was taken.
  - For virological endpoints, the date of the last cervical sample for which laboratory results were available was taken. Further note that for the analysis of 6-month persistent infection, only subjects with at least five months follow-up after the Month 6 visit (Total Vaccinated cohort) or after the Month 12 visit (ATP cohort) were included. For the analysis of 12-month persistent infection, only subjects with at least 10 months follow-up after the Month 6 visit (Total Vaccinated cohort) or after the Month 12 visit (ATP cohort) were included.

The follow-up time was calculated in days as Date of end of follow-up period – Date of vaccination, and expressed in person-years at risk (number of days/365.25).

Events detected after Month 48, resulting from the exit colposcopy, will only be counted in the analysis if the detection process was according to the management algorithms (subjects should be ASC-US/oncogenic HPV positive (by HCII) at Month 48).

This type of analysis was considered as the primary analysis because both the interim and final analyses were event-driven (conditional on the total number of events). Therefore, subjects do not have the same follow-up time. The exact method took into account the total follow-up time in each of the groups.

Confirmatory analyses: The sponsor conducted confirmatory analyses using the Cox regression and adjusted vaccine efficacy methods were performed at the final analysis. Confirmatory analyses using the unconditional asymptotic method will be performed at the end of the study when all subjects have completed study related activities and will be reported with the Month 48 results.
Reviewer's Comment: The results of the primary analyses are included in this review. Please see statistical review for any further analyses.

Analysis of safety
The analysis of solicited symptoms (days 0-6) and unsolicited symptoms/medications (days 0-29) was performed exclusively at the interim analysis, since no additional doses of vaccine were administered since the time of the interim safety analysis.

The primary analysis of solicited symptoms was based on the Interim Total Vaccinated cohort for solicited safety (safety diary card subset). The primary analysis of safety was based on the Total Vaccinated cohort and included the safety diary card subset (Interim cohort) for solicited (days 0-6) and unsolicited (days 0-29) symptoms after vaccination, and all subjects (Final cohort) for SAEs, NOCD, medically significant conditions and pregnancies during the entire study period.

A complementary analysis of the solicited symptoms and unsolicited symptoms/medications reported within 30 days after each dose was performed based on the Interim ATP cohort for safety and a complementary analysis of the SAEs, NOCD, medically significant conditions and pregnancies reported during the entire follow-up period was performed based on the Final ATP cohort for safety to supplement the primary analysis.

All safety and reactogenicity analyses were presented by vaccine group. Additionally, analyses of solicited local and general symptoms and unsolicited symptoms were done on seronegative and DNA negative subjects for both HPV-16 and/or HPV-18 at baseline, on seropositive and/or DNA positive subjects for HPV-16 and/or HPV-18 at baseline, and on DNA positive subjects for HPV-16 and/or HPV-18 at baseline. The analyses of solicited local and general symptoms and unsolicited symptoms were also done by ethnicity at the interim analysis and are included in the final clinical study report for completeness.

No formal comparisons were made between groups.

The safety analyses performed exclusively at the interim analysis, but included in this final clinical study report for completeness, included:

- solicited signs and symptoms (days 0-6) reported,
- unsolicited signs and symptoms (days 0-29) reported,
- concomitant medication and vaccination (days 0-29) reported.

The safety analyses performed at the interim and final analyses included:

- serious adverse events, pregnancies, pregnancy outcomes and adverse events related to NOCD and medically significant conditions reported.

Adverse Events related to NOCD and medically significant conditions: NOCDs and medically significant conditions were to be reported throughout the study period regardless of causal relationship to vaccination and intensity.

- **New onset chronic diseases:** Investigators were asked to identify in the eCRF adverse events that they considered as NOCD. An analysis of these events was performed (Investigator assessment). In addition, all adverse events reported during the trial were compared with a GSK pre-defined list of chronic diseases derived from MedDRA codes (see list in Appendix 1-Overview of safety). This list has been approved by the IDMC supervising the HPV project. The list was prepared prior to any analysis of the data and the events included in the list were based on the clinical judgement of a GSK physician as constituting chronic diseases. For analyses using the GSK pre-defined list of NOCD, the determination of whether a chronic disease was considered to be of new onset was based on review of the subject's pre-vaccination medical history. The proportion of subjects with at least one report of NOCD classified by MedDRA, whenever available, and reported during the entire study period is tabulated with exact 96.1% CI. Within the adverse events that were considered as NOCD (GSK assessment), a GSK physician determined whether the adverse event was an autoimmune disease. An analysis of these new onset autoimmune diseases (NOAD) was also performed. The proportion of subjects with at least one report of NOAD classified by

MedDRA, whenever available, and reported during the entire study period was tabulated with exact 96.1% CI.

- **Medically significant conditions:** Medically significant AEs were defined as AEs prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that are not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury. The list of common diseases with their corresponding MedDRA codes has been established by GSK. (See list of common illnesses in study HPV-007),

Serious adverse events: Serious adverse events and withdrawal due to adverse event(s) were described in detail. Only SAEs recorded after the first receipt of vaccine/control were included in the analysis.

Pregnancies: Pregnancies and their outcome were described in detail. Information on pregnancies was shown for different reporting periods:
1. overall (which includes subjects with unknown last menstrual period [LMP]), and
2. around vaccination (defined as a pregnancy occurring in subjects that reported their LMP between 30 days before and 45 days after vaccination).
Per GSK convention for encoding pregnancy outcomes in the safety database, abnormal infant is defined as a pregnancy outcome that includes congenital anomalies and/or other medically significant outcomes in offspring. It does not include transient neonatal events e.g. transient tachypnea of the newborn.

Concomitant medication and vaccination: The proportion of subjects who started to receive at least one concomitant medication during the 30-day follow-up period after each vaccination was calculated with 96.1% CI. The use of antipyretics and antibiotics was also reported. Differences were made whether or not the medication was taken prophylactically in anticipation of reaction to the vaccination.

Analysis of immunogenicity

- **Immune response induced by natural infection:** Anti-HPV-16 and anti-HPV-18 ELISA titers and seroconversion rates were assessed in subjects who were seropositive for HPV-16 and HPV-18 at Month 0 and HPV DNA negative for the antigen considered to determine antibody levels following clearance of natural infection.
- **Immune response induced by vaccination:** The primary analysis was based on the ATP cohort for analysis of immunogenicity. A complementary analysis based on the Total Vaccinated cohort for immunogenicity was performed to supplement the ATP analysis.
- **Immune correlates of protection:** Anti-HPV-16 and anti-HPV-18 ELISA, PBNA and V5/J4 monoclonal antibody inhibition titers and seroconversion rates were to be assessed in vaccine recipients with breakthrough HPV-16 and/or HPV-18 persistent infections and HPV-16 and/or HPV-18 associated neoplasias compared with selected non-cases (vaccine recipients without persistent infection or neoplasia matched for age, race and clinic site).

The analyses of safety and immunogenicity were performed as descriptive and no alpha was spent for interim analyses.

Changes in the conduct of the study or planned analyses
Protocol amendmentsL Thestudy was conducted according to the protocol and its amendments. There were five amendments to the study.

Amendment 1 (dated 12/3/03): The major changes were as follows:

- To improve the robustness of the data on vaccine efficacy in the prevention of CIN2+ lesions, the trigger for the final analysis was changed from 30 to 36 confirmed cases of CIN2+ associated with HPV-16 and/or HPV-18 cervical infection in the ATP cohort. This allowed study HPV-008 to be performed as a stand alone trial (without the need of pooling with study HPV-009). Therefore, a total of 18000 subjects were enrolled (instead of 13000) and the overall targeted recruitment period was extended to approximately 15 months.
- To strengthen the association of histopathologically-confirmed CIN2+ with HPV-16 or HPV-18 cervical infection for the primary objective, PCR analysis had to be performed on the lesional component of the tissue specimen (instead of on the preceding cytological specimen).
- As the specificity of the ---b(4)----- screening test was not optimal for *Neisseria gonorrhea,* a confirmatory test was offered ----b(4)----------

Amendment 2 (dated 8/17/05): The major changes were as follows:

- As the total number of study subjects was increased to 18,000 (see amendment 1), CIN2+ efficacy data would be available at the time of the first interim analysis. Therefore, the analysis plan was simplified: only one interim analysis was to be performed (to evaluate safety, efficacy and immunogenicity) when at least 23 cases of CIN2+ associated with HPV-16/18 infection have been detected. In addition, pooling with data from study HPV-009 was no longer required to provide a robust estimate of overall vaccine efficacy in the prevention of CIN2+ associated with HPV-16 or HPV-18 infection.
- The protocol was updated to indicate that for solicited and unsolicited adverse events school or work absenteeism (as applicable) had to be recorded. In addition, the post-vaccination time period for collecting unsolicited AEs was clarified (i.e. days 0-29).
- As suggested by the IDMC, access to follow-up gynecological care was included for an additional four years following the conclusion of the study for women who have a negative cytological result at the Month 48 visit, but are found positive for any oncogenic HPV detected by PCR at this visit.
- The clinical management algorithms were updated to indicate that women with ASC-US/oncogenic HPV positive results or LSIL could be immediately referred for colposcopic evaluation.
- The protocol was updated to take into account that in certain populations with very low prevalence of *Neisseria gonorrhea* infection, investigators could decide to forgo testing for *Neisseria gonorrhea*.
- GSK obtained licensure for Fendrix (hepatitis B vaccine) which contains the adjuvant AS04. Therefore, the statement that no vaccines currently licensed contain monophosphoryl lipid A (MPL) or AS04 adjuvant was removed.
- More precise information was provided for the administration of routine vaccines before each dose of study vaccine.
- For regulatory purposes in Japan, subjects of Japanese ethnicity were asked to provide evidence of their origin.

Amendment 3 (dated 7/27/06): The major changes were as follows:

- Merck's HPV vaccine, Gardasil, was licensed for use in an increasing number of countries. Therefore, the study procedures were revised to include questions at every visit to determine if subjects received an HPV vaccine outside of the study. Data obtained after a subject received an HPV vaccine outside of the study are confounded, and therefore such subjects are withdrawn from further participation in the study. Data from subjects who requested information about their treatment group assignment (i.e., request unblinding) before deciding

on immunization with a licensed HPV vaccine outside of the study are similarly confounded; therefore such subjects are also withdrawn from further participation in the study.
- Subjects withdrawn because of (1) the administration of an HPV vaccine outside of the study or (2) following a request to be unblinded to decide on immunization with a licensed HPV vaccine outside of the study, were offered an exit gynecological examination prior to concluding their participation in the study.
- The analysis plan for vaccine efficacy against persistent infection with **oncogenic HPV types** was slightly modified: persistent infection (12-month definition) was replaced by persistent infection (6-month definition) as a secondary endpoint. Vaccine efficacy against persistent infection (12-month definition) was evaluated as exploratory endpoint.
- Additional exploratory objectives were included as vaccine efficacy is also evaluated against histopathologically-confirmed vulvar and vaginal intraepithelial neoplasia (VIN and VaIN), and a supplement to the ICF was developed for these subjects. Only subjects who signed this supplement were included in these analyses.
- The analysis of safety was further clarified for pregnancies, new onset chronic diseases and medically significant AEs.
- Autoantibody testing was included for autoimmune diseases diagnosed during the study, to be performed on baseline sera collected at Month 0 and other sera samples collected during the study, if agreed by the subject or the subject's parent/guardian.

Amendment 4 (dated 10/11/06): The aim of the fourth amendment was to further clarify the analysis plan:
- For all stratified efficacy endpoints, the principal analysis was to be performed on subjects who are seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample. In addition, analyses were to be performed overall (i.e., regardless of initial serostatus) and on subjects who are seropositive (by ELISA) prior to vaccination for the corresponding HPV type considered in the analysis.
- The interim analysis was planned on the Total Vaccinated cohort (TVC), and subjects with abnormal cytology at study entry were not part of the TVC. However, this would have led to the exclusion of subjects who had HPV infection with non-vaccine types at study entry and then subsequently developed CIN2+ lesions associated with HPV-16/18, resulting in the exclusion of all such events from the current analysis. Therefore, the TVC definition for the efficacy analyses was broadened: (1) the criterion "have a normal cytology at Month 0" was changed to "have a normal or low-grade (ASC-US, LSIL) cytology at Month 0", and (2) the principal analysis was to be performed on subjects who are seronegative prior to vaccination for the corresponding HPV type present in the sample. This broadened TVC cohort, referred to as the TVC-1, served as the primary cohort for the interim efficacy analysis. For consistency, similar modifications were made to the ATP cohort definition for analysis of efficacy.
- Histopathologically-confirmed VIN1+ or VaIN1+ were to be evaluated as a separate combined endpoint, irrespective of CIN1+.
- The definition of medically significant conditions (previously referred to as conditions prompting emergency room visits or physician visits that are not related to common diseases) was further clarified.

Amendment 5 (dated 3/17/08): The aim of the fifth amendment was to clarify the cross-over immunization procedures and other end of study procedures:
- It was previously described that all subjects would be offered cross-over immunization after the trial was completed. Following the results of the interim analysis, it was recommended by the IDMC to provide the option of cross-over immunization after the database was frozen for

final analysis. Each subject is to be informed of the possibility of requesting unblinding after completion of their end of study activities (Visit 10, Month 48) and of the procedure involved.

- Exit colposcopy for women that have normal cytology and are high-risk HPV negative at the end of the study was removed due to absence of justification for colposcopy in this situation in current screening practices. As previously planned women with normal cytology but who are high-risk HPV positive will be offered participation to a four year gynecological follow-up study. All women who have had cytologically evident abnormalities (ASC-US/ oncogenic HPV positive by HCII or LSIL) present in the 12 months preceding, and including, the Month 48 visit were still to be invited for exit colposcopy.
- For all histopathological outcomes, an exploratory analysis using the "HPV type assignment" algorithm was performed. In this analysis, for cases with more than one HPV type detected in the lesion the association between the cervical lesion and the HPV types is based not only on the detection of HPV DNA in the lesion, but also considers the presence of HPV types in the two immediately preceding cytology samples.
- The secondary endpoint for immunogenicity regarding vaccine breakthrough cases was modified to state that inhibition and/or neutralization assays may be performed in addition to ELISA assays on these samples.
- Priority ranking for serology assays was modified to place neutralization assays above inhibitions assays due to high correlation observed between the latter and ELISA assays, and details of the neutralization assay was added.
- Recent references regarding the HPV vaccine and results of the interim analysis of this study were included and the reference to the investigator brochure was updated. Reference to other vaccines containing MPL and licensure of Cervarix in some countries were also added. Material Safety Data Sheets were updated for the vaccines which will be administered as cross-over vaccination.
- Clarification of suspension of study related pelvic examinations during pregnancy, and guidance for collection of vaginal and vulvar samples were added.

Other changes: Analyses were performed as planned in the protocol amendment 5 (3/17/08), amendment 2 of the RAP for efficacy (dated 8/8/08) and/or amendment 1 of the RAP for demography, immunogenicity and safety (dated 10/25/06), with the following exceptions:

- **Efficacy**
  - The primary and secondary objectives did not clearly describe the cohorts considered for efficacy analyses. For example, for the primary objective, the principal analysis was to be performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type considered in the analysis instead of on subjects who were seronegative for the corresponding HPV type present in the sample, as stated in the protocol. The same clarification applies to the definition of the study cohorts.
  - An additional exploratory analysis was performed for the incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 in subjects that were HPV DNA positive and/or seropositive for the other vaccine type at baseline in TVC-1. This analysis was not included in the RAP or protocol but was performed at the final analysis in order to further evaluate the impact of the vaccine on the progression of lesions in subjects with previous exposure to the other vaccine type.
  - An additional exploratory analysis was performed to evaluate incidence rates and vaccine efficacy against CIN1+ and CIN2+ in HPV-16 and/or HPV-18 DNA positive subjects at baseline in the TVC-2. This analysis was not described in the RAP but was performed at the final analysis in order to further evaluate the impact of the vaccine on the progression of lesions in HPV-16 and/or HPV-18 DNA positive subjects with no prevalent cervical abnormalities at baseline.

- At the final analysis the cox regression test was used instead of the log-rank test for the confirmatory analyses.
- According to amendment 2 of the RAP for efficacy, the analysis in the ATP cohort of HPV naïve women was to be performed on all evaluable subjects, for whom data concerning efficacy endpoint measures were available and who had a normal cytology at Month 0. In addition, subjects had to be negative for all oncogenic HPV types (by DNA) at Month 0, seronegative (by ELISA) at Month 0 for both HPV-16 and HPV-18 and HPV DNA negative (by PCR) at Month 6 for the corresponding HPV type in the analysis (i.e., HPV type associated with the efficacy endpoint). The definition of this ATP naïve cohort was not consistent with the previous definition used in the annex report to the interim analysis, dated July 2008, which presented additional post-hoc efficacy analyses of cross-protection and results in a HPV naïve cohort of women. At the final analysis, the analysis of efficacy in the ATP naïve cohort was performed using the definition used in the annex report to the interim analysis, i.e., on all evaluable subjects who were DNA negative for all oncogenic HPV types at Month 0 and Month 6, seronegative for HPV-16 and HPV-18 at Month 0 and had a normal cytology at Month 0. Additional analyses of efficacy using the cohort definition specified in the RAP will be performed and presented in a separate annex report.

- **Safety**
  - An error was discovered in the definition of the ATP cohort for safety before any analysis was performed. The ATP cohort for analysis of safety included those subjects who have received three doses of study vaccine/control according to their random assignment (and not "at least one dose" as was erroneously stated in the protocol/RAP).
  - The analysis of solicited symptoms (days 0-6), unsolicited symptoms (days 0-29) and concomitant medication and vaccination (days 0-29) was not performed at the final analysis. The analysis was performed exclusively at the interim analysis and is presented in this final clinical study report for completeness.
  - SAEs related to study participation or to a concurrent medication were collected and recorded from the time the subject consented to participate until she was discharged. All SAEs were reported, but only SAEs recorded after the first receipt of vaccine/control were included in the analysis.
- **Immunogenicity**
  - Seropositivity rates and GMTs were also tabulated for individual vaccine lots.
  - The protocol described that a subset of samples may also be tested using monoclonal antibody inhibition assays. This testing was not performed at the final analysis. Instead, samples were tested by anti-HPV-16 and anti-HPV-18 PBNA, since all objectives were to be assessed by PBNA and a high correlation between the antibody inhibition enzyme immunoassays and the PBNA has been demonstrated. Moreover, the PBNA measures a broader range of neutralizing epitopes and has been shown to be more sensitive and have a higher correlation with ELISA data [Dessy, 2008].
  - According to the protocol, subjects with breakthrough infection or neoplasia and a matched set of subjects without breakthrough infection or neoplasia were to be tested for anti-HPV-16 and anti-HPV 18 antibodies by ELISA, PBNA and/or V5/J4 monoclonal antibody inhibition assay at Months 7 and 24. At the final analysis, serum samples from subjects with breakthrough CIN2+ were evaluated by ELISA and PBNA at pre-vaccination and Month 7. Data on subjects with breakthrough persistent infection (6-month and 12-month definition) and CIN1+ were not available at the time of the final analysis. In addition, a matched set of subjects without breakthrough CIN2+ was not evaluated.
  - According to the protocol, all subjects were to receive the vaccine according to a 0, 1, 6-month schedule. However, some deviations in the time intervals for administration of Dose 2 and/or 3 were observed, which allowed the evaluation of the immune response in subjects who received the vaccine according to different schedules (i.e., for Dose 2 [0, 2, 6-

month schedule] and Dose 3 [within 5, 6, 7, 8 or 9 months]). These additional immunogenicity analyses were performed on subjects in the Total Vaccinated cohort who received the three vaccine doses within different time intervals.

RESULTS

Study Population Results

Study dates: The first subject was enrolled in the study on 5/6/04, the last subject was enrolled on 6/27/05, and the last subject completed her vaccination course on 6/4/06. The final event-driven analysis includes data collected up to the data lock point (DLP) of 8/31/08. The database was frozen on 10/24/08.

Number of subjects: Of the 18729 subjects enrolled in the study, 64 subjects were not vaccinated. Of the 18665 subjects vaccinated, 21 subjects from center 4923 were excluded from analyses because of potential study conduct and data integrity issues idenitified at this center,
Reviewer's Comment: The list of reasons was reviewed, and the reasons were consistent with the pre-specified study plan. (Source: STN 125259.0048, CSR 008, Supplement 3, p. 10074, not shown here).

The sponsor notes that due to the efficacy of the HPV vaccine, more subjects developed HPV 16/18 infections in the HAV group as compared to the HPV group (2117 versus 1119 subjects) and were eliminated from the ATP cohort for immunogenicity.
Reviewer's Comment: The results of the Total Vaccinated Cohort for immunogenicity were also reviewed. See Immunogenicity results.

Table 102-Study HPV-008: Number of subjects enrolled into the study as well as the number of subjects excluded from analyses with reasons for exclusion (Efficacy cohorts)

	Total			HPV		HAV	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled cohort	**18729**						
Concerns about data integrity (code 1010)	21	21					
Study vaccine dose not administrated but subject number allocated (code 1030)*	64	64					
Total Vaccinated cohort	**18644**		**100**	**9319**		**9325**	
Subjects with high-grade (ASC-H, HSIL, AGC, MALIGNANCY) or missing cytology at baseline (code 3000)	119	173		61	61	58	58
Total Vaccinated cohort for efficacy 1	**18525**		**99.4**	**9258**		**9267**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	146	148		62	63	84	85
Randomization code broken at investigator site or at GSK Safety department (code 1060)	49	51		26	26	23	25
Study vaccine dose not administered according to protocol (code 1070)	1601	1624		817	825	784	799
Subjects with a positive pregnancy test at Visit 1, 2 or 3 (code 1500)	0	281		0	147	0	129
Subjects with a history of vaccination against Hepatitis A or known clinical history of hepatitis A disease (code 1600)	7	22		4	7	3	8
Ethics committee request (code 1700)	1	1		1	1	0	0
Protocol violation (inclusion/exclusion criteria) (code 2010)	18	27		10	12	8	10
Administration of any medication forbidden by the protocol (code 2040)	20	27		8	13	12	14
Underlying medical condition forbidden by the protocol (code 2050)	123	143		57	70	66	72
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	417	452		191	207	226	245
Subjects with high-grade (ASC-H, HSIL, AGC, MALIGNANCY) or missing cytology at baseline (code 3000)	95	173		47	61	48	58
Subjects with two cervices (code 3100)	5	5		3	3	2	2
ATP cohort for efficacy	**16162**		**86.7**	**8093**		**8069**	
Subjects with abnormal (ASC-US/HCII+, ASC-US/HCII QNS, LSIL, ASC-H, HSIL, AGC, MALIGNANCY) or missing cytology at baseline (code 3010)	1515	1572		775	777	740	740
Total Vaccinated cohort for efficacy 2	**17129**		**91.9**	**8544**		**8585**	

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
Note: Subjects may have more than one elimination code assigned; in case of more than one code, the code with the lowest number was used as the reason for elimination
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered cohort (ATP, TVC-1, TVC-2) relative to the Total Vaccinated cohort
Source: STN 125259.0048, CSR 008, Table 13, p. 193

Table 103-Study HPV-008: Number of subjects enrolled into the study as well as the number of subjects excluded from analyses with reasons for exclusion (Safety and immunogenicity cohorts)

	Total			HPV		HAV	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled cohort	**18729**						
Concerns about data integrity (code 1010)	21	21					
Study vaccine dose not administrated but subject number allocated (code 1030)	64	64					
Total Vaccinated cohort	**18644**		**100**	**9319**		**9325**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	146	148		62	63	84	85
Randomization code broken at investigator site or at GSK Safety department (code 1060)	49	51		26	26	23	25
Study vaccine dose not administered according to protocol (code 1070)	1601	1624		817	825	784	799
Subjects with a positive pregnancy test at Visit 1, 2 or 3 (code 1500)	0	281		0	147	0	129
Subjects with a history of vaccination against Hepatitis A or known clinical history of hepatitis A disease (code 1600)	7	22		4	7	3	8
Ethics committee request (code 1700)	1	1		1	1	0	0
ATP safety cohort*	**16840**		**90.3**	**8409**		**8431**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	18	27		10	12	8	10
Administration of any medication forbidden by the protocol (code 2040)	20	27		8	13	12	14
Underlying medical condition forbidden by the protocol (code 2050)	123	143		57	70	66	72
Concomitant infection related to the vaccine which may influence immune response (code 2060)	2985	3237		1021	1119	1964	2117
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	365	452		177	207	188	245
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	205	313		103	148	102	165
Essential serological data missing (code 2100)	29	270		18	130	11	129
Subjects not planned to be tested (not in immunogenicity subset) (code 2500)	11162	15497		5980	7719	5182	7725
ATP immunogenicity cohort*	**1933**		**10.4**	**1035**		**898**	

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
Note: Subjects may have more than one elimination code assigned; in case of more than one code, the code with the lowest number was used as the reason for elimination
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated cohort
* Additional elimination codes may have been assigned between the interim and final analyses.
Source: STN 125259.0048, CSR 008, Table 14, p. 194

Subjects were recruited in 135 centers located in 14 countries: Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK and USA. At the time of the final analysis, there were 131 active centers as the following four centers were closed during the course of the study. Subjects in 2 of the centers were transferred to other sites. One center (4923) was closed due to data integrity issues and these subjects were excluded from analysis. For a 4th study site (5556), which had 12 subjects, the site was closed and subjects stopped participation in the study. However, subjects had either completed the study or were lost to follow-up, and subjects were included in the analyses. Therefore, the Total Vaccinated Cohort analysis is based on 132 centers.

Reviewer's Comment: GSK notified CBER that site 4923 was terminated from participation in the protocol due to lack of adequate clinical investigator oversight and failure to conduct the study according to the investigational plan. Please see review by Mr. Yimam, Bioresearch Monitoring.

Study completion and withdrawal from study: Of the 18644 vaccinated subjects, 1725 subjects withdrew from the study before the final analysis (868 subjects in the HPV group and 857 subjects in the HAV group).

- 929 subjects (463 HPV and 466 HAV) were lost to follow-up,
- 403 subjects withdrew their consent not due to an adverse event (199 subjects in the HPV group and 204 subjects in the HAV group)
- 186 subjects withdrew due to other reasons (including mainly request of unblinding to receive a licensed HPV vaccine, unknown or personal reasons and pregnancy)
- 172 subjects migrated or moved from the study area
- 15 subjects withdrew due to an SAE (7 subjects in the HPV group and 8 subjects in the HAV group), with none of these events reported as possibly related to vaccination according to the investigator.
- 8 subjects withdrew due to a non-serious AE (five subjects in the HPV group and three subjects in the HAV group), of which two events (one in each group) were considered as possibly related to vaccination according to the investigator.
- 12 subjects were withdrawn due to a protocol violation

Table 104-Study HPV-008: Number of subjects withdrawn with reason for withdrawal (TotalVaccinated cohort)

		HPV N = 9319		HAV N = 9325		Total N = 18644	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Drop-out	Yes	868	9.3	857	9.2	1725	9.3
Reason for dropout	Serious adverse event	7	0.8	8	0.9	15*	0.9
	Non-serious adverse event	5**	0.6	3	0.4	8	0.5
	Protocol violation	6	0.7	6	0.7	12	0.7
	Consent withdrawal not due to an adverse event	199	22.9	204	23.8	403	23.4
	Migrated or moved from study area	94	10.8	78	9.1	172	10.0
	Lost to follow-up	463	53.3	466	54.4	929	53.9
	Other†	94	10.8	92	10.7	186	10.8

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
* Note that five case fatalities were not included in the withdrawals due to SAEs as the Study Conclusion page of the subjects' eCRF was not yet completed at the time of database freeze for the final analysis.
** At the interim analysis, one additional subject was reported as a withdrawal due to a non-serious AE, which has been reclassified as a dropout due to consent withdrawal at the final analysis.
† Other reasons included mainly request of unblinding to receive a licensed HPV vaccine, termination (reason unknown), personal reasons and pregnancy.
Source: STN 125259.0048, CSR 008, Table 15, p. 196

Reviewer's Comment: As noted above, the proportions of subjects withdrawn for advees events were fairly evenly balanced between groups.

Completion of vacination series: The number and percentage of subjects who received the vaccine doses per group is also reported. Compliance with completion of the three-dose vaccination schedule was high in both groups: 91.6% in the HPV group and 91.9% in the HAV group.

The number of subjects at each visit is presented in Table 105 below. At the final analysis (data lock point 8/31/08), the majority of subjects (N=15663) had completed Visit 9 (at Month 36) and 3304 subjects had completed Visit 10 (at Month 48). For the analysis of efficacy, the mean

follow-up period was 1064.8 days (standard deviation of 195.6 days) or 34.9 months, based on the ATP cohort for efficacy (starting at Dose 3) and 1201.1 days (standard deviation of 289.7 days) or. 39.4 months, based on TVC-1 (starting at Dose 1). For the analysis of safety based on the Total Vaccinated cohort, the mean follow-up period from Dose 1 was 1243.3 days (standard deviation of 302.2 days), or 40.8 months.

Table 105-Study HPV-008: Number of subjects at each visit (Total Vaccinated cohort)

		HPV	HAV	Total
Study visit	**Timing**	**N**	**N**	**N**
VISIT 1	Month 0	9319	9325	18644
VISIT 2	Month 1	9105	9117	18222
VISIT 3	Month 6	8776	8801	17577
VISIT 4	Month 7	8662	8662	17324
VISIT 5	Month 12	8454	8467	16921
VISIT 6	Month 18	8177	8194	16371
VISIT 7	Month 24	8056	8070	16126
VISIT 8	Month 30	7840	7830	15670
VISIT 9	Month 36	7830	7833	15663
VISIT 9 OPT*	Month 42	671	819	1490
VISIT 10	Month 48	1648	1656	3304

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects
* Optional Visit 9, i.e. additional visit for cytology and/or colposcopy, only for subjects for whom follow-up was required six months after Visit 9 according to the clinical management algorithms.
Source: STN 125259.0048, CSR 008, Table 17, p. 197

The number of subjects for whom PCR results were available at each timepoint for the TVC is presented in Table 106 below. At the time of the final analysis, PCR results were available for the majority of the subjects up to Visit 9 (Month 36). At the time of the data lock point (DLP) for the final analysis, the samples had not yet been evaluated for the majority of subjects who had completed the Month 42 and/or 48 visits.

Table 106-Study HPV-008: Number of subjects with PCR results (SPF10/DEIA) available per timepoint (TVC)

		HPV	HAV	Total
Study visit	Timing	n	n	n
VISIT 1	Month 0	9299	9301	18600
VISIT 3	Month 6	8619	8635	17254
VISIT 5	Month 12	8262	8280	16542
VISIT 6	Month 18	7935	7934	15869
VISIT 7	Month 24	7697	7677	15374
VISIT 8	Month 30	7530	7528	15058
VISIT 9	Month 36	7258	7278	14536
VISIT 9 OPT*	Month 42	402	493	895
VISIT 10	Month 48	361	407	768

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
n = number of subjects in a given category
DEIA = DNA Enzyme Immunoassay; SPF10 = Short PCR fragment 10
* Optional Visit 9, i.e. additional visit for cytology and/or colposcopy, only for subjects for whom follow-up was required six months after Visit 9 according to the clinical management algorithms.
Source: STN 125259.0048, CSR 008, Supplement 7, p. 10081

Protocol deviations
Reviewer's Comment: The numbers of subjects excluded for a specific reason for each treatment group were comparable.

Protocol deviations not leading to exclusion of subjects from an analysis: Subjects with visits outside the protocol intervals, but within the adapted intervals, were not eliminated from any analysis.
Reviewer's Comment: The proportions of subjects who were outside the strict intervals were small and balanced in each treatment group. (Source: STN 125259.0048, CSR 008, Table 19, p. 200, not shown here).

In addition, the following protocol deviations did not lead to exclusion of subjects from the analyses:

- 107 subjects had vaccine administered into their dominant arm,
- 19 subjects received the wrong vaccine vial (but the correct treatment),
- 881 subjects received replacement vials with the correct treatment
- three subjects were reported to have been vaccinated using a longer needle than the one routinely used in HPV-008, which is a 23G1 [25mm] needle,
- one subject was febrile when the vaccine was administered,
- one subject with hyperprolactinemia was vaccinated despite a positive pregnancy test (the subject was not pregnant),
- 62 subjects requested non-emergency unblinding to receive an alternative HPV vaccine (Gardasil) according to the study operating procedure. Data obtained from these subjects prior to unblinding was validated and frozen for inclusion in the analyses.

Demographic characteristics

Efficacy cohorts: The demographic characteristics of the ATP cohort for efficacy are presented in Table 107. The demographic profile of both groups of subjects was comparable with respect to mean age, regional distribution, ethnic distribution, mean height and weight. The mean age was 19.9 years and the population was predominantly of Caucasian or East/South East Asian origin (57.4% and 21.9%, respectively).

Table 107-Study HPV-008: Summary of demographic characteristics (ATP Cohort for Efficacy)

		HPV N=8093	HAV N=8069	Total N=16162
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	19.9	19.9	19.9
	SD	3.1	3.1	3.1
	Median	20.0	20.0	20.0
	Min-Max	15-25	15-25	15-25
Region	Asia Pacific	2658 (32.8%)	2651 (32.9%)	5309 (32.8%)
	Europe	3032 (37.5%)	3037 (37.6%)	6069 (37.6%)
	Latin America	1201 (14.8%)	1184 (14.7%)	2385 (14.8%)
	North America	1202 (14.9%)	1197 914.8%)	2399 (14.8%)
Race	Black	269 (3.3%)	296 (3.7%)	565 (3.5%)
	White/Caucasian	4650 (57.5%)	4621 (57.3%)	9271 (57.4%)
	Arabic/North African	10 (0.1%)	12 (0.1%)	22 (0.1%)
	East/South East Asia	1778 (22.0%)	1769 (21.9%)	3547 (21.9%)
	South Asian	6 (0.1%)	9 (0.1%)	15 (0.1%)
	Hispanic	494 (6.1%)	471 (5.8%)	965 (6.0%)
	Chinese	671 (8.3%)	675 (8.4%)	1346 (8.3%)
	Malay	1 (0.0%)	0 (0.0%)	1 (0.0%)
	Indian	3 (0.0%)	5 (0.1%)	8 (0.0%)
	Other	208 (2.6%)	209 (2.6%)	417 (2.6%)

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = standard deviation
* Other includes mainly mixed ethnicity, native American and native Canadian.
Source: STN 125259.0048, CSR 008, Table 20, p. 201

The baseline characteristics in the ATP cohort for efficacy are presented in Table 108 below. Regarding the HPV-16 status, 81.2% of the subjects were DNA negative and seronegative, 13.6% of the subjects were DNA negative and seropositive, 2.4% of the subjects were DNA positive and seronegative, and 2.8% of the subjects were DNA positive and seropositive. Regarding the HPV-18 status, 87.4% of the subjects were DNA negative and seronegative, 10.4% of the subjects were DNA negative and seropositive, 1.2% of the subjects were DNA positive and seronegative, and 1.0% of the subjects were DNA positive and seropositive.

Table 108-Study HPV-008: Baseline characteristics overall (ATP cohort for efficacy)

		HPV N=8093	HAV N=8069	Total N=16162
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	19.9	19.9	19.9
	SD	3.1	3.1	3.1
	Median	20.0	20.0	20.0
	Min-Max	15-25	15-25	15-25
Smoking status	Smoker	2385 (29.5%)	2381 (29.5%)	4766 (29.5%)
Partners past year	At least 3	577 (8.3%)	532 (7.6%)	1109 (8.0%)
	Less than 3	6388 (91.7%)	6425 (92.4%)	12813 (92.0%)
Chlamydia	Negative	7128 (94.9%)	7138 (94.9%)	14266 (94.9%)
	Positive	387 (5.1%)	381 (5.1%)	768 (5.1%)
HPV-16 sero and DNA	DNA-, S-	6512 (81.2%)	6485 (81.2%)	12997 (81.2%)
	DNA-, S+	1078 (13.4%)	1106 (13.9%)	2184 (13.6%)
	DNA+,S-	200 (2.5%)	184 (2.3%)	384 (2.4%)
	DNA+,S+	232 (2.9%)	210 (2.6%)	442 (2.8%)
	Missing	71	84	155
HPV-18 sero and DNA	DNA-, S-	7014 (87.3%)	7005 (87.5%)	14019 (87.4%)
	DNA-, S+	840 (10.5%)	829 (10.3%)	1669 (10.4%)
	DNA+,S-	102 (1.3%)	94 (1.2%)	196 (1.2%)
	DNA+,S+	78 (1.0%)	82 (1.0%)	160 (1.0%)
	Missing	59	59	118

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
Smoker = subject who has ever smoked for six months or longer
neg = negative, pos = positive, sero = serostatus
% = n / Number of subjects with available results x 100
Source: STN 125259.0048, CSR 008, Table 21, p. 202

Reviewer's Comment: The sponsor also provided breakdown of characteristics by country. In regards to HPV sero and DNA status, there is some variation from country to country as to the proportion of subjects who are seronegative and DNA negative, but it is noted that subjects in the following countries had a lower proportion of subjects overall who were seronegative and PCR negative for HPV 16 and HPV 18 as follows: Brazil: 67.7% and 79.6%, respectively; Canada 72.5% and 80%, respectively; UK 63.4% and 75.5%, respectively; US 73.9% and 83.3%, respectively. Countries in which the subjects had a higher proportion of subjects overall who were seronegative and PCR negative for HPV 16 and/or 18 include: Belgium 88.7% (HPV 16); Italy 92.9% (HPV 18); Spain 93.5% (HPV 18); Taiwan 89.0% (HPV 16) and 91.4% (HPV 18). These differences are noted because the vaccine is optimally effective in women not yet infected with the relevant vaccine HPV type. (Source: STN 125259.0048, CSR 008, Supplement 8, p. 10082-10088, not shown here).

The gynecological history of both groups of subjects in the ATP cohort for efficacy was noted to be comparable. The majority of subjects in both groups were post-menarcheal, with only three pre-menarcheal subjects overall. 60.4% of the subjects used hormonal contraceptives, 4.7% of the subjects had an intrauterine device and 1% of the subjects were sterilized. The majority of subjects (94.2%) had no history of sexually transmitted diseases.

Table 109-Study HPV-008: Gynecological history (ATP cohort for efficacy)

		HPV N=8093	HAV N=8069	Total N=16162
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Menarchal status	Post-menarchal	8092 (100%)	8067 (100%)	16159 (100%)
	Pre-menarchal	1 (0.0%)	2 (0.0%)	3 (0.0%)
Hormonal contraceptives	No	3238 (40.0%)	3155 (39.1%)	6393 (39.6%)
	Yes	4855 (60.0%)	4914 (60.9%)	9769 (60.4%)
Intrauterine device	No	7690 (95.0%)	7717 (95.6%)	15407 (95..3%)
	Yes	403 (5.0%)	352 (4.4%)	755 (4.7%)
Sterilization	No	8009 (99.0%)	7989 (99.0%)	15998 (99.0%)
	Yes	84 (1.0%)	80 (1.0%)	164 (1.0%)
STD history	No	7651 (94.5%)	7578 (93.9%)	15229 (94.2%)
	Yes	408 (5.0%)	447 (5.5%)	855 (5.3%)
Genital Warts or condylomas	No	327 (80.1%)	349 (78.1%)	676 (79.1%)
	Yes	81 (19.9%)	97 (21.7%)	178 (20.8%)
	Missing	7685	7622	15307

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
Source: STN 125259.0048, CSR 008, Supplement 9, p. 10089

Reviewer's Comment : Baseline age and ethnic characteristics are presented for the 570 subjects who were seropositive and DNA positive at baseline. When compared to the overall ATP cohort for efficacy, a higher proportion of these subjects were taking hormonal contraceptives (82.6%) as compared to 60.4% in the overall ATP cohort for efficacy, and a higher proportion of these subjects had a history of other STD infection (16.8%) as compared to 5.3% in the overall ATP cohort for efficacy. This population consistitutes a small proportion of subjects overall. (Source: STN 125259.0048, CSR 008, Supplement 12, p. 10097, not shown here)

The cytology status of subjects in the ATP cohort for efficacy at Visit 1. Overall, 91% of subjects had normal cytology and 9% had low-grade cytology. None of the subjects had high-grade cytology at baseline, in line with the definition of the ATP cohort for efficacy.

Table 110-StudyHPV-008: Overview of cytology status and HPV DNA status of subjects at baseline (ATP cohort for efficacy)

	HPV			HAV			Total		
Characteristics at Visit 1	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
ATP efficacy cohort	8093	8093	100	8069	8069	100	16162	16162	100
Subjects with normal cytology*	**8093**	**7333**	**90.6**	**8069**	**7377**	**91.4**	**16162**	**14710**	**91.0**
Without HR-HPV	7333	6245	85.2	7377	6328	85.8	14710	12573	85.5
With HR-HPV	7333	1080	14.7	7377	1041	14.1	14710	2121	14.4
With HR-HPV other than vaccine type	7333	862	11.8	7377	844	11.4	14710	1706	11.6
With HPV vaccine type (HPV-16/18)	7333	361	4.9	7377	346	4.7	14710	707	4.8
Subjects with low-grade cytology*	**8093**	**759**	**9.4**	**8069**	**691**	**8.6**	**16162**	**1450**	**9.0**
Without HR-HPV	759	229	30.2	691	201	29.1	1450	430	29.7
With HR-HPV	759	530	69.8	691	490	70.9	1450	1020	70.3
With HR-HPV other than vaccine type	759	453	59.7	691	428	61.9	1450	881	60.8
With HPV vaccine type (HPV-16/18)	759	220	29.0	691	185	26.8	1450	405	27.9
Subjects with high-grade cytology	**8093**	**0**	**0.0**	**8069**	**0**	**0.0**	**16162**	**0**	**0.0**
Subjects with missing cytology	**8093**	**1**	**0.0**	**8069**	**1**	**0.0**	**16162**	**2**	**0.0**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects used as denominator; n = number of subjects in a given category
% = n / N x 100
HR-HPV = High-risk HPV types
Normal cytology = negative
Low-grade cytology = ASC-US or LSIL
High-grade cytology = HSIL, AGC, ASC-H or ICC
Missing cytology includes subjects with unresolved inconsistencies for laboratory data at the time of database freeze.
* PCR data is not available for all subjects.
Source: STN 125259.0048, CSR 008, Table 22, p. 203

Reviewer's Comment : In the ATP cohort for efficacy, 91% of subjects overall have a normal cytology. Even with a normal cytology, approximately 5% of subjects were infected with a vaccine HPV type, approximately 12% of subjects are infected with another HR-HPV type. Overall, 14.4% of subjects with a normal cytology are infected with one of the HR-HPV types tested. Approximately 28% of subjects with low-grade cytology were infected with one of the vaccine HPV types, and approximately 70% were infected with any of the tested HR-HPV types.

The sponsor also presents the cytological characteristics of subjects in the Total Vaccinated Cohort (TVC). The TVC includes subjects with higher grade cytological abnormalities.

Table 111-Study HPV-008: Overview of cytology status and HPV DNA status of subjects at baseline (Total Vaccinated cohort)

	HPV			HAV			Total		
Characteristics at Visit 1	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Total Vaccinated cohort	9319	9319	100	9325	9325	100	18644	18644	100
Subjects with normal cytology*	**9319**	**8394**	**90.1**	**9325**	**8449**	**90.6**	**18644**	**16843†**	**90.3**
Without HR-HPV	8394	7136	85.0	8449	7212	85.4	16843	14348	85.2
With HR-HPV	8394	1250	14.9	8449	1229	14.6	16843	2479	14.7
With HR-HPV other than vaccine type	8394	1005	12.0	8449	997	11.8	16843	2002	11.9
With HPV vaccine type (HPV-16/18)	8394	413	4.9	8449	411	4.9	16843	824	4.9
Subjects with low-grade cytology*	**9319**	**863**	**9.3**	**9325**	**817**	**8.8**	**18644**	**1680**	**9.0**
Without HR-HPV	863	256	29.7	817	229	28.0	1680	485	28.9
With HR-HPV	863	607	70.3	817	587	71.9	1680	1194	71.1
With HR-HPV other than vaccine type	863	523	60.6	817	509	62.3	1680	1032	61.4
With HPV vaccine type (HPV-16/18)	863	252	29.2	817	213	26.1	1680	465	27.7
Subjects with high-grade cytology	**9319**	**45**	**0.5**	**9325**	**43**	**0.5**	**18644**	**88**	**0.5**
Without HR-HPV	45	4	8.9	43	4	9.3	88	8	9.1
With HR-HPV	45	41	91.1	43	39	90.7	88	80	90.9
With HR-HPV other than vaccine type	45	24	53.3	43	30	69.8	88	54	61.4
With HPV vaccine type (HPV-16/18)	45	25	55.6	43	25	58.1	88	50	56.8
Subjects with missing cytology	**9319**	**17**	**0.2**	**9325**	**16**	**0.2**	**18644**	**33**	**0.2**

HPV=HPV 16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects used as denominator; n = number of subjects in a given category
% = n / N x 100
HR-HPV = High-risk HPV types
Normal cytology = negative
Low-grade cytology = ASC-US or LSIL
High-grade cytology = HSIL, AGC, ASC-H or ICC
Missing cytology includes subjects with unresolved inconsistencies for laboratory data at the time of database freeze.
* PCR data is not available for all subjects.
† During the data cleaning for final analysis, it was discovered that there was a discrepancy in the sample collection date for two baseline cytology samples with normal cytology at baseline and the results for these samples were removed from the database. These two subjects were not removed from the TVC-1 at the final analysis, such that the TVC-1 at the interim analysis is the same cohort as the TVC-1 at the final analysis.
Source: STN 125259.0048, CSR 008, Table 23, p. 204

Reviewer's Comment : The proportions of subjects in the TVC with normal or low-grade cytology and infected with any HR-HPV types are similar to those in the ATP cohort for efficacy. A very low proportion of subjects had a high grade cytological abnormality (0.5% overall). Approximately 91% of subjects with high grade cytological abnormalities were infected with a HR-HPV type, and app. 57% were infected with one or both of the vaccine HPV types.

The sponsor also presented baseline characteristics for the Total Vaccinated Cohort-1 (TVC-1) and Total Vaccinated Cohort-2 (TVC-2). These are comparable to those of the ATP cohort for efficacy which was already presented. (Source: STN 125259.0048, CSR 008, Supplements 13-18, p. 10098-10117, not shown here).

Safety cohorts

Safety cohorts defined at final analysis: The demographic characteristics of the Total Vaccinated cohort, which is the primary cohort for safety, are presented. The demographic profile of both groups of subjects was comparable with respect to mean age, regional distribution, ethnic distribution, mean height and weight. The mean age was 20 years and the population was predominantly of Caucasian or East/South East Asian origin (54.8% and 23.3%, respectively).

Table 112-Study HPV-008: Summary of demographic characteristics (Total Vaccinated cohort)

		HPV N=9319	HAV N=9325	Total N=18644
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	20.0	20.0	20.0
	SD	3.1	3.1	3.1
	Median	20.0	20.0	20.0
	Min-Max	14.0-33.0	14.0-33.0	14.0-33.0
Region	Asia Pacific	3175 (34.1%)	3177 (34.1%)	6352 (34.1%)
	Europe	3224 (34.6%)	3224 (34.6%)	6448 (34.6%)
	Latin America	1388 (14.9%)	1386 (14.9%)	2774 (14.9%)
	North America	1532 (16.4%)	1538 (16.5%)	3070 (16.5%)
Race	Black	33 (3.6%)	360 (3.9%)	693 (3.7%)
	White/Caucasian	5120 (54.9%)	5098 (54.7%)	10218 (54.8%)
	Arabic/North African	10 (0.1%)	13 (0.1%)	23 (0.1%)
	East/South East Asia	2173 (23.3%)	2173 (23.3%)	4346 (23.3%)
	South Asian	8 (0.1%)	12 (0.1%)	20 (0.1%)
	Japanese	3 (0.0%)	3 (0.0%)	6 (0.0%)
	Hispanic	668 (7.2%)	662 (7.1%)	1330 (7.1%)
	Chinese	761 (8.2%)	753 (8.1%)	1514 (8.1%)
	Malay	1 (0.0%)	1 (0.0%)	2 (0.0%)
	Indian	4 (0.0%)	6 (0.1%)	10 (0.1%)
	Other*	238 (2.6%)	244 (2.6%)	482 (2.6%)

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = standard deviation
* Other includes mainly mixed ethnicity, native American and native Canadian.
Source: STN 125259.0048, CSR 008, Table 24, p. 205

The baseline characteristics of the Total Vaccinated cohort are presented in Table 113 below. The characteristics were similar to those in the ATP cohort for efficacy. Regarding the HPV-16 status, 80.7% of the subjects were DNA negative and seronegative, 13.9% of the subjects were DNA negative and seropositive, 2.5% of the subjects were DNA positive and seronegative, and 2.9% of the subjects were DNA positive and seropositive. Regarding the HPV-18 status, 87.1% of the subjects were DNA negative and seronegative, 10.6% of the subjects were DNA negative and seropositive, 1.3% of the subjects were DNA positive and seronegative, and 1.0% of the subjects were DNA positive and seropositive.

Table 113-Study HPV-008: Baseline characteristics overall (Total Vaccinated cohort)

		HPV N=9319	HAV N=9325	Total N=18644
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	20.0	20.0	20.0
	Median	20	20	20
	Min-Max	14-33	14-33	14-33
Smoking status	Smoker	2706 (29.7%)	2726 (29.9%)	5432 (29.8%)
Partners past year	At least 3	636 (8.0%)	595 (7.5%)	1231 (7.8%)
	Less than 3	7270 (92.0%)	7322 (92.5%)	14592 (92.2%)
Chlamydia	Negative	8155 (94.5%)	8188 (94.5%)	16343 (94.5%)
	Positive	478 (5.5%)	475 (5.5%)	953 (5.5%)
HPV-16 sero and DNA	DNA-, S-	7448 (80.0%)	7430 (80.7%)	14878 (80.7%)
	DNA-, S+	1258 (13.6%)	1302 (14.1%)	2560 (13.9%)
	DNA+,S-	230 (2.5%)	228 (2.5%)	458 (2.5%)
	DNA+,S+	286 (3.1%)	250 (2.7%)	536 (2.9%)
	Missing	97	115	212
HPV-18 sero and DNA	DNA-, S-	8035 (87.0%)	8057 (87.2%)	16092 (87.1%)
	DNA-, S+	988 (10.7%)	968 910.5%)	1956 (10.6%)
	DNA+,S-	127 (1.4%)	114 (1.2%)	241 (1.3%)
	DNA+,S+	88 (1.0%)	102 (1.1%)	190 (1.0%)
	Missing	81	84	165

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
Smoker = subject who has ever smoked for six months or longer
neg = negative, pos = positive, sero = serostatus
% = n / Number of subjects with available results x 100
Source: STN 125259.0048, CSR 008, Table 25, p. 206

The gynecological history of both groups of subjects in the Total Vaccinated cohort was comparable. The majority of subjects in both groups were postmenarcheal, with only four pre-menarcheal subjects overall. 60.1% of the subjects used hormonal contraceptives, 5.2% of the subjects had an intrauterine device and 1.1% of the subjects were sterilized. The majority of subjects (93.9%) had no history of sexually transmitted diseases.

Reviewer's Comment: These characteristics were very similar to those of the ATP cohort for efficacy.

Table 114-Study HPV-008: Gynecological history (Total Vaccinated cohort)

		HPV N=9319	HAV N=9325	Total N=18644
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Menarchal status	Post-menarchal	9317 (100%)	9323 (100%)	18640 (100%)
	Pre-menarchal	2 (0.0%)	2 (0.0%)	4 (0.0%)
Hormonal contraceptives	No	3775 (40.5%)	3663 (39.3%)	7438 (39.9%)
	Yes	5544 (59.5%)	5662 (60.7%)	11206 (60.1%)
Intrauterine device	No	8818 (94.6%)	8853 (94.9%)	17671 (94.8%)
	Yes	501 (5.4%)	472 (5.1%)	973 (5.2%)
Sterilization	No	9214 (8.9%)	9229 (99.0%)	18443 (98.9%)
	Yes	105 (1.1%)	96 (1.0%)	201 (1.1%)
STD history	No	8777 (94.2%)	8723 (93.6%)	17500 (93.9%)
	Yes	503 (5.4%)	550 (5.9%)	1053 (5.6%)
Genital Warts or condylomas	No	402 (79.9%)	436 (79.3%)	838 (79.6%)
	Yes	101 (10.1%)	113 (20.5%)	214 (20.3%)
	Missing	8816	8775	17591

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
Source: STN 125259.0048, CSR 008, Supplement 20, p. 10125

Reviewer's Comment : The sponsor also presents baseline demongraphic data for the ATP chort for safety, as well as other baseline by country. These results are comparable to those presented for the TVC for safety and the ATP cohort for efficacy. (Source: STN 125259.0048, CSR 008, Supplements 21-22, p. 10126-10134, not shown here).

Safety cohorts defined at interim analysis: The summary of demographic characteristics of subjects included in the safety diary card subset (N=3184 HPV, 3187 HAV, Total 6371) is also presented, based on the Interim Total Vaccinated cohort. The demographic profile of both groups of subjects was comparable with respect to mean age, regional distribution, ethnic distribution, mean height and weight. The mean age was 20.5 years and the population was predominantly of Caucasian, Hispanic, Chinese or East/South East Asian origin (41.5%, 19.9%, 16.3% and 14.4%, respectively). The demographic characteristics of subjects included in the safety diary card subset in the Interim ATP cohort for safety are also presented.
Reviewer's Comment: These were similar to the characteristics of the Total Vaccinated Cohort. (Source: STN 125259.0048, CSR 008, Supplements 23-24, p. 10135-10136, not shown here).

Immunogenicity cohorts: The demographic characteristics of HPV and HAV recipients in the ATP cohort for immunogenicity were comparable with respect to mean age, regional distribution, ethnic distribution, mean height and weight. The mean age was 20.2 years and the population was predominantly of Caucasian, Hispanic or East/South East Asian origin (48.6%, 24.9% and 20.0%, respectively). (Source: STN 125259.0048, CSR 008, Table 26, p. 208, not shown here).

In the ATP cohort for immunogenicity are presented, 22.8% of the subjects were identified as smokers, 95.6% of the subjects had fewer than three sexual partners during the past year, and 96.3% of the subjects were negative for *Chlamydia trachomatis*. Regarding the HPV-16 status, 84.0% of the subjects were DNA negative and seronegative and 16.0% of the subjects were DNA negative and seropositive. Regarding the HPV-18 status, 89.5% of the subjects were DNA negative and seronegative and 10.5% of the subjects were DNA negative and seropositive.

Table 115-Study HPV-008: Baseline characteristics overall (ATP cohort for immunogenicity)

		HPV N=1035	HAV N=898	Total N=1933
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	20.1	20.2	20.2
	Median	20	20	20
	Min-Max	15-25	15-25	15-25
Smoking status	Smoker	246 (23.8%)	195 (21.7%)	441 (22.8%)
Partners past year	At least 3	48 (5.2%)	27 (3.5%)	75 (4.4%)
	Less than 3	868 (94.8%)	754 (96.5%)	1622 (95.6%)
Chlamydia	Negative	901 (96.4%)	793 (96.5%)	1694 (96.3%)
	Positive	34 (3.6%)	31 (3.8%)	65 (3.7%)
HPV-16 sero and DNA	DNA-, S-	865 (84.3%)	744 (83.6%)	1609 (84.0%)
	DNA-, S+	161 (15.7%)	146 (16.4%)	307 (16.0%)
	Missing	9	8	17
HPV-18 sero and DNA	DNA-, S-	931 (90.7%)	784 (88.0%)	1715 (89.5%)
	DNA-, S+	95 (9.3%)	107 (12.0%)	202 (10.5%)
	Missing	9	7	16

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
Smoker = subject who has ever smoked for six months or longer
neg = negative, pos = positive, sero = serostatus
% = n / Number of subjects with available results x 100
Source: STN 125259.0048, CSR 008, Table 27, p. 209

EFFICACY RESULTS

Efficacy results: The results of the primary, secondary and exploratory efficacy endpoints are presented in the final clinical study report, representing data collected up to the Data Lock Point for the final event-driven analysis (8/31/08). The power to assess the primary and secondary efficacy endpoints at the final analysis is shown in the Table 116.

Table 116-Study HPV-008: Overview of the assessment of primary and secondary efficacy endpoints at the final analysis

	Power[1]	Result
Primary endpoint		
CIN2+ associated with 16/18	94%	objective met
Secondary endpoints		
Virological		
12-month persistent infection with 16/18	99%	objective met
6-month persistent infection with 16/18	99%	objective met
6-month persistent infection with oncogenic types	99%	objective met
Histopathological		
CIN2+ associated with oncogenic types	62%	objective met
CIN1+ associated with 16/18	99%	objective met
CIN1+ associated with oncogenic types	91%	objective met

Source: STN 125259.0048. CSR 008, Table 28, p. 211

Reviewer's Comment: This review will discuss the CIN2+ endpoints related to HPV 16/18 in the ATP, TVC-1, TVC, and TVC-naïve cohorts; then the CIN2+ endpoints ireespective of HPV type; then the CIN2+ endpoints related to non-vaccine HPV types. These CIN2+ endpoints are discussed in detail so as to best understand the impact of the vaccine in the primary analysis population (ATP cohort for efficacy), in all subjects, and in the naïve group of subjects. The CIN1+, 12-month persistent infection and 6-month persistent infection endpoints will then be discussed for HPV 16/18 and non-vaccine HPV types in the ATP, TVC-1, TVC, and TVC-naïve cohorts. Several exploratory endpoints, including analyses of endpoints in subjects seropositive and/or PCR positive for the relevant HPV type will be briefly discussed. Finally, selected exploratory endpoints, such as reduction in cervical procedures also will be discussed, given the

potential importance of these data in broadening the understanding of the possible public health benefit of the vaccine.

Primary endpoint: CIN2+ cases associated with HPV-16/18: The principal analyses were performed on subjects who were HPV DNA negative and seronegative for the corresponding type at baseline, and vaccine efficacy was determined using the conditional exact method. Analyses were also performed overall regardless of initial serostatus, and in subjects who were seropositive for the corresponding type at baseline. Analyses by region / age and confirmatory analyses are also presented. Results were considered statistically significant if the lower limit of the 96.1% CI was above zero. At the final analysis, the primary endpoint was considered met if the lower limits of the 96.1% CI were above 30%, based on the power calculations performed prior to the study start.
Reviewer's Comment: Since an interim analysis was conducted, for the primary endpoint and each secondary endpoint, a global alpha of 0.05 was used. For the primary histopathological endpoint, the overall alpha of 0.05 was split into 0.021 for the interim analysis and 0.039 for the final analysis. For all secondary endpoints, the overall alpha of 0.05 was split into 0.021 for the interim analysis and 0.039 for the final analysis. In this review, analyses for important endpoints will be presented for subjects naïve for the relevant HPV types, then for all subjects (includes those who are naïve AND non-naïve), then for subjects in the TVC naïve (naïve for all types).

CIN2+ cases associated with HPV-16/18 in subjects who were HPV DNA negative and seronegative for the corresponding type at baseline: The primary objective of the study was to demonstrate the efficacy of the vaccine for prevention of histopathologically-confirmed CIN2+ cases associated with HPV-16 and/or HPV-18 (HPV-16/18) infection detected within the cervical lesion (by PCR) in adolescent and young adult women who were negative for HPV DNA (by PCR) at Month 0 and 6 for the corresponding HPV type considered in the analysis. The principal analysis was performed on subjects who were also seronegative (by ELISA) at baseline for the corresponding HPV type considered in the analysis. Since the study cohort included women who may have been positive by PCR for other HPV types at entry, this cohort included women at risk of developing lesions caused by prevalent infections at entry.

The final analysis was triggered with confirmation of at least 36 cases of CIN2+ associated with HPV-16/18 (by PCR) (including at least 15 cases of CIN2+ associated with HPV-18 infection) post dose 3 in subjects who were HPV DNA negative at Month 0 and 6 and seronegative at baseline. At the time of the final analysis there were 60 cases of the primary endpoint in the ATP cohort for efficacy (48 cases associated with HPV-16, 17 cases associated with HPV-18 and 5 cases associated with both HPV-16 and HPV-18) in subjects who were HPV DNA negative at Month 0 and 6, and seronegative at Month 0, for the corresponding type found in the lesion. To maintain the blinding, case numbers were assigned by the external statistician.

CIN2+ cases associated with HPV-16/18: The incidence rates and vaccine efficacy against CIN2+ associated with HPV-16/18 (by PCR) in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy is presented in Table 117. Infection with multiple HPV types was detected in 36 out of the 60 CIN2+ cases associated with HPV-16/18 (including 33 cases with co-infection with oncogenic HPV types other than HPV-16/18). In some cases subjects had longstanding infections with the other HPV type(s) detected.

Table 117-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7344	4	17689.6	0.02 [0.01, 0.06]	**92.9% [79.9, 98.3%]**
	HAV	7312	56	17663.32	0.32 [0.24, 0.42]	**-**
HPV 16	**HPV**	6303	2	15193.63	0.01 [0.00, 0.05]	**95.7% [82.9, 99.6%]**
	HAV	6165	46	14911.49	0.31 [0.22, 0.42]	**-**
HPV 18	**HPV**	6794	2	16377.95	0.01 [0.00, 0.05]	**86.7% [39.7, 98.7%]**
	HAV	6746	15	16310.82	0.09 [0.05, 0.16]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 31, p. 237

Reviewer's Comment: The 4 subjects who developed CIN2+ in the ATP cohort were infected with another oncogenic HPV type at baseline. In each case, this other oncogenic HPV type was also detected in the lesion (2 with HPV-58, 1 with HPV-52 and 1 with HPV-31). In three of these lesions, the vaccine HPV type was detected at the time of diagnosis of the CIN2+ lesion.

Of the 60 cases of CIN2+ associated with HPV-16/18 identified, there were 12 cases of CIN3+ with HPV-16/18 (9 cases of CIN3, 2 cases of AIS, and 1 case of both CIN3 and AIS) with 2 cases in the HPV group and 10 cases in the HAV group. An additional exploratory analysis was performed of vaccine efficacy against CIN3+ associated with HPV-16/18, as described in the RAP. In this exploratory analysis, the vaccine efficacy against CIN3+ associated with HPV-16/18 was statistically significant at 80.0% [96.1% CI: 0.3, 98.1]. This analysis is presented in Table 118 below.

Table 118-Study HPV-008: Incidence rates and vaccine efficacy against CIN3+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7344	2	17691.89	0.01 [0.00, 0.04]	**80.0% [0.3, 98.1%]**
	HAV	7312	10	17694.22	0.06 [0.03, 0.11]	**-**
HPV 16	**HPV**	6303	2	15193.63	0.01 [0.00, 0.05]	**67.2% [-97.1, 97.2%]**
	HAV	6165	6	14938.01	0.04 [0.01, 0.09]	**-**
HPV 18	**HPV**	6794	0	16380.25	0.00 [0.00, 0.02]	**100% [-19.3, 100%]**
	HAV	6746	5	16317.92	0.03 (0.01, 0.07]	**-**

HPV = HPV-16/18 AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
CIN3+ = CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement, 27, p. 10219

Similar results were seen in the complementary analysis in TVC-1, where there were a total of 96 cases of CIN2+ associated with HPV-16/18 in subjects who were HPV DNA negative and seronegative for the corresponding type at baseline.

Reviewer's Comment: The TVC-1 cohort were also naïve for the relevant HPV type and had a normal or low-grade cytology, although cases were counted 1 days after dose 1. Therefore, results were similar to those in the ATP cohort for efficacy in that the TVC-1 population had the same baseline characteristics as the ATP cohort. The table showing the difference between the two populations is reproduced below, and shows that subjects only needed to be seronegative and PCR negative for the relevant vaccine HPV types at D0, received 1 dose of vaccine, and cases were counted starting 1 day after dose 1.

Table 119-Study HPV-008: Efficacy Populations [CBER Generated]

Population	Protocol deviations	Pap Test Baseline	Serostatus D0	PCR status	Doses/cases counted when
ATP Cohort	No	Normal or low-grade(a)	Neg. relevant HPV	Neg. through M6 for relevant HPV type	3 doses/1 day after dose 3
TVC-1	Yes	Normal or low-grade (a)	Neg, relevant HPV	Neg. for relevant HPV type D0	1 dose/1 days after dose 1

Compared to the ATP cohort for efficacy there was 1 additional case in the HPV group and 35 additional cases in the HAV group in TVC-1. Subjects in this group may have had vaccine HPV type detected by Month 6 (prior to completion of vaccination course).

Table 120-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (TVC-1)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8040	5	23215.10	0.02 [0.01, 0.05]	**94.5% [86.2, 98.4%]**
	HAV	8080	91	23297.14	0.39 [0.31, 0.48]	**-**
HPV 16	**HPV**	6921	3	20013.94	0.01 [0.00,0.05]	**95.9% [87.0, 99.3%]**
	HAV	6923	73	19998.76	0.37 [0.28, 0.46]	**-**
HPV 18	**HPV**	7455	2	21544.80	0.01 [0.00, 0.04]	**91.6% [64.6, 99.2%]**
	HAV	7480	24	21618.46	0.11 [0.07, 0.17]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 28, p. 10220

There were 24 cases of CIN3+ with HPV-16/18 in TVC-1 (21 cases of CIN3, 2 cases of AIS and 1 case of both CIN3 and AIS) with 2 cases in the HPV group and 22 cases in the HAV group. An additional analysis of the incidence rates and vaccine efficacy against CIN3+ associated with HPV-16/18 (by PCR) in HPV DNA negative and seronegative subjects at baseline in TVC-1 is prsented. Results are presented in Table 121.

Table 121-Study HPV-008: Incidence rates and vaccine efficacy against CIN3+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (TVC-1)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8040	2	23219.03	0.01 (0.0, 0.03)	**90.9% [60.8, 99.1%]**
	HAV	8080	22	23358.12	0.09 (0.06, 0.15)	**-**
HPV 16	**HPV**	6921	2	20015.57	0.01 (0.0, 0.04)	**97.5% [43.8, 98.8%]**
	HAV	6923	16	20042.43	0.08 (0.04, 0.13)	**-**
HPV 18	**HPV**	7455	0	21547.09	0.00 (0.00,0.02)	**100% [24.2, 100%]**
	HAV	7480	7	21638.49	0.03 (0.01, 0.07)	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
CIN3+ = CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 29, p. 10221

Reviewer's Comment: In the analyses for vaccine efficacy in prevention of HPV 16/18 related CIN 2+ and 3+ in the TVC-1 as compared to the ATP cohort, a greater number of cases occurred in the HAV treatment group as compared to the HPV vaccine group (after dose 1). In the TVC-1 cohort, only one additional case of CIN 2+ related to HPV 16 occurred in the Cervarix treatment

group as compared to 9 related to HPV 18 and 27 related to HPV 16 in the HAV group. For the CIN 2+ endpoint, the point estimates of efficacy were somewhat higher for all endpoints with tighter 96.1% CIs in the TVC-1 group. For the CIN 3+ endpoint, the point estimates of efficacy were higher and/or reached statistical significance for HPV 16 and HPV 18 individually in prevention of CIN3+ associated with HPV 16 and/or HPV 18 in subjects who were naïve at baseline.

In a type-specific analysis in subjects naïve for the relevant HPV types, among all vaccinated subjects (with or without abnormal cytology) for whom data was available, the results are similar to those reported for the TVC-1 (i.e., when subjects with normal or low-grade cytology are considered) (Table 122).

Table 122-study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline with any cytology, using conditional exact method (Subset of Total Vaccinated Cohort)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8079	5	23313.61	0.02 [0.01, 0.05]	**94.6% [86.3, 98.4%]**
	HAV	8112	92	23385.43	0.39 [0.31, 0.49]	**-**
HPV 16	**HPV**	6944	3	20074.88	0.01 [0.00, 0.05]	**96.0% [87.2, 99.3%]**
	HAV	6939	74	20040.74	0.37 [0.29, 0.47]	**-**
HPV 18	**HPV**	7491	2	21634.53	0.01 [0.00, 0.03]	**91.6% [64.6, 99.2%]**
	HAV	7508	24	21699.05	0.11 [0.07, 0.17]	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 201, p. 10398

Additional analyses of the incidence rates and vaccine efficacy against CIN3+ associated with HPV-16/18 (by PCR) in HPV DNA negative and seronegative subjects at baseline among all subjects were presented. The vaccine efficacy against CIN3+ associated with HPV-16/18 was statistically significant at 91.3% [62.8, 99.1], $p<0.0001$ with 2 cases in the HPV group and 23 cases in the HAV group (Table 123).

Table 123-Study HPV-008: Incidence rates and vaccine efficacy against CIN3+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects with any cytology at baseline, using conditional exact method (Subset of Total Vaccinated cohort)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8079	2	23317.53	0.01 [0.00, 0.03]	**91.3% [62.8, 99.1%]**
	HAV	8112	23	23446.41	0.10 [0.06, 0.15]	**-**
HPV 16	**HPV**	6944	2	20076.51	0.01 [0.00, 0.04]	**88.2% [47.7, 98.9%]**
	HAV	6939	17	20084.42	0.08 [0.05, 0.14]	**-**
HPV 18	**HPV**	7491	0	21636.82	0.00 [0.00, 0.02]	**100% [24.2, 100%]**
	HAV	7508	7	21719.08	0.03 [0.01, 0.07]	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN3+ = CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 207, p. 10404

Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus: There were 71 cases of the primary endpoint in the ATP cohort for efficacy when the subject's initial serostatus for the corresponding type was not considered in the analysis. In addition to the 60 cases of the primary endpoint in seronegative subjects, there were 11 cases (2 in the HPV group and 9 in the HAV group) regardless of initial serostatus added to the analysis. Of these additional 11 cases (8 cases of CIN2 and 3 cases of CIN3), 8 cases were seropositive and 3 cases had an unknown serostatus at baseline for the corresponding type found in the lesion. In addition to the 4 cases in the HPV group, already described in the ATP cohort for efficacy in seronegative subjects, 2 additional cases were detected in the HPV group in the ATP cohort for efficacy regardless of initial serostatus (See Table 124).

Table 124-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7814	6	18784.44	0.03 [0.01, 0.07]	**90.8% [78.1, 96.9%]**
	HAV	7767	65	18719.27	0.35 [0.26, 0.45]	**-**
HPV 16	**HPV**	7372	4	17726.34	0.02 [0.01, 0.06]	**92.7% [79.3, 98.2%]**
	HAV	7276	54	17520.68	0.31 [0.23, 0.41]	**-**
HPV 18	**HPV**	7645	2	18388.48	0.01 [0.00, 0.04]	**87.6% [44.1, 98.8%]**
	HAV	7583	16	18312.59	0.09 [0.05, 0.15]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event

VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test; Source: STN 125259.0048. CSR 008, Table 36, p. 252

Reviewer's Comment: Additional cases were added to both treatment groups. These subjects had evidence of prior exposure to the relevant HPV type (positive serostatus) or serology was unknown.

In the ATP cohort for efficacy there were 15 cases of CIN3+ associated with HPV-16/18 in subjects who were HPV DNA negative regardless of serostatus, with 2 cases in the HPV group and 13 cases in the HAV group (Table 125).

Table 125-Study HPV-008: Incidence rates and vaccine efficacy against CIN3+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7814	2	18786.84	0.01 [0.00, 0.04]	**84.6% [28.2, 98.5%]**
	HAV	7767	13	18755.15	0.07 [0.04, 0.12]	**-**
HPV 16	**HPV**	7372	2	17726.45	0.01 [0.00, 0.04]	**75.3% [-32.4, 97.8%]**
	HAV	7276	8	17552.17	0.05 [0.02, 0.09]	**-**
HPV 18	**HPV**	7645	0	18390.78	0.00 [0.00, 0.02]	**100% [7.6, 100%]**
	HAV	7583	6	18319.70	0.03 [0.01, 0.07]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
CIN3+ = CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 33, p. 10225

Similar results were seen in the analysis in TVC-1, where there were a total of 112 cases of CIN2+ associated with HPV-16/18 in subjects who were HPV DNA negative at baseline, regardless of initial serostatus. Compared to the ATP cohort for efficacy there were 2 additional cases in the HPV group and 39 additional cases in the HAV group in TVC-1 regardless of initial serostatus. The vaccine efficacy against CIN2+ associated with HPV-16/18 in TVC-1 was 92.3% [96.1% CI: 83.8, 96.9] with 8 cases in the HPV group versus 104 cases in the HAV group. Statistically significant vaccine efficacy was also observed for CIN2+ associated with HPV-16 (VE=93.0% [96.1% CI: 83.5, 97.6]) and HPV-18 (VE=92.0% [96.1% CI: 66.2, 99.2]) in TVC-1.

There were 30 cases of CIN3+ with HPV-16/18 in TVC-1 (27 cases of CIN3, 2 cases of AIS and 1 case of both CIN3 and AIS) with 2 cases in the HPV group and 28 cases in the HAV group. An additional analysis of the incidence rates and vaccine efficacy against CIN3+ associated with HPV-16/18 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, in TVC-1, was also presented. The vaccine efficacy against CIN3+ associated with HPV-16/18 was statistically significant at 92.8% [96.1% CI: 70.2, 99.3]).

Similar results were noted when all subjects with all baseline cytology were considered (but in these analyses, cases are based on the type specific analyses in subjects DNA negative for the specific HPV type at baseline.)

Table 126-Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative subjects at baseline with any cytology, regardless of initial serostatus, using conditional exact method (Subset of Total Vaccinated cohort)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8610	8	24803.26	0.03 [0.01, 0.07]	**92.4% [84.0, 97.0%]**
	HAV	8619	105	24788.19	0.42 [0.34, 0.52]	**-**
HPV 16	**HPV**	8169	6	23545.05	0.03 [0.01, 0.06]	**93.1% [83.7, 97.7%]**
	HAV	8228	87	23677.31	0.37 [0.29, 0.46]	**-**
HPV 18	**HPV**	8451	2	24355.71	0.01 [0.00, 0.03]	**92.0% [66.2, 99.2%]**
	HAV	8464	25	24425.11	0.10 [0.06, 0.15]	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 202, p. 10399

Table 127-Study HPV-008: Incidence rates and vaccine efficacy against CIN3+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative subjects at baseline with any cytology, regardless of initial serostatus, using conditional exact method (Subset of Total Vaccinated cohort)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8610	2	24808.28	0.01 [0.00, 0.03]	**93.1% [71.3, 99.3%]**
	HAV	8619	29	24855.62	0.12 [0.08, 0.17]	**-**
HPV 16	**HPV**	8169	2	23547.77	0.01 [0.00, 0.03]	**91.2% [62.7, 99.1%]**
	HAV	8228	23	23727.43	0.10 [0.06, 0.15]	**-**
HPV 18	**HPV**	8451	0	24358.00	0.00 [0.00, 0.02]	**100% [36.2, 100%]**
	HAV	8464	8	24445.14	0.03 [0.01, 0.07]	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN3+ = CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
For single type: Subjects DNA negative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 209, p. 10406

Reviewer's Comment: It is important to remember that these analyses include subjects who were seronegative or seropositive for the relevant vaccine HPV type (while still being DNA negative) and had any cytology.

Results in subjects who were HPV DNA negative and seropositive for the corresponding type at baseline CIN2+ cases associated with HPV-16/18 detected in the cervical lesion: Among women who received 3 doses of Cervarix and were DNA negative for the relevant HPV type but seropositive for that type (with normal or low-grade cytology), there were 8 cases of CIN2+ associated with HPV-16, and no cases with HPV-18. Of the 8 cases (5 cases of CIN2 and 3 cases of CIN3), only 1 case in the HAV group had a single HPV type (HPV-16 only) in the lesion. There were no cases with a single type in the lesion in the HPV group. The vaccine efficacy for CIN2+ associated with HPV-16 was 66.0% [96.1% CI: -104.3, 97.1] with 2 cases in the HPV group versus 6 cases in the HAV group. As there were no cases of CIN2+ associated with HPV-18 in this analysis the vaccine efficacy was not assessed. Neither of the point estimates of efficacy reached statistical significance. (Source: STN 125259.0048, CSR 008, Supplement 39, p. 10231, not shown here).

Similar results were seen in the analysis in TVC-1, where there were 13 cases of CIN2+ associated with HPV-16, and no cases with HPV-18, in subjects who were HPV DNA negative and seropositive for the corresponding type at baseline in TVC-1. Of the 13 cases (7 cases of CIN2 and 6 cases of CIN3), 3 cases in the HAV group had a single HPV type (HPV-16 only) in the lesion. There were no cases with a single type in the lesion in the HPV group. The vaccine efficacy against CIN2+ associated with HPV-16 was 68.9% [96.1% CI: -27.8, 95.0] with 3 cases in the HPV group versus 10 cases in the HAV group. As there were no cases of CIN2+ associated with HPV-18 in this analysis the vaccine efficacy was not assessed. Neither of the point estimates for efficacy reached statistical significance. (Source: STN 125259.0048, CSR 008, Supplement 40, p. 10232, not shown here).

In subjects with any cytology, who were seropositive and PCR negative for the relevant HPV type, in a type-specific analysis, the point estimates of efficacy are as noted below.

Table 128-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seropositive subjects at baseline with any cytology at baseline, using conditional exact method (Subset of Total Vaccinated cohort*)

					Person-year rate	VE	
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**	**p-value**
HPV 16/18	**HPV**	1710	3	4865.79	0.06 [0.01, 0.19]	**68.8% [-28.3, 95.0%]**	**0.0925**
	HAV	1777	10	5058.97	0.20 [0.09, 0.37]	-	-
HPV 16	**HPV**	1162	3	3302.46	0.09 [0.02, 0.28]	**68.9% [-27.9, 95.0%]**	**0.0923**
	HAV	1211	10	3421.29	0.29 [0.13, 0.55]	-	-
HPV 18	**HPV**	907	0	2573.24	0.00 [0.00, 0.15]	-	-
	HAV	902	0	2580.19	0.00 [0.00, 0.15]	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative and seropositive for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seropositive for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 203, p. 10400

Reviewer's Comment: This analysis was considered in order to assess whether there is evidence of prevention of re-infection in subjects who had potentially cleared a prior infection with the

same type. In this specific population, very few cases of CIN2+ accrued in either treatment group, although there was a positive point estimate of efficacy. It is possible that females who clear their infection and then are re-infected may have a decrease in the number of CIN2+ lesions which develop, although this cannot be stated definitively. This population of women may have cleared a prior infection, but they may be somehow different from women who have not been previously exposed.

Analysis of subjects with CIN2+ cases associated with HPV-16/18 by region and age in subjects seronegative and PCR negative for the relevant HPV type: Additional analyses by region or age were not powered to assess vaccine efficacy, but provide an overview of the number of cases in different populations. Results from the TVC-1 are described for all endpoints for which an analysis by region is done, as the number of subjects included in each group are higher. In the TVC-1, the vaccine efficacy was 86.6% [96.1% CI: 39.3, 98.7] in Asia Pacific, 95.3% [96.1% CI: 80.9, 99.5] in Europe, 100% [96.1% CI: 52.9, 100] in Latin America and 95.7% [96.1% CI: 71.8, 99.9] in North America. The attack rate was lowest in Asia Pacific and highest in North America for this analysis. (Source: STN 125259.0048, CSR 008, Supplement 44, p. 10236, not shown here).

A sub-analysis by age in TVC-1 is also presented. These analyses are presented in Table 129 and Table 130 below.

Table 129-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline aged 15-20 years using conditional exact method (TVC-1)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	4470	4	13174.62	0.03 [0.01, 0.08]	**94.7% [85.2, 98.7%]**
	HAV	4539	76	13371.56	0.57 [0.44, 0.72]	**-**
HPV 16	**HPV**	3902	2	11510.71	0.02 [0.00, 0.07]	**96.7% [86.9, 99.7%]**
	HAV	3948	61	11668.54	0.52 [0.39, 0.68]	**-**
HPV 18	**HPV**	4173	2	12307.86	0.02 [0.00, 0.06]	**90.3% [58.1, 99.0%]**
	HAV	4252	21	12561.58	0.17 [0.10, 0.26]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
Subjects aged 15-20 years at the time of the first vaccination
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 45, p. 10237

Table 130-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline aged 21-25 years using conditional exact method (TVC-1)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	3562	1	10017.38	0.01 [0.00, 0.06]	**93.4% [54.5, 99.9%]**
	HAV	3534	15	9905.86	0.15 [0.08, 0.26]	**-**
HPV 16	**HPV**	3012	1	8482.26	0.01 [0.00, 0.07]	**91.8% [41.2, 99.9%]**
	HAV	2969	12	8313.43	0.14 [0.07, 0.26]	**-**
HPV 18	**HPV**	3274	0	9213/84	0.00 [0.00, 0.04]	**100% [-166.4, 100%]**
	HAV	3222	3	9040.11	0.03 [0.01, 0.10]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
Subjects aged 21-25 years at the time of the first vaccination
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 46, p. 10238

Reviewer's Comment : The majority of cases was observed in subjects 15-20 years of age as compared to subjects 21-25 years of age, although the point estimates of efficacy were high in both age groups (but did not reach statistical significance for HPV 18 alone in the older subgroup).

Exploratory analyses of different covariates: The sponsor notes that the combined effect of different covariates (such as age, region, number of sexual partners, hormonal contraception, occurrence of another lower genital tract infection and smoking) were evaluated. The observed adjusted vaccine efficacy against CIN2+ associated with HPV-16/18 was 91.3% [96.1% CI: 74.4, 97.0] with 4 cases in the HPV group versus 47 cases in the HAV group. Due to missing values for some covariates not all subjects were included in the analyses of adjusted vaccine efficacy which reduced the number of cases. The sponsor concluded that, based on these data, there is no indication that the evaluated covariates had an effect on vaccine efficacy. The results of the complementary analysis in TVC-1 are similar to those presented in the ATP cohort for efficacy. (Source: STN 125259.0048. CSR 008, Supplements 53-54, p. 10245-46, not shown here)

CIN2+ associated with HPV-16 only, HPV-18 only and HPV-16 or HPV-18 only: The sponsor also provided analyses in subjects who were HPV DNA negative and seronegative for the corresponding type at baseline, and vaccine efficacy was determined using the conditional exact method. In this analysis only CIN2+ lesions where a single HPV type, either HPV-16 only or HPV-18 only, was found in the lesion were considered. The incidence rates and vaccine efficacy against histopathologically-confirmed CIN2+ associated with cervical infection by HPV-16 only, HPV-18 only and HPV-16 or HPV-18 only (by PCR within the lesional component of the tissue specimen) in HPV DNA negative and seronegative subjects were presented.

Table 131-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 only, HPV-18 only and HPV-16 or HPV-18 only (by PCR) in DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7344	0	17696.08	0.00 [0.00, 0.02]	**100% [87.3, 100%]**
	HAV	7312	33	17679.45	0.19 [0.13, 0.27]	**-**
HPV 16	**HPV**	6303	0	15197.83	0.00 [0.00, 0.03]	**100% [85.7, 100%]**
	HAV	6165	29	14922.81	0.19 [0.13, 0.28]	**-**
HPV 18	**HPV**	6794	0	16380.25	0.00 [0.00, 0.02]	**100% [-67.0, 100%]**
	HAV	6746	4	16318.35	0.02 [0.01, 0.07]	**-**

Note: In this analysis only a single type was found in the lesion i.e., either HPV-16 only or HPV-18 only
HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 57, p. 293

CIN2+ associated with HPV-16/18 in women previously infected with the other vaccine type: This *post-hoc* analysis was performed to complement the equivalent analysis for 6-month persistent infection. Analyses were performed in TVC-1. The analyses were performed on subjects who were HPV DNA negative at baseline for the corresponding type assessed in the analysis and with a history of infection with the other vaccine type. Vaccine efficacy was determined using the conditional exact method.

An additional analysis of the incidence rates and vaccine efficacy against CIN2+ associated with HPV-16/18 (by PCR) in subjects with a history of infection with the other vaccine type (HPV DNA positive and/or seropositive) and HPV DNA negative and seronegative for the corresponding vaccine type at baseline in TVC-1 was presented. The vaccine efficacy against CIN2+ associated with HPV-16/18 in subjects who were infected with the other vaccine type at baseline was statistically significant at 81.3% [8.9%, 98.2%], p=0.0224 (with 2 cases in the HPV group and 11 cases in the HAV group). The vaccine efficacy against CIN2+ associated with HPV-16 in subjects with a history of HPV-18 infection and with HPV-18 in subjects with a history of HPV-16 infection was not statistically significant with few cases of each Table 132).

Table 132-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in subjects with a history of infection with the other vaccine type (HPV DNA positive and/or seropositive) and HPV DNA negative and seronegative for the corresponding vaccine type at baseline using conditional exact method (TVC-1)

					Person-year rate	VE	
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**	**p-value**
HPV 16/18	**HPV**	1643	2	4705.92	0.04 [0.00, 0.16]	**81.3% [8.9, 98.2%]**	**0.0224**
	HAV	1690	11	4852.29	0.23 [0.11, 0.42]	**-**	**-**
HPV 16	**HPV**	560	1	1602.03	0.06 [0.00, 0.37]	**79.2% [-102.2, 99.7%]**	**0.2179**
	HAV	578	5	1667.88	0.30 [0.09, 0.72]	**-**	**-**
HPV 18	**HPV**	1083	1	3103.89	0.03 [0.00, 0.19]	**82.9% [-52.3, 99.7%]**	**0.1246**
	HAV	1112	6	3184.41	0.19 [0.07, 0.42]	**-**	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots), HAV = Hepatitis A vaccine (three lots)
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
HPV-16: Subjects DNA positive or seropositive for HPV-18 at Month 0 and DNA negative and seronegative for HPV-16 at Month 0
HPV-18: Subjects DNA positive or seropositive for HPV-16 at Month 0 and DNA negative and seronegative for HPV-18 at Month 0
HPV-16/18: Subjects DNA positive or seropositive for either HPV-16 or HPV-18 at Month 0 and DNA negative and seronegative for the other vaccine type at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method), LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 88, p. 334

CIN2+ associated with HPV 16/18 in TVC-Naïve Population: The cohort of females naïve for all tested oncogenic HPV types, seronegative for HPV 16 and 18, and with a normal cytology provide a population with which to estimate efficacy in the prevention of CIN2+ in subjects not yet exposed to HPV infection. Point estimates of efficacy for prevention of CIN2+ associated with HPV 16/18 are presented in Table 133 below.

Table 133-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV naïve subjects at baseline using conditional exact method (Total cohort of HPV naïve women)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	5449	1	15810.77	0.01 (0.00, 0.04)	**98.4% (90.4, 100%)**
	HAV	5436	63	15724.71	0.40 (0.30, 0.52)	**-**
HPV 16	**HPV**	5449	1	15810.77	0.01 (0.00, 0.04)	**98.2% (89.1, 100%)**
	HAV	5436	56	15732.25	0.36 (0.26, 0.47)	**-**
HPV 18	**HPV**	5449	0	15812.40	0.00 (0.00, 0.02)	**100% (61.3, 100%)**
	HAV	5436	12	15761.28	0.08 (0.04, 0.14)	

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Reviewer's Comment: The one subject in the TVC naïve group developed a lesion associated with HPV-16 at Month 6, and HPV-43 (not included in high-risk types) was detected prior to completion of the vaccine course.

Overall CIN2+ associated with HPV-16/18, irrespective of baseline HPV DNA and Serostatus: An additional analysis of the incidence rates and vaccine efficacy against CIN2+ associated with HPV-16/18 (by PCR) in all subjects, irrespective of their baseline HPV DNA and serostatus, in the Total Vaccinated cohort was presented Table 134).

Table 134-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in all subjects, irrespective of their baseline HPV DNA and serostatus, using conditional exact method (Total Vaccinated cohort)

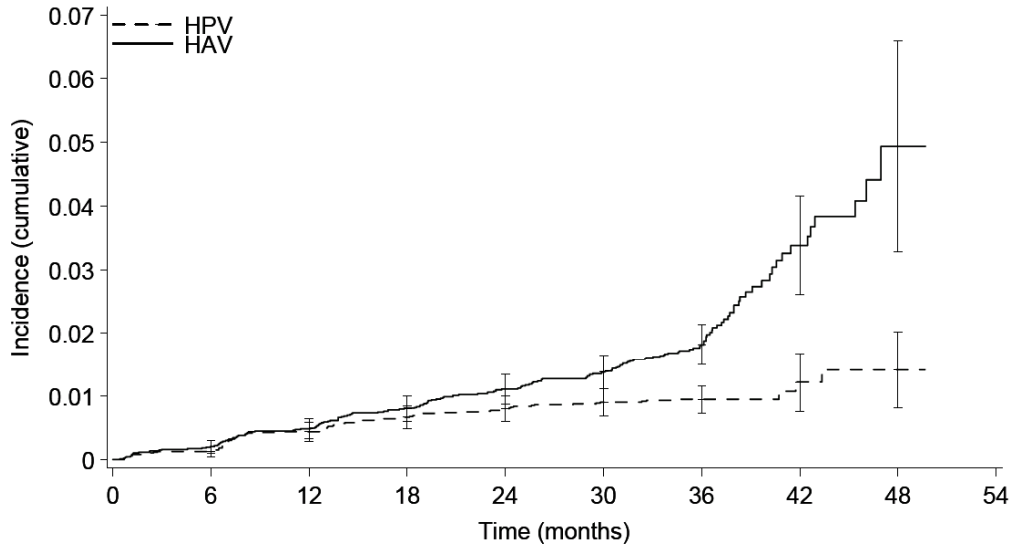
					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (yesr)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8667	82	24825.41	0.33 [0.26, 0.41]	**52.8% [37.5, 64.7%]**
	HAV	8682	174	24846.52	0.70 [0.60, 0.82]	**-**
HPV 16	**HPV**	8667	75	24837.48	0.30 [0.23, 0.38]	**50.6% [33.5, 63.6%]**
	HAV	8682	152	24878.73	0.61 [0.51, 0.72]	**-**
HPV 18	**HPV**	8667	8	24958.28	0.03 [0.01, 0.06]	**75.7% [44.4, 90.8%]**
	HAV	8682	33	25027.68	0.13 [0.09, 0.19]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
All subjects included, irrespective of their baseline HPV DNA status
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 192 p. 10391

Reviewer's Comment: The point estimates of efficacy in prevention of CIN2/3 associated with HPV 16/18 are lower for the Total Vaccinated Cohort as compared to the ATP cohort because the TVC includes subjects who are naïve AND non-naïve. There is evidence of positive impact, most likely due to presence of naïve subjects in this analysis.

Figure 20 presents the cumulative incidence curve for CIN2+, associated with HPV-16/18 in all subjects irrespective of their baseline HPV DNA and serostatus in the Total Vaccinated cohort.

Figure 20-Study HPV-008: Cumulative incidence curve for CIN2+ associated with HPV-16/18 irrespective of baseline HPV DNA and serostatus (Total Vaccinated cohort)



Number at risk										
HPV	8667	8634	8453	8255	7880	7414	3469	645	76	0
HAV	8682	8642	8450	8221	7869	7409	3452	727	67	0
Number of cases (cumulative)										
HPV	0	11	38	57	68	76	79	81	82	82
HAV	0	18	42	69	94	114	143	168	174	174

Source: STN 125259.0048. CSR 008, Supplement 193, p. 10392

CIN2+ associated with HPV-16/18 in subjects who were HPV DNA positive and/or seropositive at baseline: An exploratory analysis of the incidence rates and vaccine efficacy against CIN2+ associated with HPV-16/18 (by PCR) in HPV DNA positive and/or seropositive subjects at baseline in subjects with normal or low-grade cytology was performed. Cases were counted after day 1. The vaccine efficacy against HPV-16/18 in this population was 1.5% [-43.3, 32.3], p=0.9297, with 65 cases in the HPV group and 67 cases in the HAV group (Table 135).

Table 135-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in subjects who were HPV DNA positive and/or seropositive subjects at baseline with normal or low-grade cytology, using conditional exact method (Subset of TVC-1)

					Person-year rate	VE	
Event Type	**Group**	**N**	**n**	**T (yesr)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**	**p-value**
HPV 16/18	**HPV**	2189	65	6134.87	1.06 [0.81, 1.37]	**1.5% [-45.3, 32.3%]**	**0.9297**
	HAV	2211	67	6230.09	1.08 [0.82, 1.38]	**-**	**-**
HPV 16	**HPV**	1619	60	4512.35	1.33 [1.00, 1.73]	**2.6% [-43.9, 34.2%]**	**0.9265**
	HAV	1623	62	4539.72	1.37 [1.03, 1.77]	**-**	**-**
HPV 18	**HPV**	1095	6	3097.58	0.19 [0.07, 0.44]	**-0.1% [-299.8, 75.0%]**	**1.0000**
	HAV	1088	6	3099.59	0.19 [0.07, 0.44]	**-**	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA positive or seropositive for the corresponding HPV type at Month 0
For combined types: Subjects DNA positive or seropositive for either HPV-16 or HPV-18 at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 186, p. 10386

CIN2+ associated with HPV-16/18 in HPV DNA positive subjects at baseline: Analyses for this exploratory endpoint were performed in subjects with normal or low-grade cytology at baseline and HPV DNA positive for the corresponding type at baseline, and vaccine efficacy was determined using the conditional exact method. The vaccine efficacy against CIN2+ associated with HPV-16/18 was 37.8% [-20.9, 68.8], p=0.1216, with 18 cases in the HPV group versus 27 cases in the HAV group. The majority of cases in this analysis were associated with HPV-16 (41 cases). Only 5 cases were associated with HPV-18.
Reviewer's Comment: None of the point estimates of efficacy reach statistical significance.

The incidence rates and vaccine efficacy against CIN2+ associated with HPV-16/18 (by PCR) in HPV DNA positive subjects, regardless of initial serostatus, at baseline in subjects with normal or low-grade cytology at baseline was also presented. The vaccine efficacy against CIN2+ associated with HPV-16/18 was 0.5% [-47.7, 32.9], p=0.9235, with 62 cases in the HPV group versus 58 cases in the HAV group. The majority of cases in this analysis were associated with HPV-16 (57 in the HPV group and 52 in the HAV group) and only 12 cases were associated with HPV-18 (6 in each group). (Source: STN 125259.0048. CSR 008, Table 54, p. 290, not shown here)

The vaccine efficacy against CIN2+ associated with HPV-16/18 was -32.5% [-123.1, 20.4], p=0.3205, with 43 cases in 315 DNA positive subjects in the HPV group versus 31 cases in 290 DNA positive subjects in the HAV group. The majority of cases in this analysis were associated with HPV-16 (67 cases) and only 7 cases were associated with HPV-18. It should be noted that the study was not randomized to take into account subjects' baseline HPV status and hence differences are observed in the number of subjects per group for this analysis.

Table 136-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA positive and seropositive subjects at baseline with normal or low-grade cytology at baseline, using conditional exact method (Subset of TVC-1)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (yesr)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	315	43	821.95	5.23 [3.72, 7.15]	**-32.5% [-123.1, 20.4%]**
	HAV	290	31	784.99	3.95 [2.63, 5.70]	**-**
HPV 16	**HPV**	244	39	630.50	6.19 [4.32, 8.58]	**-31.2% [-127.8, 23.1%]**
	HAV	218	28	594.97	4.71 [3.06, 6.92]	**-**
HPV 18	**HPV**	82	4	222.49	1.80 [0.45, 4.77]	**-48.1 [-1019.1, 77.0%]**
	HAV	91	3	247.10	1.21 [0.23, 3.69]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA positive and seropositive for the corresponding HPV type at Month 0
For combined types: Subjects DNA positive and seropositive for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 122, p. 10334

GSK presented an overview of cases which developed in subjects non-naïve for the relevant HPV type.

The vaccine efficacy against CIN1+ and CIN2+ associated with HPV-16/18 in subjects who were HPV DNA positive at baseline in TVC-1 is presented. Even though there was an apparent imbalance in number of CIN2+ lesions associated with HPV-16/18 in subjects who were HPV DNA positive and seropositive at baseline in TVC-1 (43 cases versus 31 cases in HPV and HAV groups, respectively), it was less than observed at interim (33 cases versus 18 cases in HPV and HAV groups, respectively), which indicates greater accrual of cases in the HAV group than in the HPV group between the interim and final analyses. There was no difference observed for CIN1+ associated with HPV-16/18 in the same subset of subjects (44 cases versus 40 cases in HPV and HAV groups, respectively). The analysis of HPV DNA positive subjects was conducted in a small subset of subjects (N=1184) and none of the differences observed between groups in the above analysis were statistically significant. In subjects who were HPV DNA positive and/or seropositive at baseline the vaccine efficacy against CIN2+ with HPV-16/18 was 1.5% [-43.3, 32.3], p=0.9297, in TVC-1.

Table 137-Study HPV-008: Overview of vaccine efficacy against histological lesions associated with HPV-16/18 in HPV DNA positive subjects with normal or low-grade cytology (Subset of TVC-1)

Endpoint	HPV		HAV		Vaccine Efficacy			
	N	n	N	n	%	LL	UL	P-value
HPV DNA positive and seronegative subjects at baseline								
CIN2+	303	18	285	27	37.8	-20.9	68.8	0.1216
CIN1+	303	27	285	36	30.5	-20.9	60.5	0.1819
HPV DNA positive and seropositive subjects at baseline								
CIN2+	315	43	290	31	-32.5	-123.1	20.4	0.3205
CIN1+	315	44	290	40	-3.0	-66.0	35.9	1.0000
HPV DNA positive subjects at baseline, regardless of initial serostatus								
CIN2+	617	62	567	58	0.5	-47.7	32.9	0.9235
CIN1+	617	72	567	76	13.0	-23.8	38.9	0.3801

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN1+ = CIN1, CIN2, CIN3, AIS or invasive cervical cancer
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
n=number of subjects reporting at least one event in each group
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 100, p. 358

Reviewer's Comment: CBER reviewed the datasets and included subjects with all cytology, The number of cases in the HPV group increased to 54 from 43, and the number of cases in the HAV group increased from 31 to 44. In addition, there was a slightly higher proportion of subjects with a low-grade cytology in the HPV group as compared to the HAV group. The sponsor notes that the randomization scheme used in this study did not take into account the HPV DNA status at baseline. It was already noticed at the interim analysis that the distribution of subjects with low-grade cytology at baseline was not perfectly balanced between groups.

The sponsor also provided an exploratory analysis of the percentage of subjects with abnormal cytology ≥ASC-US HCII positive at baseline who went onto develop CIN2+ in the study in the two treatment groups. Cases of CIN2+ resulting from an abnormal cytology at baseline should have been diagnosed prior to Month 12, either as a result of immediate colposcopy after high-grade cytology at Month 0, or as a result of a colposcopy performed after low-grade cytology findings at Month 0 and Month 6 (ASC-US HCII+, LSIL). Overall 1484 subjects were eligible for inclusion in this analysis; 759 in the HPV group and 725 in the HAV group. Of these there were 103 cases (13.6%) of abnormal cytology progressing to CIN2+ in the HPV group, and 101 cases (13.9%) of abnormal cytology progressing to CIN2+ in the HAV group. Therefore, similar proportions of subjects with ASC-US+ at baseline progressed to CIN2+ in the HPV and HAV groups. Approximately the same proportion of subjects in each group went onto develop CIN2+ if they had an abnormal cytology at baseline (13.6% in the HPV group and 13.9% in the HAV group).

Table 138-Study HPV-008: Subjects with abnormal cytology at baseline that progress to cases of CIN2+

Group	N	n	%
HPV	759	103	13.6%
HAV	725	101	13.9%

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group, to whom at least one dose of study vaccine was administered and who had an abnormal cytology at baseline. For this endpoint, abnormal cytology was interpreted as excluding the following cytology results: missing; test not performed; negative; ASC-US, hybrid capture 2 negative.
n=number of subjects with a CIN2+ diagnosed (by the routine panel)
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
Source: STN 125259.0048. CSR 008, Supplement 191 p. 10391

Secondary histopathological endpoints: CIN2+ cases associated with oncogenic HPV types In subjects who were HPV DNA negative for the corresponding type at baseline, regardless of initial HPV serostatus

The incidence rates and vaccine efficacy of CIN2+ associated with oncogenic (high-risk) HPV (HR-HPV) types in HPV DNA negative subjects at baseline through Month 6 and with normal cytology, are presented in Table 139. The point estimate of vaccine efficacy against CIN2+ associated with HR-HPV was statistically significant (VE=61.9% [96.1% CI: 46.7, 73.2]) with 54 cases in the HPV group versus 142 cases in the HAV group. The vaccine efficacy against CIN2+ associated with HRW-HPV (High risk HPV types excluding HPV 16 and/or 18) was also statistically significant (VE=54.0% [96.1% CI: 34.0, 68.4]) with 50 cases in the HPV group versus 109 cases in the HAV group. It should be noted that the analyses of HRW-HPV may include lesions with multiple HPV types, which although associated with another oncogenic type besides HPV-16/18 may also contain HPV-16/18 within the lesion. Accordingly, the analysis of vaccine efficacy for histopathological endpoints with HRW-HPV may be confounded by the presence of HPV-16/18. This was a complex issue to review. The results are presented in women with normal cytology at baseline, who are DNA negative for the relevant HPV DNA through Month 6, and may have had any serostatus. GSK did not analyze serology for the non-vaccine HPV types at baseline, so the serostatus is not known.

Table 139-Study HPV-008: Incidence rates and vaccine efficacy of CIN2+ associated with oncogenic HPV types (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method (ATP cohort for efficacy)

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16	HPV	7372	4	17726.34	0.02	0.01	0.06	92.7	79.3	98.2	<0.0001
	HAV	7276	54	17520.68	0.31	0.23	0.41	-	-	-	-
HPV-18	HPV	7645	2	18388.48	0.01	0.00	0.04	87.6	44.1	98.8	0.0007
	HAV	7583	16	18312.59	0.09	0.05	0.15	-	-	-	-
HPV-31	HPV	7583	2	18220.46	0.01	0.00	0.04	92.0	66.0	99.2	<0.0001
	HAV	7599	25	18339.26	0.14	0.09	0.20	-	-	-	-
HPV-33	HPV	7720	12	18546.95	0.06	0.03	0.12	51.9	-2.9	78.9	0.0332
	HAV	7706	25	18596.46	0.13	0.08	0.20	-	-	-	-
HPV-35	HPV	7768	1	18674.74	0.01	0.00	0.03	83.3	-49.1	99.7	0.0702
	HAV	7764	6	18761.90	0.03	0.01	0.07	-	-	-	-
HPV-39	HPV	7609	3	18291.41	0.02	0.00	0.05	69.8	-24.2	95.2	0.0921
	HAV	7614	10	18414.11	0.05	0.02	0.10	-	-	-	-
HPV-45	HPV	7782	0	18715.82	0.00	0.00	0.02	100	-67.8	100	0.0619
	HAV	7745	4	18732.22	0.02	0.01	0.06	-	-	-	-
HPV-51	HPV	7363	10	17691.42	0.06	0.03	0.11	62.9	18.0	84.7	0.0050
	HAV	7352	27	17732.77	0.15	0.10	0.23	-	-	-	-
HPV-52	HPV	7461	12	17934.23	0.07	0.03	0.12	14.3	-108.1	65.4	0.7000
	HAV	7414	14	17925.16	0.08	0.04	0.13	-	-	-	-
HPV-56	HPV	7646	4	18388.52	0.02	0.01	0.06	59.9	-47.1	91.5	0.1181
	HAV	7638	10	18457.65	0.05	0.02	0.10	-	-	-	-
HPV-58	HPV	7709	6	18512.03	0.03	0.01	0.07	64.5	1.5	89.2	0.0225
	HAV	7702	17	18607.82	0.09	0.05	0.15	-	-	-	-
HPV-59	HPV	7720	1	18558.42	0.01	0.00	0.03	74.9	-178.6	99.6	0.3749
	HAV	7723	4	18663.51	0.02	0.01	0.06	-	-	-	-
HPV-66	HPV	7592	4	18249.66	0.02	0.01	0.06	60.0	-46.7	91.6	0.1176
	HAV	7564	10	18268.55	0.05	0.03	0.10	-	-	-	-
HPV-68	HPV	7633	5	18352.82	0.03	0.01	0.07	54.4	-49.8	88.4	0.1428
	HAV	7614	11	18396.00	0.06	0.03	0.11	-	-	-	-
HRW-HPV	HPV	7863	50	18848.93	0.27	0.19	0.35	54.0	34.0	68.4	<0.0001
	HAV	7853	109	18897.20	0.58	0.47	0.70	-	-	-	-
HR-HPV	HPV	7863	54	18842.44	0.29	0.21	0.38	61.9	46.7	73.2	<0.0001
	HAV	7853	142	18871.92	0.75	0.63	0.89	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
HRW-HPV = All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18
HR-HPV= High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 43, p. 270

Reviewer's Comment: Datasets were reviewed for cases associated with non-vaccine HPV types. Many of the CIN2+ cases included in the above analyses were associated with multiple HPV types. CBER requested that GSK provide a post-hoc analysis after excluding cases which also contained HPV 16 and/or 18. This is provided in Table 140. The LB of the 96.1% CI around the point estimate of efficacy is > 0% for HPV-31 alone and for the combined analysis for all oncogenic HPV types when HPV 16 and/or 18 are excluded from analysis (VE=37.4% [96.1% CI: .7.4, 58.2%]).

Table 140-Study HPV-008: Incidence Rates and Vaccine Efficacy against CIN2+ Associated with Oncogenic HPV Types Without Co-infections with HPV-16 or HPV-18 (by PCR) in subjects who are HPV DNA Negative at Baseline irrespective of serostatus, using Conditional Exact Method (Subset of ATP cohort)

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16	HPV	7372	0	17730.65	0.00	0.00	0.02	.	.	.	-
	HAV	7276	0	17558.14	0.00	0.00	0.02	-	-	-	-
HPV-18	HPV	7645	0	18390.78	0.00	0.00	0.02	.	.	.	-
	HAV	7583	0	18323.23	0.00	0.00	0.02	-	-	-	-
HPV-31	HPV	7583	2	18220.46	0.01	0.00	0.04	89.4	53.7	99.0	0.0002
	HAV	7599	19	18343.66	0.10	0.06	0.17	-	-	-	-
HPV-33	HPV	7720	12	18546.95	0.06	0.03	0.12	42.7	-26.4	75.4	0.1207
	HAV	7706	21	18598.70	0.11	0.07	0.18	-	-	-	-
HPV-35	HPV	7768	1	18674.74	0.01	0.00	0.03	74.9	-178.3	99.6	0.2186
	HAV	7764	4	18763.84	0.02	0.01	0.06	-	-	-	-
HPV-39	HPV	7609	3	18291.41	0.02	0.00	0.05	39.6	-235.1	91.5	0.7265
	HAV	7614	5	18414.20	0.03	0.01	0.07	-	-	-	-
HPV-45	HPV	7782	0	18715.82	0.00	0.00	0.02	100.0	-4933.4	100.0	0.4988
	HAV	7745	1	18735.00	0.01	0.00	0.03	-	-	-	-
HPV-51	HPV	7363	9	17691.42	0.05	0.02	0.10	35.5	-67.0	76.6	0.3067
	HAV	7352	14	17741.17	0.08	0.04	0.14	-	-	-	-
HPV-52	HPV	7461	12	17934.23	0.07	0.03	0.12	-50.0	-346.2	46.2	0.5032
	HAV	7414	8	17927.85	0.04	0.02	0.09	-	-	-	-
HPV-56	HPV	7646	4	18388.52	0.02	0.01	0.06	49.8	-98.9	89.8	0.2664
	HAV	7638	8	18459.07	0.04	0.02	0.09	-	-	-	-
HPV-58	HPV	7709	6	18512.03	0.03	0.01	0.07	39.7	-93.0	83.1	0.3318
	HAV	7702	10	18613.02	0.05	0.02	0.10	-	-	-	-
HPV-59	HPV	7720	1	18558.42	0.01	0.00	0.03	49.7	-1011.9	99.3	1.0000
	HAV	7723	2	18665.48	0.01	0.00	0.04	-	-	-	-
HPV-66	HPV	7592	4	18249.66	0.02	0.01	0.06	33.3	-201.3	87.3	0.5480
	HAV	7564	6	18272.51	0.03	0.01	0.07	-	-	-	-
HPV-68	HPV	7633	4	18353.45	0.02	0.01	0.06	49.9	-98.7	89.8	0.2661
	HAV	7614	8	18398.68	0.04	0.02	0.09	-	-	-	-
HPV-HRW	HPV	7863	48	18849.57	0.25	0.18	0.34	37.4	7.4	58.2	0.0092
	HAV	7853	77	18918.23	0.41	0.32	0.51	-	-	-	-
HPV-HR	HPV	7863	48	18849.57	0.25	0.18	0.34	37.4	7.4	58.2	0.0092
	HAV	7853	77	18918.23	0.41	0.32	0.51	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots) = Vaccine group
HAV = Hepatitis A vaccine (three lots) = Control group
N=number of subjects included in each group
Subjects not accounted as case in CIN2+ associated with HPV types 16/18
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6 (subjects are in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 and Month 6
HPV-HRW = All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18
HPV-HR = High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits; P-value=Two-sided Fisher Exact test

Similar analyses were conducted for subjects in the TVC naïve cohort. The first analysis includes cases which may also contain HPV 16 and/or 18 (Table 141).

Table 141-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with oncogenic HPV types (by PCR) in HPV naïve subjects at baseline using conditional exact method (Total cohort of HPV naïve women)

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16	HPV	5449	1	15810.77	0.01	0.00	0.04	98.2	89.1	100	<0.0001
	HAV	5436	56	15732.25	0.36	0.26	0.47	-	-	-	-
HPV-18	HPV	5449	0	15812.40	0.00	0.00	0.02	100	61.3	100	0.0002
	HAV	5436	12	15761.28	0.08	0.04	0.14	-	-	-	-
HPV-31	HPV	5449	0	15812.40	0.00	0.00	0.02	100	78.3	100	<0.0001
	HAV	5436	20	15758.82	0.13	0.08	0.20	-	-	-	-
HPV-33	HPV	5449	5	15804.70	0.03	0.01	0.08	72.3	19.1	92.5	0.0065
	HAV	5436	18	15757.89	0.11	0.07	0.18	-	-	-	-
HPV-35	HPV	5449	1	15811.06	0.01	0.00	0.04	75.1	-176.3	99.6	0.2181
	HAV	5436	4	15769.13	0.03	0.01	0.07	-	-	-	-
HPV-39	HPV	5449	3	15808.83	0.02	0.00	0.06	66.8	-41.4	94.8	0.0917
	HAV	5436	9	15767.50	0.06	0.02	0.11	-	-	-	-
HPV-45	HPV	5449	0	15812.40	0.00	0.00	0.02	100	-19.5	100	0.0310
	HAV	5436	5	15768.25	0.03	0.01	0.08	-	-	-	-
HPV-51	HPV	5449	2	15809.41	0.01	0.00	0.05	88.3	47.9	98.9	0.0004
	HAV	5436	17	15760.92	0.11	0.06	0.18	-	-	-	-
HPV-52	HPV	5449	7	15802.95	0.04	0.02	0.09	36.5	-88.4	80.3	0.3583
	HAV	5436	11	15764.34	0.07	0.03	0.13	-	-	-	-
HPV-56	HPV	5449	0	15812.40	0.00	0.00	0.02	100	-67.1	100	0.0622
	HAV	5436	4	15766.14	0.03	0.01	0.07	-	-	-	-
HPV-58	HPV	5449	3	15807.28	0.02	0.00	0.06	72.8	-8.9	95.6	0.0348
	HAV	5436	11	15766.43	0.07	0.03	0.13	-	-	-	-
HPV-59	HPV	5449	0	15812.40	0.00	0.00	0.02	100	-514.5	100	0.2494
	HAV	5436	2	15770.57	0.01	0.00	0.05	-	-	-	-
HPV-66	HPV	5449	1	15810.44	0.01	0.00	0.04	83.4	-48.0	99.7	0.0699
	HAV	5436	6	15767.25	0.04	0.01	0.09	-	-	-	-
HPV-68	HPV	5449	2	15807.74	0.01	0.00	0.05	71.5	-60.3	97.5	0.1088
	HAV	5436	7	15766.42	0.04	0.02	0.09	-	-	-	-
HRW-HPV	HPV	5449	21	15782.25	0.13	0.08	0.21	68.8	47.1	82.4	<0.0001
	HAV	5436	67	15725.85	0.43	0.33	0.55	-	-	-	-
HR-HPV	HPV	5449	22	15780.62	0.14	0.09	0.22	77.7	63.5	87.0	<0.0001
	HAV	5436	98	15698.87	0.62	0.50	0.77	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 273, p. 10469

Reviewer's Comment : In a *post-hoc* analysis, the number of cases included in Table 141 above also included HPV 16 and/or 18. If those lesions were excluded, the case splits would decrease Table 142).

Table 142-Study HPV-008: Cases of CIN2+ in Cervarix and HAV Arms, by HPV Type, Excluding cases where lesions were found to contain HPV 16 or HPV 18 DNA by PCR [CBER generated]

	Cervarix N=5449	Control (Havrix) N=5436
HPV type	Total cases	Total-# cases minus cases which also contain 16/18
31	0	20-[7]=13
33	5	18-[3]=15
35	1	4-[2]=2
39	3	9-[5]=4
45	0	5-[4]=1
51	2	17-[14]=3
52	7	11-[8*]=3
56	0	4 –[4]=0
58	3	11-[6*]=5
59	0	2-[1*]=1
66	1	6-[3]=3
68	2	7-[5]=2

* more than one CIN2+ lesion detected

Reviewer's Comment: In a further post-hoc analysis, CBER presented the number of lesions which developed in subjects who were naïve for any HR HPV type by PCR and had a negative cytology (Table 142). The number of lesions which also contained a vaccine HPV type is shown in brackets. This number was subtracted from the total number of lesions to illustrate the number of cases which occurred without apparent impact from prevention of an HPV-type included in the vaccine. For HPV-31, after excluding lesions which also include HPV-16 and/or HPV-18, there are 0 cases in the Cervarix group and 13 cases in the Havrix group related to HPV-31. For the lesions associated with HPV-45, 4 of these lesions were also associated with HPV 16, and one other was associated with HPV-58. For HPV-33, the case split decreases to 15:5 after exclusion of cases which also include HPV 16/18. For HPV-51, the majority of lesions in the Havrix group also include HPV 16 and/or 18. This observation demonstrates the difficulty of assessing the precise nature of the preventive effect of the vaccine on oncogenic HPV types not included in the vaccine (i.e., cross-protection). Additionally, it is not clear as to how different HPV types present in one lesion impact on other HPV types also present in the lesion, and if there is interaction among different HPV types as they relate to CIN2+ development. In the Cervarix group, none of the CIN2+ lesions that developed in women HPV naïve at baseline contained HPV-16 or 18 when analyzed for other HR-HPV types. CBER requested that GSK conduct a *post-hoc* analysis and provide point estimates of efficacy after excluding cases which included HPV 16 and/or 18 from the type specific analysis. These results are provided in Table 143 below. After excluding HPV 16 and/or 18 containing lesions, the point estimate of efficacy is maintained for HPV-31 alone among HR-HPV types.

Table 143-Study HPV-008: CIN2+ related to HPV Types without Co-Infections with HPV-16 or HPV-18 (by PCR) in subjects HPV DNA Negative at baseline, using conditional exact method (TVC Naïve women)

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16	HPV	5449	0	15812.40	0.00	0.00	0.02	.	.	.	-
	HAV	5436	0	15771.55	0.00	0.00	0.02	-	-	-	-
HPV-18	HPV	5449	0	15812.40	0.00	0.00	0.02	.	.	.	-
	HAV	5436	0	15771.55	0.00	0.00	0.02	-	-	-	-
HPV-31	HPV	5449	0	15812.40	0.00	0.00	0.02	100.0	64.7	100.0	0.0001
	HAV	5436	13	15762.81	0.08	0.04	0.14	-	-	-	-
HPV-33	HPV	5449	5	15804.70	0.03	0.01	0.08	66.8	-0.8	91.2	0.0263
	HAV	5436	15	15758.97	0.10	0.05	0.16	-	-	-	-
HPV-35	HPV	5449	1	15811.06	0.01	0.00	0.04	50.1	-1002.8	99.3	0.6245
	HAV	5436	2	15771.07	0.01	0.00	0.05	-	-	-	-
HPV-39	HPV	5449	3	15808.83	0.02	0.00	0.06	25.2	-381.9	90.1	0.7262
	HAV	5436	4	15767.59	0.03	0.01	0.07	-	-	-	-
HPV-45	HPV	5449	0	15812.40	0.00	0.00	0.02	100.0	-4915.1	100.0	0.4994
	HAV	5436	1	15771.09	0.01	0.00	0.04	-	-	-	-
HPV-51	HPV	5449	2	15809.41	0.01	0.00	0.05	33.5	-544.5	95.2	0.6871
	HAV	5436	3	15771.01	0.02	0.00	0.06	-	-	-	-
HPV-52	HPV	5449	7	15802.95	0.04	0.02	0.09	-132.9	-1442.1	50.2	0.3435
	HAV	5436	3	15770.44	0.02	0.00	0.06	-	-	-	-
HPV-56	HPV	5449	0	15812.40	0.00	0.00	0.02	.	.	.	-
	HAV	5436	0	15771.55	0.00	0.00	0.02	-	-	-	-
HPV-58	HPV	5449	3	15807.28	0.02	0.00	0.06	40.2	-232.0	91.6	0.5072
	HAV	5436	5	15768.49	0.03	0.01	0.08	-	-	-	-
HPV-59	HPV	5449	0	15812.40	0.00	0.00	0.02	100.0	-4915.0	100.0	0.4994
	HAV	5436	1	15770.95	0.01	0.00	0.04	-	-	-	-
HPV-66	HPV	5449	1	15810.44	0.01	0.00	0.04	66.8	-361.1	99.5	0.3743
	HAV	5436	3	15768.61	0.02	0.00	0.06	-	-	-	-
HPV-68	HPV	5449	2	15807.74	0.01	0.00	0.05	0.2	-1481.1	93.7	1.0000
	HAV	5436	2	15770.22	0.01	0.00	0.05	-	-	-	-
HPV-HRW	HPV	5449	21	15782.25	0.13	0.08	0.21	40.1	-8.7	67.9	0.0618
	HAV	5436	35	15746.77	0.22	0.15	0.31	-	-	-	-
HPV-HR	HPV	5449	21	15782.25	0.13	0.08	0.21	40.1	-8.7	67.9	0.0618
	HAV	5436	35	15746.77	0.22	0.15	0.31	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots) = Vaccine group
HAV = Hepatitis A vaccine (three lots) = Control group
N=number of subjects included in each group
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
* Subjects not accounted as case in CIN2+ associated with HPV types 16/18
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

CIN2+ in subjects PCR positive for oncogenic HPV types at baseline: The vaccine efficacy in subjects who were HPV DNA positive for the corresponding HPV type at baseline in this analysis was 4.4% (96.1% CI: -24.4, 26,5%) with 129 cases in the HPV group and 132 cases in the HAV group. (Source: STN 125259.0048. CSR 008, Supplement 200, p. 10397, not shown here).

Overall CIN2+ irrespective of HPV cervical infection and irrespective of baseline HPV DNA and serostatus: An additional analysis of the incidence rates and vaccine efficacy against all CIN2+ irrespective of HPV DNA type detected in the lesion, in all subjects, irrespective of their baseline HPV DNA and serostatus, in the Total Vaccinated cohort was presented. The vaccine efficacy in this analysis was 30.4% [16.4, 42.1], p<0. 0001, with 224 cases in the HPV group and 322 cases in the HAV group. This result is consistent with the result seen in TVC-1.

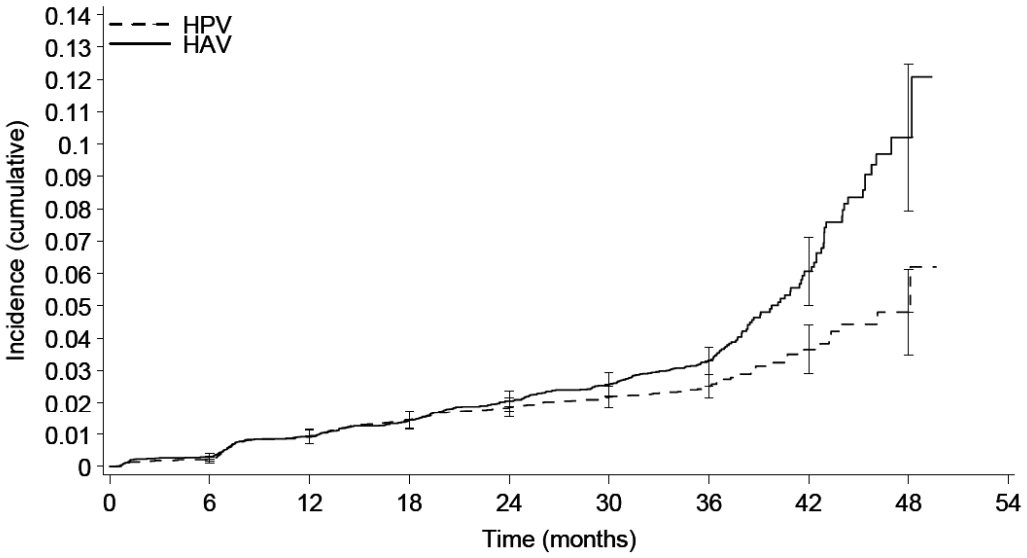
Table 144-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+, irrespective of HPV DNA results, irrespective of subjects HPV DNA and serostatus at baseline using conditional exact method (Total Vaccinated cohort)

				Person-year rate	VE
Group	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV	8667	224	24627.29	0.91 [0.79, 1.04]	**30.4% [16.4, 42.1%]**
HAV	8682	322	24658.87	1.31 [1.16, 1.46]	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
All subjects included, irrespective of their baseline HPV DNA status
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 87, p. 332

The cumulative incidence of CIN2+, irrespective of HPV DNA results in the lesion and irrespective of subject's baseline HPV DNA and serostatus in the Total Vaccinated cohort was assessed. At the time of the final event-driven analysis the majority of subjects had completed the Month 30 visit. Data was available for half of the subjects that had completed the Month 36 visit (3400 subjects in the HPV group and 3391 subjects in the HAV group) at the final analysis. At this time point it was already possible to see the overall efficacy of the vaccine as the curves diverge. Although there were few subjects who attended the Months 42 Visit or completed the study (Month 48 Visit), the CIs are large, but not overlapping at these time points (Figure 21).

Figure 21-Study HPV-008: Cumulative incidence curve for CIN2+ irrespective of HPV DNA results in all subjects, irrespective of their baseline HPV DNA and serostatus (Total Vaccinated cohort for efficacy)



Number at risk										
HPV	8667	8628	8414	8190	7796	7319	3400	622	72	0
HAV	8682	8634	8412	8170	7795	7321	3391	700	62	0
Number of cases (cumulative)										
HPV	0	19	79	124	158	181	202	218	223	224
HAV	0	26	81	122	173	212	261	301	321	322

Time in months represents the actual time from first vaccination to when the case was identified.

Source: STN 125259.0048. CSR 008, Figure 4, p. 333

In an additional analysis of the incidence rates and vaccine efficacy against CIN3+ irrespective of HPV DNA results in all subjects, irrespective of their baseline HPV DNA and serostatus, in the Total Vaccinated cohort was also presented. The vaccine efficacy against CIN3+ overall was statistically significant at 33.4% [9.1, 51.5], p=0.0058 with 77 cases in the HPV group and 116 cases in the HAV group (Table 145).

Table 145-Study HPV-008: Incidence rates and vaccine efficacy against CIN3+ irrespective of HPV DNA results in all subjects, irrespective of their baseline HPV DNA and serostatus, using conditional exact method (Total Vaccinated cohort)

				Person-year rate	VE
Group	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV	8667	77	24844.85	0.31 [0.24, 0.39]	**33.4% [9.1, 51.5%]**
HAV	8682	116	24914.35	0.47 [0.38, 0.56]	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN3+ = CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
All subjects included, irrespective of their baseline HPV DNA status
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 195, p. 10394

An analysis of the incidence rates and vaccine efficacy against CIN2+ irrespective of HPV DNA results in HPV naïve subjects, in the Total cohort revealed the vaccine efficacy against CIN2+ overall in this cohort to be statistically significant at 70.2% [54.7, 80.9], p<0.0001 with 33 cases in the HPV group and 110 cases in the HAV group (Table 146).

Table 146-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ irrespective of HPV DNA results, in HPV naïve subjects at baseline, using conditional exact method (Total cohort of HPV naïve women)

				Person-year rate	VE
Group	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV	5449	33	15771.51	0.21 [0.14, 0.303]	**70.2% [54.7, 80.9%]**
HAV	5436	110	15609.39	0.70 [0.57, 0.85]	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 290, p. 10485

An additional analysis of the incidence rates and vaccine efficacy against CIN3+ irrespective of HPV DNA results in HPV naïve subjects at baseline, in the Total cohort, revealed the vaccine efficacy against CIN3+ overall to be statistically significant at 87.0% [96.1% CI: 54.9, 97.7] with 3 cases in the HPV group and 23 cases in the HAV group (Table 147).

Table 147-Study HPV-008: Incidence rates and vaccine efficacy against CIN3+ irrespective of HPV DNA results, in HPV naïve subjects at baseline, using conditional exact method (Total cohort of HPV naïve women)

				Person-year rate	VE
Group	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV	5449	3	15809.08	0.02 [0.00, 0.06]	**87.0% [54.9, 97.7%]**
HAV	5436	23	15755.51	0.15 [0.09, 0.22]	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN3+ = CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at
Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 291, p. 10485

Analysis by region of CIN2+ cases associated with oncogenic HPV types

In HPV DNA negative subjects at baseline, regardless of initial HPV serostatus, point estimates of efficacy varied by region. In the TVC-1, the vaccine efficacy against CIN2+ associated with HR-HPV was 69.7% [34.9, 87.3], p=0.0004 in Asia Pacific, 51.1% [27.9, 67.4], p<0.0001 in Europe, 52.5% [6.5, 77], p=0.0173 in Latin America and 67.7% [34.7, 85.3], p=0.0004 in North America. The attack rate was lowest in Asia Pacific and similar in Latin America, Europe and North America for this analysis.

Reviewer's Comment: The vaccine efficacy against non-vaccine HPV types collectively in each region in the TVC-1(HRW-HPV) is as follows: Asia-Pacific: VE=69.2% [27.3, 88.6%]; Europe: VE=38.4% [6.5, 59.9%]; Latin America: 43.3% [-14.8, 73.1%]; North America: 45.0% [-25.1, 77.2%]. Although the number of subjects in Asia-Pacific and Europe regions is higher than in Latin America or North America, vaccine efficacy for individual non-vaccine HPV types did not reach statistical significance given the small number of individual cases. (Source: STN 125259.0048, CSR 008, Supplement 85, p. 10283, not shown here).

Secondary virological endpoints

Persistent infection (12-month definition) with HPV-16/18: The principal analyses were performed on subjects who were HPV DNA negative and seronegative for the corresponding type at baseline, and vaccine efficacy was determined using the conditional exact method. Analyses were also performed overall, regardless of initial serostatus, and in subjects who were seropositive for the corresponding type at baseline. Results were considered statistically significant if the lower limits of the 96.1% CI were above zero.

Results in subjects who were HPV DNA negative and seronegative for the corresponding type at baseline: The incidence rates and vaccine efficacy against 12-month persistent infection with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy are shown in Table 148.

Table 148-HPV-008: Incidence rates and vaccine efficacy against persistent infection (12-month definition) with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7035	21	17534.22	0.12 [0.07, 0.19]	**91.2% [85.9, 94.8%]**
	HAV	6984	233	17176.79	1.36 [1.18, 1.55]	-
HPV 16	**HPV**	6052	18	15087.19	0.12 [0.07, 0.19]	**90.1% [83.5, 94.4%]**
	HAV	5903	175	14552.68	1.20 [1.02, 1.40]	-
HPV 18	**HPV**	6508	3	16260.51	0.02 [0.00, 0.06]	**95.8% [86.6, 99.2%]**
	HAV	6440	70	16068.02	0.44 [0.34, 0.56]	-

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
Subjects have at least 10 months of follow-up after Month 12
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 38, p. 268

When this endpoint is analyzed in the TVC-1, and when cases are counted after dose 1, additional cases are accrued in each treatment group as compared to ATP cohort, although a higher number accrues in the HAV group (114) vs. 32 in the HPV group. Point estimates are somewhat lower because subjects did not receive all 3 doses of vaccine in this analysis. However, all point estimates of efficacy are $\geq$ 83.7% and LBs of the 96.1% are >72.0%.

GSK also provided an analysis regardless of serostatus and point estimates were similar to those seen in the ATP cohort. This last analysis includes subjects who were seronegative as well as seropositive (or unknown). GSK has also presented the analyses in subjects seropositive and PCR negative for the relevant HPV type. There were 2 cases in the HPV group and approximately 24 in the HAV group. The combined analysis for HPV 16/18 reached statistical significance and individually for HPV 16, but not for HPV-18. (Source: STN 125259.0048. CSR 008, Supplement 57, p. 10249, not shown here). There are fewer cases of CIN2+ detected in this specific cohort in either group. In comparing the result of prevention of CIN 2+ in subjects seropositive and PCR negative, as compared to prevention of persistent infection 12 month duration in the ATP cohort of efficacy, the point estimates of efficacy for prevention of CIN 2+ were lower and did not reach statistical significance. In addition, there were no cases of CIN 2+ related to HPV 18. (See Table 149 below)

Table 149-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seropositive subjects at baseline using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	1510	2	3588.35	0.06 [0.01, 0.21]	**65.8% [-105.7%]**
	HAV	1547	6	3681.95	0.16 [0.06, 0.37]	**-**
HPV 16	**HPV**	1018	2	2416.02	0.08 [0.01, 0.31]	**66.0% [-104.3, 97.1%]**
	HAV	1047	6	2461.75	0.24 [0.08, 0.55]	**-**
HPV 18	**HPV**	803	0	1898.82	0.00 [0.00, 0.21]	**-**
	HAV	790	0	1896.34	0.00 [0.00, 0.21]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seropositive at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seropositive at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 39, p. 10231

Analysis by region of cases of 12-month persistent infection with HPV-16/18: In the TVC-1, point estimates of vaccine efficacy were similar among the four geographical regions in which the study was conducted. (Source: STN 12529.0048, CSR 008, Supplement 60, p. 10252, not shown here).

Reviewer's Comment: Not every case of persistent infection becomes a case of CIN 2+ related to the relevant HPV type, but the results do parallel each other. In subjects who are seronegative and PCR negative for the relevant HPV type in the ATP cohort for efficacy, all point estimates of efficacy reach statistical significance for endpoints related to HPV 16/18, HPV 16, and HPV 18.

Persistent infection (6-month definition) with HPV-16/18
Results in subjects who were HPV DNA negative and seronegative for the corresponding type at baseline: The incidence rates and vaccine efficacy against 6-month persistent infection with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy are presented in Table 150. Similar results are noted in the TVC-1 cohort as well. (Source: STN 125259.0048. CSR 008, Supplement 65, p. 10257, not shown here)

Table 150-Study HPV-008: Incidence rates and vaccine efficacy against persistent infection (6-month definition) with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7177	32	17710.83	0.18 [0.12, 0.26]	**93.8% [91.0, 95.9%]**
	HAV	7122	497	17046.33	2.92 [2.65, 3.20]	-
HPV 16	**HPV**	6163	23	15227.55	0.15 [0.09, 0.23]	**93.7% [90.1, 96.1%]**
	HAV	6018	345	14509.05	2.38 [2.12, 2.66]	-
HPV 18	**HPV**	6642	9	16431.15	0.05 [0.02, 0.11]	**95.3% [90.7, 98.0%]**
	HAV	6567	188	16079.85	1.17 [1.00, 1.36]	-

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
Subjects have at least 5 months of follow-up after Month 12
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 40, p. 263

Results in subjects who were HPV DNA negative for the corresponding type at baseline, regardless of their initial HPV serostatus: The incidence rates and vaccine efficacy against 6-month persistent infection with HPV-16/18 in HPV DNA negative subjects at baseline, regardless of initial serostatus, in the ATP cohort for efficacy, are very similar to those point estimates in seronegative and PCR negative subjects in the ATP cohort

Results in subjects who were HPV DNA negative and seropositive for the corresponding type at baseline: These results are presented in the ATP cohort for efficacy. As noted for 12-month persistent infection in this specific population, point estimates of efficacy are approximately 80% (and reach statistical significance for HPV 16/18, HPV 16, and HPV 18 (although the LB of the 96.1% CI is 0.7%). (Source: STN 125259.0048. CSR 008, Supplement 67, p. 10258, not shown here)

Analysis by region of cases of 6-month persistent infection with HPV-16/18: The regional distribution and incidence rates of cases of 6-month persistent infection with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline in the TVC-1 are similar for the 4 geographical regions. (Source: STN 125259.0048. CSR 008, Supplement 70, p. 10262, not shown here).

Reviewer's Comment: GSK also presented analyses of prevention of 6-month and 12-month persistent infection with non-vaccine HPV types. The CIN2+ endpoint was considered clinically relevant for assessing possible impact on the vaccine for these other HPV types.

CIN1+ cases associated with HPV-16/18
Results in subjects who were HPV DNA negative and seronegative for the corresponding type at baseline: CIN1+ cases associated with HPV-16/18 detected in the cervical lesion
There were a total of 104 cases of CIN1+ associated with HPV-16/18 in subjects who were seronegative and HPV DNA negative at baseline in the ATP cohort for efficacy. In addition to the 60 cases of CIN2+ associated with HPV-16/18, there were 44 cases of CIN1 associated with HPV-16/18 in this cohort.. For this analysis, the association with HPV-16 and/or HPV-18 was

based on the detection of viral DNA by PCR in the biopsy sample and did not consider the presence of other oncogenic type(s) in the biopsy sample or the detection of HPV type(s) in the cervical samples prior to collection of the biopsy. These results are shown in Table 151.

Table 151-Study HPV-008: Incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7344	8	17688.32	0.05 [0.02, 0.09]	**91.7% [82.4, 96.7%]**
	HAV	7312	96	17630.23	0.54 [0.44, 0.67]	**-**
HPV 16	**HPV**	6303	5	15193.07	0.03 [0.01, 0.08]	**93.0% [82.2, 97.9%]**
	HAV	6165	70	14894.55	0.47 [0.36, 0.60]	**-**
HPV 18	**HPV**	6794	3	16377.24	0.02 [0.00, 0.06]	**90.4% [67.7, 98.3%**
	HAV	6746	31	16294.66	0.19 [0.13, 0.27]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN1+ = CIN1, CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 45, p. 275

Similar results were seen in the analysis in TVC-1. (Source: STN 125259.0048. CSR 008, Supplement 92, p. 10296, not shown here)

Results in subjects who were HPV DNA negative for the corresponding type at baseline, regardless of their initial HPV serostatus:
CIN1+ cases associated with HPV-16/18 detected in the cervical lesion in subjects seropositive and PCR negative for the relevant HPV type: Point estimates of efficacy are similar to those in the ATP cohort. (Source: STN 125259.0048. CSR 008, Table 47, p. 277, not shown here)

Results in subjects who were HPV DNA negative and seropositive for the corresponding type at baseline
CIN1+ cases associated with HPV-16/18 detected in the cervical lesion: There were a total of 16 cases of CIN1+ associated with HPV-16/18 in subjects who were HPV DNA negative and seropositive for the corresponding type at baseline, in the ATP cohort for efficacy. In addition to the 8 cases of CIN2+ associated with HPV-16/18 there were 8 cases of CIN1 in this cohort. Only CIN1+ lesions associated with HPV-16 were detected. The vaccine efficacy against CIN1+ associated with HPV-16 was 66.1% [96.1% CI: -17.9, 92.6], with 4 cases in the HPV group versus 12 cases in the HAV group. As there were no cases of CIN1+ associated with HPV-18 and, vaccine efficacy for CIN1+ was not determined in this cohort. (Source: STN 125259.0048, CSR 008, Supplement 96, 10300, not shown here)
Reviewer's Comment: CIN1+ does not have the same rate of progression to more advanced lesions or invasive cancer as CIN2 or CIN3. As noted for CIN 2+, there were higher point estimates of efficacy for prevention of persistent infection in the subgroup who are seropositive and DNA negative for the relevant HPV type. This subgroup has already cleared their infection, and may not have the same rate of progression to CIN 1+ or CIN 2+ as subjects who have not yet been exposed.

Similar results are observed for CIN1+ associated with HPV 16 and/or 18. None of the point estimates of efficacy reach statistical significance in subjects who are PCR positive (with or without seropositivity) for the relevant HPV type. The point estimates of efficacy for CIN1+ are presented in Table 152 below.

Table 152-Study HPV-008: Incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA positive and seropositive subjects at baseline using conditional exact method (TVC-1)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	315	44	819.06	5.37 [3.84, 7.31]	**-3.0% [-66.0, 35.9%]**
	HAV	290	40	766.88	5.22 [3.66, 7.21]	-
HPV 16	**HPV**	244	39	629.45	6.20 [4.32, 8.60]	**-6.4% [-78.1, 36.2%]**
	HAV	218	34	583.79	5.82 [3.95, 8.27]	-
HPV 18	**HPV**	82	5	220.65	2.27 [0.69, 5.47]	**9.3% [-281.4, 79.6%]**
	HAV	91	6	240.18	2.50 [0.86, 5.61]	-

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN1+ = CIN1, CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA positive for the corresponding HPV type at Month 0
For combined types: Subjects DNA positive for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 123, p. 10335

Efficacy by geographical region CIN1+: Point estimates of efficacy were lower in Asia Pacific as compared to the other 3 regions, although there were fewer cases identified in Asia Pacific and Latin America.

CIN1+ cases associated with oncogenic HPV types in subjects who were HPV DNA negative for the corresponding type at baseline, regardless of initial HPV serostatus: The vaccine efficacy against CIN1+ associated with HR-HPV was statistically significant (VE=45.9% [33.1, 56.4]) with 151 cases in the HPV group versus 279 cases in the HAV group. The vaccine efficacy against CIN1+ associated with HRW-HPV (oncogenic HPV types excluding HPV-16/18) was also statistically significant (VE=37.3% [21.7, 49.9]) with 146 cases in the HPV group versus 233 cases in the HAV group. However, CIN1+ has a much lower rate of progression to cervical cancer, and the analyses related to prevention of CIN2+ with other oncogenic HPV types has most clinical relevance.

CIN1+ irrespective of baseline status and HPV DNA type in the lesion: To be complete, the point estimates of efficacy are presented for this cohort.

Table 153-Study HPV-008: Incidence rates and vaccine efficacy against CIN1+ irrespective of HPV DNA results in all subjects, irrespective of their baseline HPV DNA and serostatus, using conditional exact method (Total Vaccinated cohort)

				Person-year rate	VE
Group	**N**	**n**	**T (yesr)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV	8667	451	24314.25	1.85 [1.68, 2.04]	**21.7% [10.7, 31.4%]**
HAV	8682	577	24350.77	2.37 [2.17, 2.58]	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
All subjects included, irrespective of their baseline HPV DNA status
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 196, p. 10394

In subjects seropositive and PCR positive for the relevant HPV type, the point estimates of efficacy are near 0 or just below, and none reach statistical significance in subjects who are PCR positive (with or without seropositivity) for the relevant HPV type. (Source: STN 125259.0048. CSR 008, Supplement 123, p. 10335, not shown here).

In females in the TVC naïve population, the point estimate of efficacy for prevention of CIN1+ irrespective of HPV DNA results is lower than that for CIN2+ (Table 154).

Table 154-Study HPV-008: Incidence rates and vaccine efficacy against CIN1+ irrespective of HPV DNA results, in HPV naïve subjects at baseline, using conditional exact method (Total cohort of HPV naïve women)

				Person-year rate	VE
Group	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV	5449	106	15718.63	0.67 [0.55, 0.82]	**50.1% [35.9, 61.4%]**
HAV	5436	211	15611.66	1.35 [1.17, 1.56]	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
Subjects DNA negative for all high-risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 292, p. 10486

Analysis of CIN1+ cases associated with oncogenic HPV types by region
In DNA negative subjects at baseline, regardless of initial HPV serostatus: In the TVC-1, the vaccine efficacy against CIN1+ associated with HR-HPV was 41.0% [7.6, 62.9], p=0.0105 in Asia Pacific, 38.1% [19.4, 52.7], p<0.0001 in Europe, 37.3% [2.8, 60.1], p=0.0247 in Latin America and 54.6% [29.5, 71.3], p=0.0001 in North America. The attack rate was lowest in Asia Pacific and similar in Latin America, Europe and North America for this analysis. When HPV 16 and 18 were excluded, the point estimates of efficacy did not reach statistical significance in Asia Pacific areas (VE=35.4%; 96.1% CI: -4.6, 60.5%); or Latin America (VE=28.3%; 96.1% CI: -13.6, 55.1%); but did reach statistical significance for Europe (VE=29.5%; 96.1% CI: 7.0,

46.8%); and North America (VE=43.5%; 96.1% CI: 9.9, 65.1%). (Source: STN 125259.0048. CSR 008, Supplement 111, p. 10317-319, not shown here).

Any cytological abnormality (ASC-US+) associated with HPV-16/18: The incidence rates and vaccine efficacy against any cytological abnormality (ASC-US+) associated with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy was also presented. The vaccine efficacy against ASC-US+ associated with HPV-16/18 was statistically significant (VE=88.5% [96.1% CI: 84.4, 91.7]), with 51 cases in the HPV group versus 434 cases in the HAV group. Statistically significant vaccine efficacy was also observed for ASC-US+ associated with HPV-16 and HPV-18 with point estimates above 88% for each type.

Table 155-Study HPV-008: Incidence rates and vaccine efficacy against any cytological abnormality (ASC-US+) associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7340	51	17626.05	0.29 [0.21, 0.39]	**88.5% [84.4, 91.7%]**
	HAV	7312	434	17266.01	2.51 [2.27, 2.77]	**-**
HPV 16	**HPV**	6299	33	15146.28	0.22 [0.15, 0.31]	**88.6% [83.3, 92.4%]**
	HAV	6165	279	14664.92	1.90 [1.67, 2.15]	**-**
HPV 18	**HPV**	6790	20	16344.72	0.12 [0.07, 0.19]	**90.3% [84.4, 94.4%]**
	HAV	6746	204	16104.12	1.27 [1.09, 1.46]	**-**

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 59, p. 295

Reviewer's Comment: Pap testing is a screening test and does not directly result in definitive treatment. Furthermore, the sensitivity and specificity are < 100% and normal cytology does not automatically indicate lack of pathology. These results are of interest, but are not appropriate surrogate endpoints for cervical cancer.

Vulvar or vaginal intraepithelial neoplasia (VIN or VaIN) 1+ associated with HPV-16/18: The incidence rates and vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 (by PCR) in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy are presented. There were 12 cases of VIN1+/VaIN1+ associated with HPV-16/18 included in this analysis. The vaccine efficacy against VIN1+/VaIN1+ associated with HPV-16/18 was statistically significant (VE=80.0% [0.3, 98.1], p=0.0221), with 2 cases in the HPV group versus 10 cases in the HAV group. There were 2 cases of VIN1+/VaIN1+associated with HPV-16 in the HPV group and 6 in the HAV group. There were only 4 cases of VIN1+/VaIN1+ associated with HPV-18, which were all in the HAV group. (Source: STN 125259.0048. CSR 008, Table 63, p. 302, not shown here)

Reviewer's Comment: The clinical significance of VIN1 and VaIN 1 in of themselves is not clear, and it is unclear as to their acceptance as valid histopathological entities. In this

exploratory analysis, there were too few cases of VIN2/3 or VaIN 2/3 to assess efficacy in prevention of these more clinically relevant lesions.

Reduction of local cervical therapy: This exploratory endpoint is of interest. The incidence rates and vaccine efficacy in reduction of local cervical therapy (LEEP, Cone, Knife or Laser) in all subjects, irrespective of their baseline HPV DNA status are also presented Table 156).

Table 156-Study HPV-008: Incidence rates and vaccine efficacy in reduction of local cervical therapy in all subjects, irrespective of their baseline HPV DNA and serostatus, using conditional exact method (Total Vaccinated cohort)

				Person-year rate	VE
Group	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV	8667	180	24697.19	0.73 [0.62, 0.85]	**24.7% [7.4, 38.9%]**
HAV	8682	240	24789.24	0.97 [0.84, 1.11]	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
All subjects included, irrespective of their baseline HPV DNA status
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 198, p. 10395

An analysis of the incidence rates and vaccine efficacy in reduction of local cervical therapy in HPV naïve subjects at baseline, in the Total cohort is presented in Table 157.

Table 157-Study HPV-008: Incidence rates and vaccine efficacy in reduction of local cervical therapy, in HPV naïve subjects at baseline, using conditional exact method (Total cohort of HPV naïve women)

				Person-year rate	VE	
Group	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**	**p-value**
HPV	5449	26	15781.26	0.16 [0.11, 0.25]	**68.8% [50.0, 81.2%]**	**<0.0001**
HAV	5436	83	15717.20	0.53 [0.42, 0.66]	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
Subjects DNA negative for all high-risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 294, p. 10487

Incident infection with HPV-16/18: The incidence rates and vaccine efficacy against incident infection with HPV-16/18 (by PCR) in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy are shown in Table 158.

Table 158-Study HPV-008: Incidence rates and vaccine efficacy against incident infection with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7346	263	17543.39	1.49 [1.31, 1.69]	**76.7% [73.2, 79.9%]**
	HAV	7320	1074	16758.81	6.41 [6.01, 6.82]	-
HPV 16	**HPV**	6304	139	15238.99	0.91 [0.76, 1.09]	**80.9% [76.8, 84.4%]**
	HAV	6172	687	14389.05	4.77 [4.41, 5.17]	-
HPV 18	**HPV**	6796	134	16440.91	0.82 [0.68, 0.97]	**74.4% [68.7, 79.3%]**
	HAV	6751	509	15960.45	3.19 [2.90, 3.49]	-

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 69, p. 309

Similar results were seen for the analysis in TVC-1.

Clearance of HPV-16/18 infection in subjects who were HPV DNA positive at baseline: Clearance was defined as the first negative sample for HPV DNA (by PCR) for the corresponding HPV type after Month 0, after which no positive samples occur, i.e., subjects should be negative at the last visit for which a DNA result is available. For the calculation of vaccine efficacy for clearance endpoints, the ratio of event rates is based on the rate of subjects not cleared i.e., obtained by subtracting the number of cleared subjects from the number of subjects HPV DNA positive for that type at baseline (N-n). Subjects who were HPV-16 and HPV-18 DNA positive were considered to have cleared their infections if they had cleared the infection for either HPV-16 or HPV-18. The incidence rates and vaccine efficacy for clearance of HPV-16/18 infection (by PCR) in HPV DNA positive and seronegative subjects at baseline are presented. No significant differences were observed between the HPV and HAV group. The vaccine efficacy for clearance of HPV-16/18 was -3.0% [-58.4, 32.9], p=1.0000. (Source: STN 125259.0048. CSR 008, Table 72, p. 314, not shown here). A similar result was found in the TVC-1 cohort, where no significant differences were observed between the HPV and HAV group. The vaccine efficacy for clearance of HPV-16/18 was 5.9% [96.1% CI: -39.3, 36.4].

Persistent infection (6-month definition) with HPV-16/18 after two doses of vaccine: Of the 977 subjects who received two doses of vaccine or control, only 382 subjects could be evaluated for vaccine efficacy against 6-month persistent infection with HPV-16/18 regardless of initial serostatus due to either lack of follow-up information or unsuitability for inclusion in the efficacy analysis. The vaccine efficacy against 6-month persistent infection with HPV-16 or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects who received only two doses of the study vaccine are presented. The vaccine efficacy was statistically significant at 100% [37.5, 100], with 0 cases in the HPV group and 8 cases in the HAV group in TVC-1. However, the number of subjects included in this analysis was limited, as few subjects received only two doses and were eligible for the analysis. (Source: STN 125259.0048. CSR 008, Table 85, p. 328, not shown here).

Additional exploratory endpoints: The following exploratory endpoints were not described in the protocol or RAP, but were performed to complement existing analyses or at the request of regulatory authorities.

CIN2+ associated with HPV-16/18 in women previously infected with the other vaccine type: This *post-hoc* analysis was performed to complement the equivalent analysis for 6-month persistent infection. Analyses were performed in TVC-1. The analyses were performed on subjects who were HPV DNA negative at baseline for the corresponding type assessed in the analysis and with a history of infection with the other vaccine type, and vaccine efficacy was determined using the conditional exact method.

The vaccine efficacy against CIN2+ associated with HPV-16/18 in subjects who were infected with the other vaccine type at baseline was statistically significant at 81.3% [96.1% CI: 8.9%, 98.2%] (with 2 cases in the HPV group and 11 cases in the HAV group). The vaccine efficacy against CIN2+ associated with HPV-16 in subjects with a history of HPV-18 infection and with HPV-18 in subjects with a history of HPV-16 infection was not statistically significant with few cases of each (Table 159).

Table 159-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in subjects with a history of infection with the other vaccine type (HPV DNA positive and/or seropositive) and HPV DNA negative and seronegative for the corresponding vaccine type at baseline using conditional exact method (TVC-1)

					Person-year rate	VE	
Event Type	**Group**	**N**	**n**	**T (years)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**	**p-value**
HPV 16/18	**HPV**	1643	2	4705.92	0.04 [0.00, 0.16]	**81.3% [8.9, 98.2%]**	**0.0224**
	HAV	1690	11	4852.29	0.23 [0.11, 0.42]	**-**	**-**
HPV 16	**HPV**	560	1	1602.03	0.06 [0.00, 0.37]	**79.2% [-102.2, 99.7%]**	**0.2179**
	HAV	578	5	1667.88	0.30 [0.09, 0.72]	**-**	**-**
HPV 18	**HPV**	1083	1	3103.89	0.03 [0.00, 0.19]	**82.9% [-52.3, 99.7%]**	**0.1246**
	HAV	1112	6	3184.41	0.19 [0.07, 0.42]	**-**	**-**

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots), HAV = Hepatitis A vaccine (three lots)
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
HPV-16: Subjects DNA positive or seropositive for HPV-18 at Month 0 and DNA negative and seronegative for HPV-16 at Month 0
HPV-18: Subjects DNA positive or seropositive for HPV-16 at Month 0 and DNA negative and seronegative for HPV-18 at Month 0
HPV-16/18: Subjects DNA positive or seropositive for either HPV-16 or HPV-18 at Month 0 and DNA negative and seronegative for the other vaccine type at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method), LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 88, p. 334

Reviewer's Comment: This is presented to demonstrate that a woman may derive benefit from prevention of one of the vaccine HPV types even if she is infected with or has been infected with the other vaccine HPV type.

The sponsor notes that many primary endpoint cases in the ATP cohort for efficacy contained multiple HPV types (36 of the 60 cases, 60%) and the majority had another oncogenic HPV type present, besides HPV-16/18 (33 of the 60 cases, 55%). Because multiple HPV types were detected in many lesions, the specific cause of the lesion cannot be definitively determined. The sponsor indicates that further exploratory testing (e.g., laser capture microdissection or type

specific detection of expression of the HPV E4 gene by immunohistochemistry) might be helpful in further evaluating the causative role of a detected HPV type in a lesion, although the results of such testing are not currently available. In other analyses presented by the sponsor, high efficacy is demonstrated for lesions in which only HPV 16 or HPV 18 is detected.

Sub-analyses by region / age and confirmatory analyses: Additional sub-analyses by region or age in HPV DNA negative subjects were not powered to assess vaccine efficacy, but provide an overview of the number of cases in different populations. Analyses of CIN2+ associated with HPV-16/18 by region are consistent with the results overall and showed that there were generally more cases in Europe and North America than in Asia Pacific and Latin America. Analyses by age showed that there were more CIN2+ cases associated with HPV-16/18 in the younger age group (15 to 20 years) than in the older age group (21 to 25 years). Analyses of secondary endpoints associated with HPV-16/18 and oncogenic HPV types by region (North America, Latin America, Europe and Asia Pacific) are consistent with the results overall.

SAFETY RESULTS

Total Vaccinated cohort analysis: The Interim Total Vaccinated cohort for solicited safety included the subset of subjects from selected study sites who completed and returned a safety diary card (safety diary card subset, N=6371). Compliance with the returning of safety diary cards was at least 95.4% after each dose in the HPV and HAV groups, and ≥96.6% of subjects in each group had data available for assessment of solicited and unsolicited adverse events.

The Total Vaccinated cohort for unsolicited safety included the safety diary card subset (Interim cohort) for solicited (days 0-6) and unsolicited (days 0-29) symptoms after vaccination, and all subjects (Final cohort) for SAEs, pregnancy outcomes, NOCDs and medically significant conditions during the entire study period.

Overall incidence of adverse events: These are presented per subject in Table 160 below. There was no apparent increase in symptoms as one progresses from dose 1 to dose 2 to dose 3 (entire table not reproduced here).

Table 160-Study HPV-008: Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day follow-up period after each dose and overall in subjects included in the safety diary card subset (Interim Total Vaccinated cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Overall/subject	HPV	3077	2913	*94.7% (93.8, 95.4%)*	3076	2614	*85.0% (83.7, 86.2%)*	3077	2807	*91.2% (90.2, 92.2%)*
	HAV	3080	2773	*90.0% (88.9, 91.1%)*	3080	2614	*81.6% (80.2, 83.0%)*	3080	2460	*79.9% (78.4, 81.3%)*

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
For overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Source: STN 125259.0048. CSR 008, Table 102, p. 363
The Percentages in italics have 95% CIs which are not overlapping.

Reviewer's Comment: There are higher proportions of subjects in the Cervarix group with any solicited adverse event in the 30 days after any dose per subject. There are more pronounced differences in the proportions of subjects with a solicited local adverse event as compared to the differences in systemic adverse events. No statistical comparisons were pre-specified, but the 95% CIs do not overlap.

Table 161-Study HPV-008: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 30-day follow-up period after each dose and overall in subjects included in the safety diary card subset (Interim Total Vaccinated cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Overall/subject	HPV	3077	867	*28.2% (26,6, 29.8%)*	3076	526	*17.1% (15.8, 18.5%)*	3077	560	*18.2% (16.9, 19.6%)*
	HAV	3080	515	*16.7% (15.4, 18.1%)*	3080	418	*13.6% (12.4, 14.8%)*	3080	151	*4.9% (4.2, 5.7%)*

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
The Percentages in italics have 95% CIs which are not overlapping.
Source: STN 125259.0048. CSR 008, Supplement 295, p. 10498

Reviewer's Comment : Cervarix recipients experienced a higher proportion of Grade 3 symptoms (solicited and unsolicited) per subject, and although 95% CIs did not overlap. The differences were most pronounced for local symptoms.

The incidence of solicited symptoms reported within 7 days after each dose is also presented as well as proportion of grade 3 symptoms.

Table 162-Study HPV-008: Incidence and nature of solicited symptoms reported during the 7-day follow-up period after each dose and overall per subject included in the safety diary card subset (Interim Total Vaccinated cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Dose 1	HPV	3068	2772	*90.4% (89.3, 91.4%)*	3067	2137	*69.7% (68.0, 71.3%)*	3068	2690	*87.7% (86.5, 88.8%)*
	HAV	3072	2465	*80.2% (78.8, 81.6%)*	3072	2014	*65.6% (63.8, 67.2%)*	3071	2086	*67.9% (66.2, 69.6%)*
Dose 2	HPV	2900	2275	*78.4% (76.9, 79.9%)*	2896	1583	*54.7% (52.8, 56.5%)*	2898	2181	*75.3% (73.6, 76.8%)*
	HAV	2920	1950	*66.8% (65.0, 68.5%)*	2920	1390	*47.6% (45.8, 49.4%)*	2920	1657	*56.7% (54.9, 58.6%)*
Dose 3	HPV	2726	2264	*83.1% (81.6, 84.4%)*	2724	1544	*56.7% (54.8, 58.6%)*	2726	2193	*80.4% (78.9, 81.9%)*
	HAV	2759	1858	*67.3% (65.6, 69.1%)*	2759	1311	*47.5% (45.6, 49.4%)*	2759	1608	*58.3% (56.4, 60.1%)*
Overall/subject	HPV	3077	2862	*93.0% (92.1, 93.9%)*	3076	2426	*78.9% (77.4, 80.3%)*	3077	2805	*91.2% (90.1, 92.1%)*
	HAV	3080	2688	*87.3% (86.0, 88.4%)*	3080	2304	*74.8% (73.2, 76.3%)*	3080	2458	*79.8% (78.3, 81.2%)*

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
The Percentages in italics have 95% CIs which are not overlapping.
Source: STN 125259.0048. CSR 008, Supplement 298, p. 10501

Reviewer's Comment: In the 7-day period after each dose and overall per subject, the proportion of subjects with a solicited any, systemic or local symptom was higher in the Cervarix subjects as compared to the Havrix group, and none of the 95% CIs around the proportions overlapped. Grade 3 symptoms are also presented in the 7 days after vaccination.

Table 163-Study HPV-008: Incidence and nature of grade 3 solicited symptoms reported during the 7-day follow-up period after each dose and overall in subjects included in the safety diary card subset (Interim Total Vaccinated cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Dose 1	HPV	3068	379	*12.4% (11.2, 13.6%)*	3067	172	5.6% (4.8, 6.5%)	3068	279	*9.1% (8.1, 10.2%)*
	HAV	3072	185	*6.0% (5.2, 6.9%)*	3072	138	4.5% (3.8, 5.3%)	3071	67	*2.2% (1.7, 2.8%)*
Dose 2	HPV	2900	241	*8.3% (7.3, 9.4%)*	2896	102	3.5% (2.9, 4.3%)	2898	181	*6.2% (5.4, 7.2%)*
	HAV	2920	126	*4.3% (3.6, 5.1%)*	2920	89	3.0% (2.5, 3.7%)	2920	48	*1.6% (1.2, 2.2%)*
Dose 3	HPV	2726	338	*12.4% (11.2, 13.7%)*	2724	150	*5.5% (4.7, 6.4%)*	2726	259	*9.5% (8.4, 10.7%)*
	HAV	2759	115	*4.2% (3.5, 5.0%)*	2759	68	*2.5% (1.9, 3.1%)*	2759	59	*2.1% (1.6, 2.7%)*
Overall/subject	HPV	3077	731	*23.8% (22.3, 25.3%)*	3076	355	*11.5% (10.4, 12.7%)*	3077	560	*18.2% (16.9, 19.6%)*
	HAV	3080	362	*11.8% (10.6, 12.9%)*	3080	257	*8.3% (7.4, 9.4%)*	3080	150	*4.9% (4.2, 5.7%)*

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
The Percentages in italics have 95% CIs which are not overlapping.
Source: STN 125259.0048. CSR 008, Supplement 299, p. 10502

Reviewer's Comment: The proportion of subjects with a Grade 3 solicited symptom in the 7 days after vaccination is almost identical to the proportions reported in the 30 day period after vaccination, indicating that the majority of Grade 3 local symptoms occurred in the 7 days after vaccination. Most of the 95% CIs do not overlap or the Grade 3 solicited symptoms.

Subjects with a previous exposure to HPV (seropositive and/or PCR positive) did not have higher incidence rates of solicited adverse events as compared to subjects previously unexposed. (Source: STN 125259.0048. CSR 008, Table 103, p. 364, not shown here).

The sponsor also presented these adverse events by ethnicity. It is noted that a somewhat higher proportion of subjects who were white had any symptom, general symptom, or local symptom, in the 7 days after any vaccination. The results are presented per subject (Table 164).

Table 164-Study HPV-008: Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day follow-up period overall/subject by ethnicity (Interim Total Vaccinated cohort)

			Any symptom			General symptoms			Local symptoms		
	Group	Ethnicity	N	n	%	N	n	%	N	n	%
Overall/subject	HPV	Black	134	129	96.3%	134	110	82.1%	134	117	87.3%
		White	1303	1286	98.7%	1303	1201	92.2%	1303	1303	97.9%
		Asian	936	856	91.5%	936	753	80.4%	936	936	85.6%
		Hispanic	615	562	91.4%	615	481	78.2%	615	615	87.5%
		Other*	89	80	89.9%	88	69	78.4%	88	89	85.4%
	HAV	Black	144	127	88.2%	144	111	77.1%	144	103	71.5%
		White	1310	1263	96.4%	1310	1205	92.0%	1310	1163	88.8%
		Asian	945	795	84.1%	945	682	72.2%	945	682	72.2%
		Hispanic	593	507	85.5%	593	446	75.2%	593	438	73.9%
		Other*	88	81	92.0%	88	70	79.5%	88	74	84.1%

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
White = White/Caucasian
* Other includes mainly mixed ethnicity, native American and native Canadian.
For overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: STN 125259.0048. CSR 008, Supplement 305, p. 10508-509

Solicited local adverse events: The percentage of doses followed by solicited local symptoms during the 7-day post-vaccination period was higher in the HPV group compared to the HAV group. The incidence of grade 3 solicited local symptoms during the 7-day post-vaccination period was also higher in the HPV group compared to the HAV group.

Table 165-Study HPV-008: Incidence of solicited local symptoms reported during the 7-day (Days 0 to 6) post-vaccination period following each dose and overall in subjects included in the safety diary card subset (Interim Total Vaccinated cohort)

	HPV		HAV	
	n/N	% (95% CI)	n/N	% (95% CI)
Dose 1				
Pain-				
All	2662/3068	*86.8% (85.5, 87.9%)*	2014/3071	*65.6% (63.9, 67.3%)*
Grade 3	253/3068	*8.2% (7.3, 9.3%)*	61/3071	*2.0% (1.5, 2.5%)*
Redness (mm) -				
All	778/3068	*25.4% (23.8, 26.9%)*	511/3071	*16.6% (15.3, 18.0%)*
>50	8/3068	0.3% (0.1, 0.5%)	2/3071	0.1% (0.0, 0.2%)
Swelling (mm)-				
All	676/3068	*22.0% (20.6, 23.5%)*	323/3071	*10.5% (9.5, 11.7%)*
>50	31/3068	*1.0% (0.7, 1.4%)*	6/3071	*0.2% (0.1, 0.4%)*
Dose 2				
Pain-				
All	2155/2898	*74.4% (72.7, 75.9%)*	1588/2920	*54.4% (52.6, 56.2%)*
Grade 3	156/2898	*5.4% (4.6, 6.3%)*	41/2920	*1.4% (1.0, 1.9%)*
Redness (mm) -				
All	783/2898	27.0% (25.4, 28.7%)	444/2920	*15.2% (13.9, 16.6%)*
>50	12/2898	0.4% (0.2, 0.7%)	2/2920	0.1% (0.0, 0.2%)
Swelling (mm)-				
All	693/2898	*23.9% (22.4, 25,5%)*	275/2920	*9.4% (8.4, 10.5%)*
>50	23/2898	*0.8% (0.5, 1.2%)*	5/2920	*0.2% (0.1, 0.4%)*
Dose 3				
Pain-				
All	2150/2726	*78.9% (77.3, 80.4%)*	1548/2759	*56.1% (54.2, 58.0%)*
Grade 3	226/2726	*8.3% (7.3, 9.4%)*	54/2759	*2.0% (1.5, 2.5%)*
Redness (mm) -				
All	884/2726	*32.4% (30.7, 34.2%)*	446/2759	*16.2% (14.8, 17.6%)*
>50	19/2726	*0.7% (0.4, 1.1%)*	0/2759	*0.0% (0.0, 0.1%)*
Swelling (mm)-				
All	840/2726	*30.8% (29.1, 32.6%)*	289/2759	*10.5% (9.4, 11.7%)*
>50	33/2726	*1.2% (0.8, 1.7%)*	5/2759	*0.2% (0.1, 0.4%)*
Overall/subject				
Pain-				
All	2786/3077	*90.5% (89.5, 91.6%)*	2402/3080	*78.0% (76.5, 79.4%)*
Grade 3	502/3077	*16.3% (15.0, 17.7%)*	136/3080	*4.4% (3.7, 5.2%)*
Redness (mm) -				
All	1348/3077	*43.8% (42.0, 45.6%)*	851/3080	*27.6% (26.1, 29.2%)*
>50	37/3048	*1.2% (0.8, 1.7%)*	3/3080	*0.1% (0.0, 0.3)*
Swelling (mm)-				
All	1292/3077	*42.0% (40.2, 43.8%)*	609/3080	*19.8% (18.4, 21.2%)*
>50	74/3077	*2.4% (1.9, 3.0%)*	15/3080	*0.5% (0.3, 0.8%)*

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
* Grade 3 pain corresponds to pain that prevents normal activity.
Data in italics show 95% CIs which did not overlap.
Source: STN 125259.0048, CSR 008, Table 104, p. 366-367

Reviewer's Comment: As noted, for the solicited local adverse events, the proportions of subjects with solicited local adverse events was higher in Cervarix recipients as compared to Havrix recipients, and most of the 95% CIs did not overlap. The proportion of Cervarix recipients with swelling increased from dose 1 (app. 22% to app. 31%, 95% CIs did not overlap), as well the proportion of Cervarix recipients with injection site redness. The proportion of subjects with pain decreased from dose 1 to dose 2 (app. 87% to 79%, 95% CIs did no overlap), and redness (25% to 32%, 1st and 3rd dose with 95% CIs that do not overlap). A decrease in the proportion of subjects with pain was noted in Havrix recipients (66% to 56%, 95% CIs do not overlap), but there no progressive increase in redness or swelling or redness in Havrix recipients.

Grade 3 pain occurred in app. 16% of Cervarix recipients as compared to 4% of Havrix subjects. Grade 3 redness and swelling (>50 mm) were infrequently reported in most subjects (as high as 2.4% for swelling in Cervarix recipients compared to 0.5% Havrix recipients, and 1.2% Grade 3 erythema in Cervarix recipients as compared to 0.1% of Havrix recipients).

The sponsor notes that despite the higher incidence of solicited local symptoms in the HPV group, no impact on compliance for completion of the three-dose vaccination schedule was observed (91.6% in the HPV group and 91.9% in the HAV group). Over the full vaccination regimen, the most frequent local symptom leading to school or work absenteeism was injection site pain, occurring in 1.1% [0.8, 1.5] of subjects in the HPV group versus 0.5% [95% CI: 0.3, 0.8] of subjects in the HAV group.

Urticaria within 30 minutes after vaccination was infrequently reported among HPV vaccine recipients, occurring 0%, 0.1%, and 0.1% of vaccines after doses 1, 2, and 3, respectively. (Source: STN 125259.0048, CSR 008, Table 105, p. 367, not shown here).

Solicited local symptoms lasted approximately three days in the HPV group compared to two days in the HAV group. Solicited local symptoms had an intensity of grade 3 for approximately one-and-one-half days in the HPV group and one day in the HAV group. (Source: STN 125259.0048, CSR 008, Supplements 306-307, p. 10510-10513, not shown here).

The incidence of solicited local symptoms observed for subjects who were seropositive and/or DNA positive for either HPV-16 or HPV-18 at baseline, seronegative and DNA negative for HPV-16 and HPV-18 at baseline, or DNA positive for either HPV-16 or HPV-18 at baseline was comparable to the incidence observed for the Total Vaccinated cohort. (Source: STN 125259.0048, CSR 008, Table 106, p. 369, not shown here).

The sponsor also presented solicited local adverse events by ethnicity. A higher proportion of subjects of white ethnicity complained of pain, redness, and swelling as compared to black subjects, for both HPV and HAV vaccines. A summary table of symptoms per subject by ethnic background is presented for HPV and HAV vaccines in Table 166 below.
Reviewer's Comment: No conclusions can be drawn from this observation.

Table 166-Study HPV-008: Incidence of solicited local symptoms reported during the 7-day (Days 0 to 6) post-vaccination period overall per subject included in the safety diary card subset by ethnicity (Interim Total Vaccinated cohort)

Symptom-Group	Black		White/Caucasian		Asian		Hispanic		Other	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Pain-HPV	117/134	87.3%	1264/1303	95.9%	794/936	84.8%	535/615	87.0%	76/89	85.4%
Pain-HAV	102/144	70.8%	1138/1310	86.9%	659/945	69.7%	431/593	72.7%	72/88	81.8%
Redness-HPV	34/134	25.4%	694/1303	53.3%	429/936	45.8%	157/615	25.5%	34/89	38.2%
Redness-HAV	30/144	20.8%	429/1310	32.7%	268/945	28.4%	91/593	15.3%	33/88	37.5%
Swelling-HPV	48/134	35.8%	596/1303	45.7%	444/936	47.4%	174/615	28.3%	30/89	33.7%
Swelling-HAV	27/144	18.8%	270/1310	20.6%	214/945	22.6%	75/593	12.6%	23/88	26.1%

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259.0048, CSR 008, Supplement 311, p. 10520-10523

Solicited general adverse events: Overall, the incidence of solicited general symptoms within 7 days after vaccination was slightly higher in the HPV group compared to the HAV group. The incidence of solicited general symptoms assessed as grade 3, as possibly related to vaccination according to the investigator and as grade 3 and possibly related to vaccination according to the

investigator was also higher in the HPV group compared to the HAV group. The CIs calculated for the percentage of doses followed by solicited symptoms were extremely narrow because of the large sample size. CIs did not overlap between the two groups for several symptoms (although the sponsor considered these differences to be medically meaningful). The CIs for grade 3 symptoms did overlap, except for grade 3 myalgia.

The most frequently reported solicited general symptoms in both groups were fatigue, myalgia and headache, and are presented in Table 167 below.

- Fatigue was reported by 57.6% and 53.6% of subjects in the HPV and HAV group, respectively.
- Myalgia was reported by 52.2% and 44.9% of subjects in the HPV and HAV group, respectively.
- Headache was reported by 54.1% and 51.3% of subjects in the HPV and HAV group, respectively.

Table 167-Study HPV-008: Incidence of solicited general symptoms reported during the 7-day (Days 0 to 6) post-vaccination period overall in subjects included in the safety diary card subset (Interim Total Vaccinated cohort)

Symptom	n/N	% (95% CI)	n/N	% (95% CI)
Arthralgia				
All	633/3076	20.6% (19.2, 22.1%)	551/3080	17.9% (16.6, 19.3%)
Grade 3	32/3076	1.0% (0.7, 1.5%)	23/3080	0.7% (0.5, 1.1%)
Fatigue				
All	1771/3076	*57.6% (55.8, 59.3%)*	1652/3080	*53.6% (51.9, 55.4%)*
Grade 3	126/3076	4.1% (3.4, 4.9%)	99/3080	3.2% (2.6, 3.9%)
Fever (° C) Axilla				
All	381/3076	12.4% (11.2, 13.6%)	337/3080	10.9% (9.9, 12.1%)
>39.0	18/3076	0.6% (0.3, 0.9)	10/3080	0.3% (0.2, 0.6%)
Gastrointestinal				
All	850/3076	27.6% (26.1, 29.3%)	841/3080	27.3% (25.7, 28.9%)
Grade 3	60/3076	2.0% (1.5, 2.5%)	61/3080	2.0% (1.5, 2.5%)
Headache				
All	1665/3076	54.1% (52.3, 55.9%)	1579/3080	51.3% (49.5, 53.0%)
Grade 3	131/3076	4.3% (3.6, 5.0%)	108/3080	3.5% (2.9, 4.2%)
Myalgia				
All	1606/3076	*52.2% (50.4, 54.0%)*	1382/3080	*44.9% (43.1, 46.6%)*
Grade 3	141/3076	*4.6% (3.9, 5.4%)*	47/3080	*1.5% (1.1, 2.0%)*
Rash				
All	312/3076	10.1% (9.1, 11.3%)	258/3080	8.4% (7.4, 9.4%)
Grade 3	8/3076	0.3% (0.1, 0.5%)	5/3080	0.2% (0.1, 0.4%)
Urticaria				
All	298/3076	9.7% (8.7, 10.8%)	244/3080	7.9% (7.0, 8.9%)
Grade 3	29/3076	0.9% (0.6, 1.4%)	30/3080	1.0% (0.7, 1.4%)

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
For Overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Rel = possibly related to vaccination according to the investigator
For all symptoms except urticaria: Grade 3 = prevents normal activity
For urticaria: Grade 3 = distributed on at least 4 body areas
Absent = events which resulted in school or work absenteeism.
Data in italics show 95% CIs which did not overlap
Source: STN 125259.0048, CSR 008, Table 107, p. 371-375

Reviewer's Comment: The proportions of subjects with solicited general symptoms were reviewed after dose 1, dose 2, and dose 3. There was no increase in the proportion of subjects

who developed a solicited general adverse event with successive doses of Cervarix(a slight decrease in the proportion of subjects from dose 1 to dose 2 was noted), with similar proportions when comparing doses 2 and 3. A similar pattern was noted for recipients of Havrix. There was a higher proportion of Cervarix recipients with myalgia as well as Grade 3 myalgia (95% CIs do not overlap).

The mean duration of solicited general symptoms, including grade 3 symptoms, was similar between both groups. Mean duration of grade 3 myalgia was 1.7 and 1.8 days in the HPV and HAV groups, respectively. (Source: STN 125259.0048, CSR 008, Supplements 306-307, p. 10510-10513, not shown here).

Over the full vaccination regimen, solicited general symptoms which resulted in school or work absenteeism were limited. The most frequent general symptom leading to school or work absenteeism was headache, occurring in 1.5% of subjects in the HPV group versus 1.3% of subjects in the HAV group.

The incidence of solicited general symptoms observed for subjects who were seropositive and/or DNA positive for either HPV-16 or HPV-18 at baseline, seronegative and DNA negative for HPV-16 and HPV-18 at baseline, or DNA positive for either HPV-16 or HPV-18 at baseline was comparable to the incidence observed for the Total Vaccinated cohort. (Source: STN 125259.0048, CSR 008, Table 108, p. 376, not shown here).

Unsolicited adverse events: During the 30-day post-vaccination period, unsolicited symptoms were reported by a similar number of subjects and after a similar number of doses in both groups. Overall, 42.5% and 43.6% of subjects reported at least one unsolicited symptom Table 168). Also, a similar percentage of subjects in both groups (7.6% HPV and 6.9% HAV) reported unsolicited symptoms assessed as grade 3.

Table 168-Study HPV-008: Percentage of subjects with unsolicited symptoms classified by MedDRA Primary System Organ Class within the 30-day (Days 0 to 29) post-vaccination period in subjects included in the safety diary card subset (Interim Total Vaccinated cohort)

Primary System Organ Class	HPV N=3184	HAV N=3187
	n(%)	n(%)
At least one symptom	1354 (42.5%)	1389 (43.6%)
Blood and Lymphatic system disorders	9 (0.3%)	14 (0.4%)
Cardiac Disorders	5 (0.2%)	3 (0.1%)
Congenital, familial and genetic disorders	0 (0.0%)	2 (0.1%)
Ear and labyrinth disorders	15 (0.5%)	23 (0.7%)
Endocrine disorders	0 (0.0%)	4 (0.1%)
Eye disorders	31 (1.0%)	35 (1.1%)
Gastrointestinal disorders	154 (5.2%)	192 (6.0%)
General disorders and administration site conditions	244 (7.7%)	227 (7.1%)
Hepatobiliary disorders	0 (0.0%)	2 (0.1%)
Immune system disorders	10 (0.3%)	19 (0.6%)
Infections and Infestations	793 (24.9%)	807 (25.3%)
Injury, poisoning, and procedural complications	44 (1.4%)	65 (2.0%)
Investigations	4 (0.1%)	5 (0.2%)
Metabolism and Nutrition disorcders	6 (0.2%)	7 (0.2%)
Musculoskeletal and connective tissue disorders	158 (5.0%)	144 (4.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (0.2%)	4 (0.1%)
Nervous system disorders	321 (10.1%)	340 (10.7%)
Pregnancy, puerperium and perinatal disorders	2 (0.1%)	1 (0.0%)
Psychiatric disorders	30 (0.9%)	42 (1.3%)
Renal and urinary disorders	13 (0.4%)	12 (0.4%)
Reproductive system and breast disorders	144 (4.5%)	178 (5.6%)
Respiratory, thoracic and mediastinal disorders	160 (5.0%)	167 (5.2%)
Skin and subcutaneous tissue disorders	80 (2.5%)	91 (2.9%)
Surgical and medical procedures	9 (0.3%)	15 (0.5%
Vascular disorders	13 (0.4%)	8 (0.3%)

HPV = HPV-16/18 (vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval
Source: STN 125259.0048, CSR 008, Supplement 319, p. 10578

Reviewer's Comment : All 95% CIs around percentages overlap. Table 169 includes specific Preferred Terms which occurred > 1% in any group. 95% CIs around percentages did not overlap for the two groups. The most common unsolicited adverse events in the 30 days after vaccination was headache, influenza, gynecological chlamydia, pharyngolaryngeal pain and dizziness.

GSK indicated that a slightly higher proportion of subjects in the HPV group experienced injection site nodule (0.6% HPV, 0.1% HAV), injection site pruritus (0.4% HPV and 0.2% HAV), dyspepsia (0.3% HPV and 0.2% HAV), and infectious mononucleosis (0.3% HPV and 0.2% HAV).

Table 169-Study HPV-008: Percentage of subjects with unsolicited symptoms (≥1% in any group) classified by MedDRA Primary System Organ Class and High Level Term within the 30-day (Days 0 to 29) post-vaccination period in subjects included in the safety diary card subset (Interim Total Vaccinated cohort)

Primary System Organ Class	Preferred Term	HPV N=3184	HAV N=3187
		n(%)	n(%)
Gastrointestinal disorders	Abdominal pain upper	38 (1.2%)	40 (1.3%)
	Nausea	18 (0.6%)	47 (1.5%)
General and disorders and administration site disorders	Injection site bruising	58 (1.8%)	57 (1.8%)
Infections and Infestations	GYN Chlamydial infections	132 (4.1%)	140 (4.4%)
	Influenza	155 (4.9%)	177 (5.6%)
	Nasopharyngitis	111 (3.5%)	109 (3.4%)
	Pharyngitis	55 (1.7%)	56 (1.8%)
	URI	36 (1.1%)	43 (1.3%)
	UTI	48 (1.5%)	46 (1.4%)
	Vaginal infection	73 (2.3%)	70 (2.2%)
Musculoskeletal and connective tissue disorders	Back pain	41 (1.3%)	40 (1.3%)
	Pain in extremity	35 (1.1%)	27 (0.8%)
Nervous system disorders	Dizziness	88 (2.8%)	83 (2.6%)
	Headaches	218 (6.8%)	2461(7.6%)
Reproductive system and breast disorders	Dysmenorrhea	67 (2.1%)	74 (2.3%)
Respiratory, thoracic and mediastinal disorders	Cough	47 (1.5%)	50 (1.6%)
	Pharyngolaryngeal pain	94 (3.0%)	86 (2.7%)
	Upper respiratory tract signs and symptoms	104 (3.3%)	92 (2.9%)

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
At least one symptom = at least one symptom experienced (regardless of the MedDRA High Level Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259.48, CSR HPV-008, Supplement 317, p. 10-565-10576 and text

There are few specific unsolicited adverse events in the 30 days after any dose graded as Grade 3, and generally comparable proportions of subjects experienced grade 3 events. The two grade 3 events which occurred ≥0.5% in any group were influenza (0.7% HPV, 0.6% HAV) and nasopharyngitis (0.5% HPV, 0.4% HAV).

There were generally comparable proportions of subjects who were seropositive and/or DNA positive (854 HPV group and 858 in HAV group total) at baseline in the treatment groups who reported an unsolicited adverse event in the 30 days after vaccination (375 [43.9%] HPV, 383 [44.6%] HAV). The events which occurred at ≥ 1% in either group are presented in Table 170.

Table 170-Study HPV-008: Percentage of subjects with unsolicited symptoms (≥1% in either treatment group) classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0 to 29) post-vaccination period in subjects who were seropositive and/or DNA positive for either HPV-16 or HPV-18 at baseline (Interim Total Vaccinated cohort)

Primary System Organ Class	Preferred Term	HPV N=854	HAV N=858
		n(%)	n(%)
Gastrointestinal disorders	Abdominal pain upper	9 (1.1%)	8 (0.9%)
General disorders and administration site conditions	Fatigue	11 (1.3%)	9 (1.0%)
	Injection site bruising	17 (2.0%)	17 (2.0%)
	Pyrexia	11 (1.3%)	8 (0.9%)
Infections and infestations	GU tract gonococcal infection	12 (1.4%)	7 (0.8%)
	GYN Chlamydial infection	55 (6.4%)	49 (5.7%)
	Influenza	32 (3.7%)	34 (4.0%)
	Nasopharyngitis	22 (2.6%)	24 (2.8%)
	Pharyngitis	19 (2.2%)	14 (1.6%)
	Sinusitis	8 (0.9%)	10 (1.2%)
	UTI	11 (1.3%)	12 (1.4%)
	Vaginal infection	20 (2.3%)	29 (2.3%)
Musculoskelatal and connective tissue disorder	Back pain	9 (1.1%)	15 (1.7%)
	Pain in extremity	7 (0.8%)	12 (1.4%)
Nervous system disorders	Dizziness	22 (2.6%)	28 (3.3%)
	Headache	66 (7.7%)	63 (7.3%)
Reproductive system and breast disorders	Dysmenorrhea	13 (1.5%)	14 (1.6%)
Respiratory, thoracic and mediastinal disorders	Cough	13 (1.5%)	11 (1.3%)
	Pharyngolaryngeal pain	25 (2.9%)	19 (2.2%)

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, CSR 008, Supplement 334, p. 10639-10645

There were generally comparable proportions of subjects who were seronegative and DNA negative for both vaccine HPV types at baseline (965 [42.2%] in the HPV group and 991 [43.3%] in the HAV group) who reported an unsolicited adverse event in the 30 days after vaccination. The events which occurred at ≥ 1% in either group are presented in Table 171 below.

Table 171-Study HPV-008: Percentage of subjects with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0 to 29) post-vaccination period in subjects who were seronegative and DNA negative for both HPV-16 and HPV-18 at baseline (Interim Total Vaccinated cohort)

Primary System Organ Class	Preferred Term	HPV N=2289	HAV N=2289
		n(%)	n(%)
At least one symptom		965 (42.2%)	991 (43.3%)
Gastrointestinal disorders	Abdominal pain upper	28 (1.2%)	31 (1.4%)
	Nausea	16 (0.7%)	30 (1.3%)
General disorders and administration site conditions	Injection site bruising	40 (1.7%)	40 (1.7%)
Infections and Infestations	GU tract gonococcal infection	27 (1.2%)	31 (1.4%)
	Gynecological Chlamydia infection	74 (3.2%)	88 (3.8%)
	Influenza	122 (5.3%)	142 (6.2%)
	Nasopharyngitis	88 (3.8%)	85 (3.7%)
	Pharyngitis	36 (1.6%)	42 (1.8%)
	Upper respiratory tract infection	26 (1.1%)	33 (1.4%)
	UTI	37 (1.6%)	34 (1.5%)
	Vaginal infection	53 (2.3%)	50 (2.2%)
	Vulovaginal mycotic infection	21 (0.9%)	23 (1.0%)
Musculoskelatal and connective tissue disorder	Back pain	31 (1.4%)	25 (1.1%)
	Pain in extremity	28 (1.2%)	15 (0.7%)
Nervous system disorders	Dizziness	64 (2.8%)	54 (2.4%)
	Headache	152 (6.6%)	177 (7.7%)
Reproductive system and breast disorders	Dysmenorrhea	54 (2.4%)	58 (2.5%)
Respiratory, thoracic and mediastinal disorders	Cough	34 (1.5%)	37 (1.6%)
	Pharyngolaryngeal pain	67 (2.9%)	67 (2.9%)

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259.48, CSR 008, Supplement 335, p. 10646-10655

Reviewer's Comment: There was no apparent increase in unsolicited events in the 30 days after vaccination in the seropositive/PCR positive subjects as compared to subjects who were seronegative and DNA negative for both vaccine HPV types.

There were generally comparable proportions of subjects DNA positive for either HPV-16 or HPV-18 at baseline (120 (49.4%) in the HPV group and 106 (47.7%) in the HAV group) and reported an unsolicited adverse event in the 30 days after vaccination. The events which occurred at ≥ 1% in either group are presented in Table 172 below.

Table 172-Study HPV-008: Percentage of subjects with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0 to 29) post-vaccination period in subjects who were DNA positive for either HPV-16 or HPV-18 at baseline (Interim Total Vaccinated cohort)

Primary System Organ Class	Preferred Term	HPV N=243	HAV N=222
		n(%)	n(%)
At least one symptom		120 (49.4%)	106 (47.7%)
Gastrointestinal disorders	Abdominal pain upper	2 (0.8%)	5 (2.3%)
	Diarrhea	2 (0.8%)	3 (1.4%)
	Nausea	1 (0.4%)	5 (2.3%)
	Vomiting	3 (1.2%)	3 (1.4%)
General disorders and administration site conditions	Fatigue	3 (1.2%)	3 (1.4%)
	Injection site bruising	7 (2.9%)	5 (2.3%)
	Injection site paresthesia	4 (1.6%)	0 (0.0%)
	Injection site pruritus	3 (1.2%)	1 (0.5%)
Infections and Infestations	Ear infection	1 (0.4%)	3 (1.4%)
	GU tract gonococcal infection	2 (0.8%)	3 (1.4%)
	Gynecological Chlamydia infection	19 (7.8%)	18 (8.1%)
	Influenza	14 (5.8%)	8 (3.6%)
	Nasopharyngitis	8 (3.3%)	6 (2.7%)
	Pharyngitis	5 (2.1%)	3 (1.4%)
	Sinusitis	2 (0.8%)	4 (1.8%)
	Upper respiratory tract infection	2 (0.8%)	3 (1.4%)
	UTI	6 (2.5%)	6 (2.7%)
	Vaginal infection	4 (1.6%)	4 (1.8%)
	Vulovaginal mycotic infection	4 (1.6%)	1 (0.5%)
Musculoskelatal and connective tissue disorder	Back pain	4 (1.6%)	4 (1.8%)
Nervous system disorders	Dizziness	5 (2.1%)	7 (3.2%)
	Headache	22 (9.1%)	14 (6.3%)
	Somnolence	3 (1.2%)	1 (0.5%)
Reproductive system and breast disorders	Dysmenorrhea	4 (1.6%)	3 (1.4%)
Respiratory, thoracic and mediastinal disorders	Cough	4 (1.6%)	5 (2.3%)
	Nasal congestion	3 (1.2%)	2 (0.9%)
	Pharyngolaryngeal pain	6 (2.5%)	4 (1.8%)
Skin and subcutaneous tissue disorders	Pruritus	1 (0.4%)	4 (1.8%)

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, CSR 008, Supplement 336, p. 10656-10659

Concomitant medication and vaccination: A similar percentage of subjects in both groups used concomitant medication during the 30-day post-vaccination period. The use of concomitant medication was also reported after a similar percentage of doses. A limited number of subjects in both groups (≤5 subjects) used prophylactic medication in anticipation of post-vaccination events.

Table 173-Study HPV-008: Incidence of concomitant medication during the 30-day (Days 0 to 29) post-vaccination period by dose and overall in subjects included in the safety diary card subset (Interim Total Vaccinated cohort)

	HPV					HAV				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1										
Any	3184	1458	45.8	44.0	47.5	3187	1495	46.9	45.2	48.7
Any antipyretic	3184	705	22.1	20.7	23.6	3187	714	22.4	21.0	23.9
Prophylactic antipyretic	3184	2	0.1	0.0	0.2	3187	1	0.0	0.0	0.2
Any antibiotic	3184	334	10.5	9.4	11.6	3187	342	10.7	9.7	11.9
Prophylactic antibiotic	3184	0	0.0	0.0	0.1	3187	0	0.0	0.0	0.1
Dose 2										
Any	3036	837	27.6	26.0	29.2	3045	861	28.3	26.7	29.9
Any antipyretic	3036	433	14.3	13.0	15.6	3045	421	13.8	12.6	15.1
Prophylactic antipyretic	3036	3	0.1	0.0	0.3	3045	2	0.1	0.0	0.2
Any antibiotic	3036	261	8.6	7.6	9.7	3045	291	9.6	8.5	10.7
Prophylactic antibiotic	3036	2	0.1	0.0	0.2	3045	1	0.0	0.0	0.2
Dose 3										
Any	2818	763	27.1	25.4	28.8	2834	743	26.2	24.6	27.9
Any antipyretic	2818	377	13.4	12.1	14.7	2834	363	12.8	11.6	14.1
Prophylactic antipyretic	2818	0	0.0	0.0	0.1	2834	0	0.0	0.0	0.1
Any antibiotic	2818	215	7.6	6.7	8.7	2834	195	6.9	6.0	7.9
Prophylactic antibiotic	2818	0	0.0	0.0	0.1	2834	0	0.0	0.0	0.1
Overall/dose										
Any	9038	3058	33.8	32.9	34.8	9066	3099	34.2	33.2	35.2
Any antipyretic	9038	1515	16.8	16.0	17.5	9066	1498	16.5	15.8	17.3
Prophylactic antipyretic	9038	5	0.1	0.0	0.1	9066	3	0.0	0.0	0.1
Any antibiotic	9038	810	9.0	8.4	9.6	9066	828	9.1	8.5	9.7
Prophylactic antibiotic	9038	2	0.0	0.0	0.1	9066	1	0.0	0.0	0.1
Overall/subject										
Any	3184	1994	62.6	60.9	64.3	3187	2002	62.8	61.1	64.5
Any antipyretic	3184	1042	32.7	31.1	34.4	3187	1029	32.3	30.7	33.9
Prophylactic antipyretic	3184	5	0.2	0.1	0.4	3187	3	0.1	0.0	0.3
Any antibiotic	3184	685	21.5	20.1	23.0	3187	695	21.8	20.4	23.3
Prophylactic antibiotic	3184	2	0.1	0.0	0.2	3187	1	0.0	0.0	0.2

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects who started to take the specified concomitant medication at least once during the mentioned period
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses after which the specified concomitant medication was started at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, CSR 008, Table 113, p. 381

Serious adverse events: At the time of the final analysis, 1724 SAEs were reported in 1400 subjects, of whom 701 (7.5%) subjects were in the HPV group and 699 (7.5%) subjects were in the HAV group. The number of doses followed by one or more SAEs and the number of events experienced were also similar between both groups. In review of the table which presents SAEs the number of events reported for a specific preferred term was small in each group. Table 174 below presents SAEs which were reported by $\geq$1% in either treatment group.

Table 174-Study HPV-008: Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term reported ≥ 0.1% of subjects in either treatment group during the entire follow-up period (Total Vaccinated cohort)

Primary System Organ Class	Preferred Term	HPV N=9319	HAV N=3187
		n(%)	n(%)
At least one symptom		701 (7.5%)	699 (7.5%)
Gastrointestinal disorders	Abdominal pain	10 (0.1%)	13 (0.1%)
	Abdominal pain upper	3 (0.0%)	5 (0.1%)
	Gastritis	8 (0.1%)	4 (0.0%)
	Cholecystitis	6 (0.1%)	4 (0.0%)
	Cholelithiasis	9 (0.1%)	8 (0.1%)
Immune system disorders	Hypersensitivity	2 (0.0%)	5 (0.1%)
Infections and Infestations	Acute tonsillitis	6 (0.1%)	7 (0.1%)
	Appendicitis	41 (0.4%)	50 (0.5%)
	Cellulitis	2 (0.0%)	6 (0.1%)
	Gastroenteritis	10 (0.1%)	14 (0.2%)
	Infectious mononucleosis	8 (0.1%)	10 (0.1%)
	PID	11 (0.1%)	5 (0.1%)
	Peritonsillar abscess	8 (0.1%)	8 (0.1%)
	Pneumonia	16 (0.2%)	10 (0.1%)
	Pyelonephritis	18 (0.2%)	10 (0.1%)
	Pyelonephritis acute	17 (0.2%)	11 (0.1%)
	Tonsillitis	11 (0.1%)	7 (0.1%)
	UTI	5 (0.1%)	12 (0.1%)
Injury, poisoning, and procedural complications	Concussion	7 (0.1%)	4 (0.0%)
	Joint dislocation	1 (0.0%)	6 (0.1%)
	Ligament rupture	3 (0.0%)	8 (0.1%)
	Post-procedural hemorrhage	5 (0.1%)	3 (0.0%)
	Road traffic accident	7 (0.1%)	10 (0.1%)
	Wrist fracture	2 (0.0%)	5 (0.1%)
Musculoskeletal and connective tissue disorders	Back pain	5 (0.1%)	2 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine leiomyoma	1 (0.0%)	6 (0.1%)
Nervous system disorders	Headache	5 (0.1%)	1 (0.0%)
Pregnancy, puerperium and perinatal disorders	Abortion missed	14 (02%)	21 (0.2%)
	Abortion spontaneous	61 (0.7%)	50 (0.5%)
	Abortion spontaneous complete	34 (0.4%)	33 (0.4%)
	Abortion spontaneous incomplete	42 (0.5%)	34 (0.4%)
	Blighted ovum	7 (0.1%)	7 (0.1%)
	Ectopic pregnancy	13 (0.1%)	6 (0.1%)
	Hyperemesis gravidarum	5 (0.1%)	4 (0.0%)
	Intra-uterine death	7 (0.1%)	6 (0.1%)
	Pre-eclampsia	6 (0.1%)	7 (0.1%)
	Premature labor	16 (0.2%)	7 (0.1%)
	Stillbirth	6 (0.1%)	5 (0.1%)
Psychiatric disorders	Depression	18 (0.2%)	14 (0.2%)
	Suicide attempt	7 (0.1%)	8 (0.1%)
Reproductive system and breast disorders	Endometriosis	2 (0.0%)	5 (0.1%)
	Ovarian cyst	11 (0.1%)	10 (0.1%)
	Ovarian cyst ruptured	3 (0.0%)	8 (0.1%)
Respiratory, thoracic and mediastinal disorders	Asthma	6 (0.1%)	7 (0.1%)

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259.48, CSR 008, Table 115, p. 383-393

Non-fatal SAEs: Of the 1724 SAEs reported at the time of the final analysis, 1704 SAEs were non-fatal. Overall, the most frequently reported SAEs during the entire follow-up period in terms of the Primary System Organ Class (SOC) were events related to infections and infestations and pregnancy, puerperium and perinatal conditions. The most common non-fatal SAE under the SOC of infections and infestations was appendicitis [41 (0.4%) subjects in the HPV group and 50 (0.5%) subjects in the HAV group]. Concerning the SOC pregnancy, puerperium and perinatal conditions, the most frequently reported events were associated with spontaneous abortion (complete/incomplete spontaneous abortion and missed abortion including blighted ovum). All these events were reported with a similar incidence in both groups overall.
Reviewer's Comment: Please see discussion for pregnancy outcomes around the time of vaccination.

The observed incidence of SAEs was lower for subjects who were seronegative and DNA negative for HPV-16 and HPV-18 at baseline compared to subjects who were DNA positive for either HPV-16 or HPV-18 at baseline. This trend was observed in both HPV and HAV groups. No difference in the pattern of SAEs was observed between the HPV and HAV groups in the vaccinated DNA positive cohort.

Table 175-Study HPV-008: Overview of the incidence of Serious Adverse Events reported during the entire follow-up period in subgroups by baseline seropositivity and/or DNA positivity status (Total Vaccinated cohort)

	HPV					HAV				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Total Vaccinated cohort	9319	701	7.5	7.0	8.1	9325	699	7.5	7.0	8.0
Vaccinated seropositive and/or DNA positive cohort	2409	221	9.2	8.1	10.4	2419	207	8.6	7.5	9.7
Vaccinated seronegative and DNA negative cohort	6802	472	6.9	6.3	7.6	6788	489	7.2	6.6	7.8
Vaccinated DNA positive cohort	690	76	11.0	8.8	13.6	649	58	8.9	6.9	11.4

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, CSR 008, Table 116, p. 394

Fatal events: At the time of the final analysis, 20 fatal events were reported for 17 subjects (nine in the HPV group and eight in the HAV group). Road traffic accidents were the most common causes of death. None of the fatal events were assessed as possibly related to vaccination by the investigator.

Table 176-Study HPV-008: Listing of Serious Adverse Events with fatal outcome (Total Vaccinated cohort)

Group	Sub. No.	Case Id	Age at onset (Year)	Verbatim	Preferred term	System Organ Class	Dose	Day of onset*	Duration (days)	Causality	Outcome
HPV	8746	B0435108A	23	Deceased apparently drowned	Drowning	General disorders and administration site conditions	3	217	1	N	Fatal
			23	Murdered	Homicide	Social circumstances	3	217	1	N	Fatal
	17678	B0532335A	28	Deep vein thrombosis	Deep vein thrombosis	Vascular disorders	3	1167	4	N	Fatal
	18105	B0457152A	21	Gun shot wound to head	Gun shot wound	Injury, poisoning and procedural complications	3	686	1	N	Fatal
	20945	B0474261A	21	Septicemia	Sepsis	Infections and infestations	3	758	4	N	Fatal
	22586	B0451319A	22	Subarachnoid hemorrhage	Subarachnoid haemorrhage	Nervous system disorders	3	537	28	N	Fatal
	71903	B0405036G	27	Pyoderma gangrenous	Pyoderma gangrenosum	Skin and subcutaneous tissue disorders	3	555	76	N	Fatal
	76286	B0389032A	22	Gestational trophoblastic tumour	Gestational trophoblastic tumour	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	151	786	N	Fatal
			24	Possible lung metastasis	Metastases to lung	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	889	48	N	Fatal
	76544	B0520627A	22	Motorcycle accident	Road traffic accident	Injury, poisoning and procedural complications	1	1124	1	N	Fatal
	89479	B0517289A	27	Cardio-respiratory collapse	Cardiopulmonary failure	Cardiac disorders	3	770	1	N	Fatal
			27	Pneumococcal sepsis	Pneumococcal sepsis	Infections and infestations	3	770	1	N	Fatal
HAV	1899	B0404036A	20	Automobile accident	Road traffic accident	Injury, poisoning and procedural complications	3	30	1	N	Fatal
	6054	B0444101A	18	Automobile accident	Road traffic accident	Injury, poisoning and procedural complications	3	317	1	N	Fatal
	6726	B0399114A	18	Osteosarcoma	Bone sarcoma	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	165	335	N	Fatal
	14290	B0496456A	20	Suicide	Completed suicide	Psychiatric disorders	3	817	1	N	Fatal
	16201	B0510451A	19	Death-unknown cause	Death	General disorders and administration site conditions	3	817	1	N	Fatal
	16505	B0381211A	20	Motor vehicle accident	Road traffic accident	Injury, poisoning and procedural complications	2	101	1	N	Fatal
	18876	B0406806A	25	Diabetic ketoacidosis	Diabetic ketoacidosis	Metabolism and nutrition disorders	1	154	7	N	Fatal
	70443	B0531865A	25	Homicide	Homicide	Social circumstances	3	961	1	N	Fatal

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
* Number of days after last vaccine dose
Sub No. = Subject number
Case Id = Case identification
Source: STN 125259.48, CSR 008, Table 137, p. 479

Narratives are provided for the events excluding those related to trauma (since the shortest time to event was 101 days after the last vaccination.

HPV Group:

Subject no. 17678 (HPV group): In September 2007, **two years after the third dose of HPV vaccine,** this 28-year-old subject experienced back pain with associated weight loss. Symptoms persisted prompting the subject to consult a physician on 12/29/07. The subject was hospitalized. A pleural fluid cytology was negative for malignant cells and the cell block showed numerous red blood cells with some lymphocytes in a background of eosinophilic amorphous material. Back pain with progressive weight loss persisted prompting the subject to consult her attending physician again. Chest X-ray was done on 4/2/08 revealing a massive pleural effusion, and right hemi-thorax with a pulmonary mass lesion (underlying pulmonary tuberculosis to rule out). Her attending physician suggested hospital admission; however the subject consulted another physician who prescribed anti-tuberculosis medications. The subject had poor compliance with the medications due to financial constraints. In July 2008, the subject noticed sudden enlargement of abdomen with associated weakness and decrease in appetite. Abdominal and pelvic ultrasound, performed on 8/4/08, revealed moderate to large amount of ascites. Rest of abdominal structures were unremarkable. Chest X-ray performed on 8/5/08 and revealed no change in the status of homogenous opacity occupying the whole right lung field. Rest of chest structures treatment (unspecified). Initial impression was abdomino-pelvic tuberculosis, ascites and massive pleural effusion. The subject also presented a swollen right leg and a deep vein thrombosis was also considered. A paracentesis was done. The peritoneal fluid cytology result showed few degenerated atypical cells present. On 8/26/08, a chest ultrasound was performed and revealed a complicated right pleural effusion with an approximate volume of 800cc, left minimal pleural

effusion, left atelectasis and consolidation and a mass measuring 4.1x3.8cm in right apex.. A transvaginal ultrasound was performed and revealed that the posterior uterine serosa was not well defined, suggestive of adhesions. The borders of both ovaries were also hazy because of dense adhesions. There was massive low level echo fluid in the abdomino-peritoneal cavity with fibrin/septal formation. The posterior peritoneum was thickened. On 8/27/08, the sputum acid-fast bacilli exam was negative. On --b(6)--, the subject suddenly became agitated, dyspneic, with hypotension and tachycardia. She went into cardiopulmonary arrest and was not revived after resuscitation maneuvers. The probable cause of death is pulmonary embolism. Pulmonary tuberculosis was the impression of the subject's previous physician. The death certificate showed that the immediate cause of death was massive pulmonary embolism and the cause to consider is deep venous thrombosis right. The investigator's diagnosis was: **pulmonary embolism, deep venous thrombosis, pulmonary mass (pulmonary tuberculosis versus malignancy).** It could not be confirmed if the pulmonary mass was pulmonary tuberculosis or a malignancy.
Reviewer's Comment: It appears unlikely that the pulmonary mass (whether this was TB or cancer) was related to vaccination. The Pulmonary embolism and DVT appear related to this underlying condition.

Subject no. 20945 (HPV group): On 6/3/07, **two years after the third dose of HPV vaccine,** this 21-year-old subject experienced fever. On 6/4/07, the subject also experienced dyspnea, and was admitted to hospital with fever, headache and severe vomiting during three days. The subject was diagnosed as having pharyngitis. She was given anti-emetics, antipyretics and antibiotics. On 6/5/07, the subject had more severe symptoms and was admitted in hospital again with dyspnea, epigastric pain and chest discomfort. The physical examination revealed enlarged and infected tonsils, her lungs were clear and her abdomen was tender at epigastrium. The subject was diagnosed as having "tonsillitis and hyperventilation syndrome". She was admitted and was treated with intravenous fluids and antibiotics. Her father took her back home without doctor's permission. The subject died on --b(6)-. Cause of death was **septicemia,** but the primary source could not be identified. An autopsy was not performed.
Reviewer's Comment: It is unlikely that this septicemia was related to vaccination.

Subject no. 71903 (HPV group): On 12/18/04, 1/15/05, and 6/4/05, the subject received the first, second and third doses of HPV vaccine. The subject had a medical history of Crohn's disease, apparently **diagnosed in August 2005** ***[2 months after dose 2]*** (no details were given), asthma bronchial and sulfa allergy. On 12/12/05, **five months after the third dose of HPV vaccine**, this 26-year-old subject was hospitalized to investigate a diarrhea of four days duration. An endoscopic evaluation showed erosive gastritis in antrum with signs of bleeding. No biopsy was performed. On 11/25/05, the subject reported 18 kg weight loss, abdominal pain and diarrhea with blood and mucus. The subject was treated with cotrimoxazole and ciprofloxacine. On 12/1/05, six months after the third dose of HPV vaccine, and 'few days after treatment with co-trimoxazole and ciprofloxacin' the subject experienced skin rash, muscular pain, hypotension, fever and malaise and was hospitalized in the intensive care unit. The dermatologic evaluation diagnosed Stevens Johnson syndrome and skin and lymphatic node biopsies were performed. The skin biopsy was compatible with Stevens Johnson syndrome. Since the subject reported allergy in the past to Sulfas and Ciprofloxacin and she received these medications in the last months, the treating physicians diagnosed Stevens Johnson syndrome related to the use of these medications. During hospitalization, she developed an anaphylactic shock due to a contrast medium. On 2/20/06, eight months after the third dose of HPV vaccine, the subject developed a cervical lymphadenopathy. No more details concerning this event were given. On 3/10/06, this subject developed a lesion in the left axilla region. She consulted the dermatologist who prescribed Erythromycin and recommended hospitalization. She went to the emergency room on 3/13/06 complaining of bloody diarrhea, dysphagia, cervical edema and left axillar lesion with signs of

inflammation. During her hospitalization the subject developed pneumonia and had episodes of bloody diarrhea. Several biopsies were performed as follows: the intestinal biopsy (cecum and rectum) showed cryptitis with chronic inflammation; the biopsy of cervical lymphadenopathy showed reactive lymphoid hyperplasia; the result of the skin biopsy in the left axilla region showed ulcerative chronic inflammation. A kidney biopsy was performed due to elevated urinary protein loss without specific findings. Other skin biopsies that were taken showed vascular alterations and dermal necrosis: neutrophilic vasculitis of small vessels with leucocytoclastic and fibrinoid necrosis of vascular walls with IgA traces. A reactive vasculitis was suspected. On 3/25/06, a CT scan showed irregular nodule in the lungs. A lung biopsy was performed and showed chronic eosinophilic pneumonia with lympho-histiocitary infiltrate in the lung parenchyma. The final diagnosis was unspecific skin and subcutaneous affection; however the possible diagnosis for all these lesions was hypersensitivity vasculitis of small vessels in lungs, kidney and intestine, probably Henoch-Schoenlein purpura (leucocytoclastic vasculitis, unknown cause). Based on the endoscopic findings and biopsies, the initial diagnosis of Crohn's disease was changed to inflammatory bowel disease. On 5/12/06, 11 months after the third dose of HPV vaccine, the subject developed purpuric lesions in the legs. The final diagnosis was Henoch Schonlein Purpura. She was hospitalized and the lesions were treated with corticosteroids with improvement. On 10/5/06, this subject developed rib osteomyelitis in thorax and was hospitalized. The treating physician initiated antibiotics on 10/10/06 and performed a resection of the fifth rib. This event was considered as possibly due to corticosteroid therapy and immunosuppression. On 10/25/06, the subject presented with elevated liver enzymes, which was associated with a diagnosis of probable cholestatic hepatitis due to the chronic use of drugs. In addition, Hepatitis C infection was diagnosed by serology test. On 1/10/07, the subject experienced a worsening of the skin lesions associated with skin infection and elevation of the liver enzymes. The subject was diagnosed with pyoderma gangrenous and was hospitalized. During the hospitalization, the treating physician considered the diagnosis of osteomyelitis and hepatitis due to medications (probably dapsone and fluconazole). Although all the hepatotoxic drugs were suspended, the liver enzymes did not recover. On --b(6)-, the subject experienced a shock without response to resuscitation maneuvers. In the subject's hospital chart, the cause of death was reported as acute respiratory failure following SAE of pyoderma gangrenous. Autopsy was not authorized by the subject's family.
Reviewer's Comment: This subject had a very complicated course, with reported inflammatory bowel disease (initially diagnosed as Crohn's but then changed to IBD) approximately 2 months after dose 3 of vaccine. The later episode of Stevens Johnson syndrome was apparently related to use of antibiotics to which she was allergic, as well as anaphylaxis related to IV contrast. Other conditions ensued with subsequent death. There was also a late diagnosis of Hepatitis C by serology (no information is provided on viral load determination). Although an association between the receipt of HPV vaccine and the development of IBD cannot be established with certainty, many of the other events appear to have occurred due to other agents.

Subject no. 76286 (HPV group): On 7/18/05, **five months after the second dose of HPV vaccine**, this 22-year-old subject was reported to be pregnant. The subject was exposed to the vaccine before conception. The subject's past medical history included one previous term pregnancy and two hydatidiform moles prior to vaccination, in 2002 and 2003. The subject did not seek any prenatal consultation. On3/29/06, based on her LMP, the subject had passed the estimated date of delivery, and considering her past medical history, a transvaginal ultrasound and beta-serum determination was recommended to rule out hydatidiform mole. Quantified human chorionic gonadotropin (HCG) was 248.9 mIU/mL. Doppler and transvaginal ultrasounds suggested **gestational trophoblastic tumor** in the posterior myometrium, probable invasive mole or choriocarcinoma. The subject was incompliant with the physician's recommendations for treatment and denied any further consultation. On 7/27/07, the subject started to experience back

and chest pain, haemoptysis and a palpable mass on left shoulder. On -b(6)-, the subject died at home due to respiratory failure. No autopsy was done. Final diagnosis was: **gestational trophoblastic neoplasia with probable pulmonary metastasis.**
Reviewer's Comment: This subject had a history of 2 prior hydatiform moles prior to vaccination. The gestational trophoblastic tumor was unlikely to be related to vaccination.

Subject no. 89479 (HPV group): On 12/26/07, **two years after the third dose of HPV vaccine**, this 27-year-old subject experienced headache and flu-like symptoms. The subject went to the emergency room on --b(6)-- and died later that night. It was unknown whether an autopsy was performed. The causes of death were **pneumococcal sepsis** and cardiorespiratory collapse. No further information was obtained.
Reviewer's Comment: It is unlikely that pneumococcal sepsis was related to vaccination.

HAV Group:
Subject no. 6726 (HAV group): On 10/12/05, **six months after the third HAV vaccine dose**, this 18-year-old subject developed a right thigh edema. A bone biopsy revealed **osteosarcoma.** The subject was treated with chemotherapy. Several imaging examinations, including CT pelvis scan, magnetic resonance imaging, chest X-ray costal arches. Because of these findings and no response to chemotherapy, amputation of the distal third of the femur was performed on 7/4/06. The subject's clinical status worsened, mainly the respiratory status, and the subject died on --b(6)--. The autopsy revealed osteosarcoma of the distal third of the right femur with lymphatic metastasis. Cause of death from the death certificate was: acute hypovolemia, bronchopneumonia and **metastatic osteosarcoma.**
Reviewer's Comment: It is unlikely that the osteogenic carcinoma was related to vaccination.

Subject no. 14290 (HAV group): This 20-year-old subject was found dead, **two years after the third dose of HAV vaccine**. According to a medico-legal autopsy, the reason of death was suicide.
Reviewer's Comment: It is unlikely that this event was related to vaccination.

Subject no. 16201 (HAV group): On --b(6)--, **three years after the third dose of HAV vaccine,** this 19-year-old subject died. The **cause of death is unknown**. An autopsy report cannot be released until after all forensic analyses are completed. Additional information is unknown at this time.
Reviewer's Comment: This subject died 3 years after dose 3 HAV. No cause was specified and it is difficult to link this death to vaccination.

Subject no. 18876 (HAV group): This subject had a maternal family history of diabetes mellitus. On 6/15/05, **15 days after the first dose of HAV vaccine,** she was diagnosed with **insulin-dependent diabetes mellitus.** The subject only received the first dose of HAV vaccine. On 11/1/05, six months after the first dose of HAV vaccine, this 25-year-old subject experienced malaise and dyspnea. She was hospitalized and was diagnosed with diabetic ketoacidosis. On 11/5/05, the subject's relatives decided to take her home against medical advice. On --b(6)--, the subject died at home. An autopsy was not performed.
Reviewer's Comment: The time between vaccination and diagnosis of IDDM was 15 days. There was a family history of diabetes mellitus and it was not noted whether she had symptoms prior to vaccination. The investigator assessed the event as unrelated to vaccination.

In addition, 22 fetal, neonatal or infant deaths were reported during this study. An summary of all events across studies is provided in the Overview of Safety, with tables in Appendix B.

The sponsor also provided a tabulation of SAEs which were assessed as related to vaccination by the investigator.

Table 177-Study HPV-008: Listing of Serious Adverse Events assessed by the investigator as related or possibly related to study vaccine (Total Vaccinated cohort)

Group	Sub. No.	Case Id	Age at onset (Year)	Verbatim	Preferred term	System Organ Class	Dose	Day of onset*	Duration (days)	Causality	Outcome
HPV	1520	A0562529A	24	Grand mal seizure	Grand mal convulsion	Nervous system disorders	1	7	1	Y	Recovered/ resolved
	2272	B0484180A	17	Chronic urticaria	Urticaria chronic	Skin and subcutaneous tissue disorders	3	586	.	Y	Not recovered/ not resolved
	5520	B0392625A	25	Erythema nodosum	Erythema nodosum	Skin and subcutaneous tissue disorders	2	31	75	Y	Recovered/ resolved
	5993	B0407813A	19	Epilepsy	Epilepsy	Nervous system disorders	3	1	.	Y	Recovering/ resolving
	6603	B0386506A	23	Acute thrombocytopenia	Thrombocytopenia	Blood and lymphatic system disorders	3	32	405	Y	Recovered/ resolved
	7847	B0395458A	23	Hepatitis a	Hepatitis A	Infections and infestations	3	70	16	Y	Recovered/ resolved
	13828	B0350206A	17	Migraine	Migraine	Nervous system disorders	2	13	148	Y	Recovered/ resolved
	19506	B0346460A	19	Diarrhea	Diarrhoea	Gastrointestinal disorders	1	0	8	Y	Recovered/ resolved
			19	Fever	Pyrexia	General disorders and administration site conditions	1	0	8	Y	Recovered/ resolved
	70805	B0492161A	19	Spontaneous abortion	Abortion spontaneous	Pregnancy, puerperium and perinatal conditions	3	78	1	Y	Recovered/ resolved
	71903	B0405036A	26	Anaphlactic shock	Anaphylactic shock	Immune system disorders	3	180	21	Y	Recovered/ resolved
			26	Stevens johnson syndrome	Stevens-Johnson syndrome	Skin and subcutaneous tissue disorders	3	180	21	Y	Recovered/ resolved
		B0405036C	26	Skin affection	Skin disorder	Skin and subcutaneous tissue disorders	3	261	.	Y	Not recovered/ not resolved
		B0405036D	26	Inflammatory bowel disease	Inflammatory bowel disease	Gastrointestinal disorders	3	72	.	Y	Not recovered/ not resolved
			27	Henoch schonlein purpura	Henoch-Schonlein purpura	Skin and subcutaneous tissue disorders	3	342	.	Y	Not recovered/ not resolved
		B0405036E	26	Diarrhea	Diarrhoea	Gastrointestinal disorders	3	157	.	Y	Not recovered/ not resolved
	76139	B0412787A	25	Spontaneous abortion	Abortion spontaneous	Pregnancy, puerperium and perinatal conditions	3	109	3	Y	Recovered/ resolved
HAV	4598	B0403561A	17	Missed abortion	Abortion missed	Pregnancy, puerperium and perinatal conditions	3	242	1	Y	Recovered/ resolved
	10876	B0381654A	25	Exacerbation of psoriasis	Psoriasis	Skin and subcutaneous tissue disorders	2	16	398	Y	Recovered/ resolved
	11126	B0348116A	21	Anaphylaxis	Anaphylactic reaction	Immune system disorders	1	0	2	Y	Recovered/ resolved
	13147	B0350207A	16	Headache	Headache	Nervous system disorders	1	0	6	Y	Recovered/ resolved
			16	High fever	Pyrexia	General disorders and administration site conditions	1	0	6	Y	Recovered/ resolved
	18579	B0440633A	22	Stillbirth	Stillbirth	Pregnancy, puerperium and perinatal conditions	3	288	4	Y	Recovered/ resolved
	76168	B0416342A	19	Spontaneous abortion	Abortion spontaneous	Pregnancy, puerperium and perinatal conditions	3	139	4	Y	Recovered/ resolved

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
* Number of days after last vaccine dose
Sub No. = Subject number
Case Id = Case identification
Source: STN 125259.48, CSR 008, Table 138, p. 481-482

A summary narrative of subjects for whom at least one SAE considered as possibly related to vaccination according to the investigator was reported, is provided.

HPV Group:
Subject no. 1520 (HPV group): This case concerns a 24-year-old subject with a current medical history of grand mal convulsions which was diagnosed during childhood, although she had not had seizures in over 15 years. The subject's treatment included semisodium valproate (Depakote) for seizures and mood disorder, lamotrigine (Lamictal) for seizures and fluoxetine for depression. The subject had decided to stop taking her anti-seizure medication the week of her first

vaccination with the investigational product without supervision from her neurologist or the investigators. This subject experienced a **grand mal convulsion** episode **seven days after the first dose of HPV vaccine.** The subject was treated with intravenous medication (unspecified) to stop the seizure and was kept under observation for approximately two hours. The subject withdrew from the study due to personal issues. Although the SAE was reported as possibly related to study vaccine, in the follow-up it was reported that "the cause of this event is presumed to be due to the fact that the subject stopped taking Lamictal. However, the small possibility that this event has a relationship to the study vaccine cannot be ruled out completely." This event was also considered to be possibly related with the subject's pre-existing seizure disorder.
Reviewer's Comment: It would appear that the seizure was possibly related to discontinuation of anti-seizure meds rather than vaccination.

Subject no. 2272 (HPV group): This case concerns a 17-year-old subject who developed **chronic urticaria 19 months after the third dose of HPV vaccine.** The subject was also complaining of abdominal pain and lymphadenopathy. She was hospitalized to evaluate possible autoimmune illness. The subject had a positive antinuclear antibody; ANA titer was 1:160. Etiology of the urticaria was unknown at the time of reporting. The subject was treated with prednisone. At the time of last follow up, the subject still had fatigue and developed a food allergy to fish and nuts. The subject had elevated thyroglobulin antibodies, but was stable and doing well. The event was unresolved at time of reporting.
Reviewer's Comment: The chronic urticaria developed 19 months after dose 3 which appears be a rather long interval between vaccination and event.

Subject no. 5520 (HPV group): This case concerns a 25-year-old subject who experienced **erythema nodosum, 31 days after the second dose of HPV vaccine**. The subject's medical history included tonsillitis which was treated with amoxicillin and nimesulide one month before the event occurred. The subject was taking oral contraceptives at the time the event occurred. The subject developed erythematous cutaneous lesions and local pain in the left leg, was diagnosed with phlebitis and treated with drosperidone and mesulide. The symptoms worsened and she received antibiotic treatment. She was evaluated by the vascular surgeon who excluded phlebitis and deep venous thrombosis and considered a possible diagnosis of cellulitis. Following a negative blood test, and since there was no fever, treatment was suspended and the diagnosis of erythema nodosum was made. On follow-up, the subject reported that the symptoms and clinical signs of erythema nodosum in her legs had resolved after approximately 10 weeks. Three months after the first episode, the subject developed sinusitis, which was treated with amoxicillin. On the third day of treatment with amoxicillin, she developed mild erythematous lesions on her legs. The event resolved when amoxicillin was stopped. Thus, the most likely cause of erythema nodosum was considered to be amoxicillin. However, the investigator considered also that there was reasonable possibility that this event may have been caused by the vaccine or the oral contraceptive.
Reviewer's Comment: The event was possibly related to vaccination, but may also been related to antibiotic, in view of the recurrence of the EN after a second course of antibiotics.

Subject no. 5993 (HPV group): This case concerns a 19-year-old subject who was diagnosed with an **epileptic crisis, one day after the third dose of HPV vaccine.** She had no history of convulsive crisis or cranial trauma in the past but had occasionally consumed cannabis and chloroform (once or twice a year). The subject experienced three episodes of convulsive crisis within a period of one week. She was treated with carbamazepine. Six weeks later, the subject was still on carbamazepine and had not experienced further crisis. Electroencephalography was reported as normal.

Reviewer's Comment: An association between the event and vaccination cannot be determined with certainty.

Subject no. 6603 (HPV group): This case concerns a 22-year-old subject who experienced **acute thrombocytopenia 32 days after the third dose of HPV vaccine.** The subject experienced vaginal and gingival bleeding, and signs of bleeding in the skin (petechiae) were noted. The subject had no recent history of viral infection, but had a **history of idiopathic thrombocytopenia diagnosed in her first week of life.** Relevant laboratory results showed a platelet count of 3000, anemia, leukopenia and an antinuclear antibody titer of 1:1024. She received platelet and immunoglobulin transfusions and 12 days later left the hospital free of symptoms and with a platelet count of 56000. Seven days after discharge the subject again experienced mouth and nasal bleeding and her platelet count was 2000. She was treated with dexamethasone and was discharged without symptoms on continuing dexamethasone treatment. Diagnosis was confirmed as acute thrombocytopenia. The subject was evaluated by a rheumatologist who established as the final diagnosis incomplete systemic lupus erythematosus (SLE), since the subject met two of the five diagnostic criteria for SLE. The subject started treatment with chloroquine and is in good general health status. Eighty-three days after the onset of symptoms the platelet count was 196000. At the time of last follow up, the subject reported to be free of symptoms. The investigator considered that there was a reasonable possibility that this event may have been caused by the investigational product, but also considered the acute thrombocytopenia to be secondary to the systemic lupus erythematosus.
Reviewer's Comment: Thrombocytopenia occurred 32 days after dose 3. This subject also had a history of thrombocytopenia as an infant, although that event may have been related to an acute illness. This subject had a positive ANA and was diagnosed with lupus.

Subject no. 7847 (HPV group): This case concerns a 23-year-old subject who experienced **Hepatitis A infection 71 days after receiving the third dose of HPV** vaccine. The subject developed pruritus, vomiting and weight loss. Relevant tests included increase of transaminases and bilirubin and Hepatitis A antigen positive. The event resolved.
Reviewer's Comment: It appears unlikely that an acute case of hepatitis A disease was related to vaccination with HPV vaccine.

Subject no. 13828 (HPV group): This case concerns a 17-year-old subject with history of psychological disorder. Subject experienced "neurological symptoms" described as vertigo, paresthesia, slurred speech, blurred vision, and headache **13 days after the second dose of HPV vaccine.** In the first episode, the vertigo lasted for more than one hour. The symptoms subsequently recurred but with milder intensity. During a period of one month, the subject experienced frequent right unilateral headaches. Based on the symptoms and a family history of epilepsy (mother), epilepsy was suspected. Results from laboratory tests, neurological examination and brain Magnetic Resonance Imaging were normal. The events resolved after 148 days. The neurologist's final diagnosis was **migraine.** The investigator considered that there was a reasonable possibility that the migraine may be related to the study vaccine, but also considered that the migraine might be associated with an underlying medical condition.
Reviewer's Comment: This event occurred 13 days after receipt of dose 2 and may have been related to vaccination, but may have also been related to an underlying condition present prior to vaccination.

Subject no. 19506 (HPV group): This case concerns a 19-year-old subject who developed fever, diarrhea and fatigue during the **night following administration of the first dose of HPV vaccine.** She was hospitalized and diagnosed as having **fever and diarrhea**. The subject was treated with paracetamol, domperidone (Motilium) and ofloxacin (Tarivid). Stool test was

recommended but subsequently not performed since the diarrhea has ceased. The events resolved after eight days.
Reviewer's Comment: The diarrhea and fever may have also been related to an intercurrent gastroenteritis.

Subject no. 70805 (HPV group): This case concerns a 19-year-old subject who received the first, second and third dose of HPV vaccine on 4/18/05, 5/9/05, and 9/26/05. The subject used Ortho Tri-Cyclen Lo as contraception method (inconsistent use). Her LMP occurred on 9/19/05. On -b(6)-, **78 days after the third dose of HPV vaccine,** this 19-year-old subject developed **spontaneous abortion after 12 weeks** and 2 days of pregnancy by LMP. The subject was exposed to the vaccine during the first trimester of pregnancy. The subject was treated with dilation and curettage. Pathological report stated tissue mixed with clotted blood; no gross evidence of fetal or placental tissue. The event resolved on 12/13/05.
Reviewer's Comment: This spontaneous abortion occurred in a subjects who was vaccinated 1 week after her LMP, and the event was possibly related to vaccination. (See discussion regarding spontaneous abortions in overall safety.)

Subject no. 76139 (HPV group): This case concerns a 26-year-old subject with a past medical history of two full-term pregnancies. On 3/31/05, 4/28/05, and 9/22/05, the subject received the first, second and third dose of HPV vaccine. On 12/2/05, the subject had a positive urine pregnancy test. Her LMP occurred on 10/17/05 (slightly < 4 weeks after dose 3). The subject was exposed to the vaccine before conception. On –b(6)--, **109 days after the third dose of HPV** vaccine, the subject experienced vaginal spotting after 12 weeks of pregnancy which progressed to vaginal bleeding that lasted for three days. The subject had a **spontaneous abortion.** No medical consultation was done; however, she self-medicated with amoxicillin trihydrate. When the subject experienced vaginal bleeding, she saw blood clots and white spongy tissue which may represent a decidual cast. No gestational sac nor embryo was identified. The investigator considered that there was a reasonable possibility that the spontaneous abortion may have been caused by the study vaccine as the subject did not have any other medical condition that may have caused the event, as she had not taken any other medication apart from the study vaccine and as she had no previous history of abortion. The event resolved on 1/11/06.
Reviewer's Comment: This subject's LMP was < 4 weeks after dose 3, and she subsequently experienced a spontaneous abortion. The event was considered possibly related to vaccination. (Please see overall safety section for discussion on spontaneous abortions which occurred in pregnancies with onsets around the time of vaccination.)

HAV Group:
Subject no. 4598 (HAV group): This case concerns a 17-year-old subject who received the first, second and third vaccine dose on 12/9/04, 1/13/05, and 6/6/05. On 12/9/05, **six months after the third vaccine dose, the subject was reported to be pregnant.** The subject smoked 10-15 cigarettes per day during her pregnancy and was treated with Diclectin from 2005 until 2/3/06 for nausea. Depo-Provera injections were used as contraception method (last injection was given in August 2005). Her LMP occurred on 10/21/05. The subject was exposed to the vaccine before conception. On 2/3/06, **eight months after the third vaccine dose**, the subject went to the emergency room with lower abdominal pain, cramping and vaginal bleeding. An ultrasound antenatal screen revealed a fetal pole consistent with eight weeks and four days in size with a negative heart beat. A diagnosis of **missed abortion** was made. Dilation and curettage were performed by the local obstetrician/gynecologist. Oxytocin infusion was given intravenously. The event resolved on 2/3/06. No post-treatment problems were observed.
Reviewer's Comment: This subject became pregnant approximately 6 months after dose 3 and experienced a spontaneous abortion 2 months later.

Subject no. 10876 (HAV group): This case concerns a 25-year-old subject who experienced an **exacerbation of psoriasis 16 days after receiving the second dose of HAV vaccine.** The subject's relevant previous medical history included psoriasis diagnosed seven years ago. The subject experienced an episode of throat infection (throat culture was not performed) three days before the psoriasis exacerbation. The subject developed red spots on palms, wrist and elbows with rapid exacerbation and extensive generalization of lesions. These lesions caused moderate to intensive pruritus. After evaluation by a dermatologist and receiving treatment, the subject recovered from the exacerbation of psoriasis. The investigator considered this event to be possibly related to vaccination or to the subject's previous throat infection.
Reviewer's Comment: As noted, the exacerbation of the subject's psoriasis was possibly related to infection or to vaccination.

Subject no. 11126 (HAV group): This case concerns a 21-year-old subject who developed **urticaria and collapsed to the floor several minutes after the first dose of HAV vaccine.** The subject did not develop shock, and did not experience bronchospasm or angioedema. She was tachycardic (120 bpm). Blood pressure was within normal limits. The subject was diagnosed as having anaphylaxis. The subject was treated with adrenaline and oxygen and was taken to the ER where she was recovering approximately one hour later. The event resolved.
Reviewer's Comment: This subject experienced a probable allergic reaction to HAV vaccine.

Subject no. 13147 (HAV group): This case concerns a 16-year-old subject who experienced pyrexia and headache a **few hours after the first dose of HAV vaccine**. The subject went to the hospital ER and received Paracetamol. The subject returned home after 12 hours of observation. She subsequently developed urticaria and muscular pain. The events resolved after six days. On follow up evaluation, the urticaria had disappeared, she was in good condition but had cough, itching in the throat and enlarged lymph nodes in the neck. The subject had this cough for three weeks prior to the study entry but had not informed study personnel. Two weeks later, she was in good health condition. The investigator considered that the **fever and headache** could be related to the investigational product, or to incidental illness.
Reviewer's Comment: This event may have been related to vaccination or to intercurrent illness.

Subject no. 18579 (HAV group): This case concerns a 22-year-old subject whose past medical history included one full-term pregnancy with normal birth. On 4/29/05, 5/26/05, and 10/11/05, the subject received the first, second and third vaccine dose. The subject used Marvelon as contraception method. Her LMP occurred on 1/21/06. The subject was exposed to the vaccine before conception. On --b(6)--, **nine months after the third vaccine dose** and after 26 weeks of pregnancy, the subject experienced a **stillbirth**. On the same day, she noticed absence of fetal movements and went to the hospital. No other associated symptoms such as abdominal tightening or vaginal bleeding were observed. A pelvic ultrasound revealed a gestational age of 26 weeks and fetal death in utero. Labor was induced with intravaginal misoprostol. On ---------b(6)--, she eventually delivered via spontaneous vaginal delivery, after b(6) days of induction, to a dead baby boy, macerated stillbirth. No fetal autopsy was performed. The event resolved on 29 July 2006. On the same day, she was discharged with mefenamic acid and cloxacillin sodium. At the time of reporting, the subject was in stable conditions.
Reviewer's Comment: This subject became pregnant approximately 3 months after dose 3, and the pregnancy ended in a stillbirth.

Subject no. 76168 (HAV group): This case concerns a 19-year-old subject whose past medical history included two full-term pregnancies with normal birth. The subject is a smoker (0.96 pack/year) with a family history of diabetes mellitus at the subject's paternal side (grandmother). The father has a family history of hypertension. On 4/28/05, 5/26/05, and 10/21/05, the subject

received the first, second and third vaccine dose. The subject had her LMP on 12/10/05. No contraception method was used. She presumed that she was pregnant. There were no other associated signs and symptoms reported until 3/7/06, when she sought consultation at the local health center. Blood pressure at that time was 90/60 mmHG. She was given ferrous sulfate. On3/9/06, **five months after the third vaccine dose and 13 weeks of pregnancy by LMP,** the subject experienced vaginal spotting with no other associated symptoms. On 3/10/06, spotting progressed to bleeding (subject did not seek medical care). On 3/11/06, she started to experience vaginal bleeding with hypogastric pain. On --b(6)--, she underwent completion curettage. She was discharged the same day with minimal bleeding. The subject was treated with methylergometrine maleate for uterine contraction and uterotonic, ferrous sulfate and ascorbic acid. The event resolved on --b(6)--. At the time of reporting, she was asymptomatic and the pelvic examination was grossly normal. The investigator considered that there was a reasonable possibility that the **spontaneous abortion** may have been caused by investigational product because of the temporal relationship between the last dose and the subject's last normal menstrual period, which is 50 days. Though there are many other factors such as presence of diabetes and hypertension in the family, smoking history and multigravidity at the age of 20, with an exposure to vaccine during the early/critical age of gestation, the investigator cannot totally rule out the possibility of its association.
Reviewer's Comment: This subject became pregnant < 2 months after receipt of dose 3 of vaccine, and subsequently experienced a spontaneous abortion.

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study: At the time of the final analysis, a total of eight non-serious AEs leading to premature discontinuation of the study were reported, of which five in the HPV group and three in the HAV group.

Table 178-Study HPV-008: Non-serious AEs which led to premature discontinuation from study [CBER generated]

Case number	Event (treatment, possible etiology)	Time to Event
HPV		
586	Dry skin	9 days after dose 1
2740	Headache (possibly related)	Day of dose 1
11600	Acne	18 days after dose 1
17037	Nausea	17 days after dose 1
76264	Ovarian cyst	1 month after dose 1
HAV		
3190	Hypoaesthesia	12 days after dose 1
10302	Facial pain	Day of dose 1
8959	Gastroenteritis	*Before vaccination*

In addition, 12 subjects died as a result of a road traffic accident (three subjects), suicide (two subjects), homicide, bone sarcoma, diabetic ketoacidosis, sepsis, gestational trophoblastic tumour and metastases to lung, pneumococcal sepsis and cardiopulmonary failure, or cause not specified. None of these SAEs were assessed as possibly related to vaccination according to the investigator. The sponsor notes that five case fatalities were not included in the withdrawals due to SAEs as the Study Conclusion page of the subjects' eCRF was not yet completed at the time of database freeze for the final analysis. These events included deep vein thrombosis (Subject no. 17678), subarachnoid hemorrhage (Subject no. 22586), pyoderma gangrenosum (Subject no. 71903) and road traffic accident (Subject no. 76544) in the HPV group and homicide (Subject no. 70443) in the HAV group.

Table 179-Study HPV-008: Listing of Serious Adverse Events leading to premature discontinuation of study vaccine and/or study (Total Vaccinated cohort)

Group	Sub. No.	Case Id	Age at onset (Year)	Verbatim	Preferred term	System Organ Class	Dose	Day of onset*	Duration (days)	Causality	Outcome
HPV	8746	B0435108A	23	Deceased apparently drowned	Drowning	General disorders and administration site conditions	3	217	1	N	Fatal
			23	Murdered	Homicide	Social circumstances	3	217	1	N	Fatal
	18105	B0457152A	21	Gun shot wound to head	Gun shot wound	Injury, poisoning and procedural complications	3	686	1	N	Fatal
	18389	B0386140A	23	Abortion spontaneous complete	Abortion spontaneous complete	Pregnancy, puerperium and perinatal conditions	1	142	2	N	Recovered/ resolved
	20945	B0474261A	21	Septicemia	Sepsis	Infections and infestations	3	758	4	N	Fatal
	22364	B0382729A	25	Dermatological infection on face	Skin infection	Infections and infestations	2	1	13	N	Recovered/ resolved
	76286	B0389032A	22	Gestational trophoblastic tumour	Gestational trophoblastic tumour	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	151	786	N	Fatal
			24	Possible lung metastasis	Metastases to lung	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	889	48	N	Fatal
	89479	B0517289A	27	Cardio-respiratory collapse	Cardiopulmonary failure	Cardiac disorders	3	770	1	N	Fatal
			27	Pneumococcal sepsis	Pneumococcal sepsis	Infections and infestations	3	770	1	N	Fatal
HAV	1899	B0404036A	20	Automobile accident	Road traffic accident	Injury, poisoning and procedural complications	3	30	1	N	Fatal
	3365	B0405860A	16	Motor vehicle accident	Road traffic accident	Injury, poisoning and procedural complications	3	239	.	N	Not recovered/ not resolved
	6054	B0444101A	18	Automobile accident	Road traffic accident	Injury, poisoning and procedural complications	3	317	1	N	Fatal
	6726	B0399114A	18	Osteosarcoma	Bone sarcoma	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	165	335	N	Fatal
	14290	B0496456A	20	Suicide	Completed suicide	Psychiatric disorders	3	817	1	N	Fatal
	16201	B0510451A	19	Death-unknown cause	Death	General disorders and administration site conditions	3	817	1	N	Fatal
	16505	B0381211A	20	Motor vehicle accident	Road traffic accident	Injury, poisoning and procedural complications	2	101	1	N	Fatal
	18876	B0406806A	25	Diabetic ketoacidosis	Diabetic ketoacidosis	Metabolism and nutrition disorders	1	154	7	N	Fatal

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
* Number of days after last vaccine dose
Sub No. = Subject number
Case Id = Case identification
Note: Five case fatalities were not included in the withdrawals due to SAEs as the Study Conclusion page of the subjects' eCRF was not yet completed at the time of database freeze for the final analysis, i.e. deep vein thrombosis (Subject no. 17678), subarachnoid haemorrhage (Subject no. 22586), pyoderma gangrenosum (Subject no. 71903) and road traffic accident (Subject no. 76544) in the HPV group and homicide (Subject no. 70443) in the HAV group.
Source: STN 125259.48, CSR 008, Table 139, p. 483-484

New Onset Chronic Diseases: Overall, the number of subjects experiencing an NOCD (as assessed by GSK) was similar in the HPV and HAV groups: 251 (2.7%) and 268 (2.9%) subjects, respectively.

Table 180-Study HPV-008: Percentage of subjects reporting New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term during the entire follow-up period (Total Vaccinated cohort)

		HPV N = 9319				HAV N = 9325			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		251	2.7	2.4	3.0	268	2.9	2.5	3.2
Blood and lymphatic system disorders (10005329)	Idiopathic thrombocytopenic purpura (10021245)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Thrombocytopenia (10043554)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	4	0.0	0.0	0.1	3	0.0	0.0	0.1
	Basedow's disease (10004161)	3	0.0	0.0	0.1	2	0.0	0.0	0.1
	Goitre (10018498)	3	0.0	0.0	0.1	7	0.1	0.0	0.2
	Hyperthyroidism (10020850)	4	0.0	0.0	0.1	3	0.0	0.0	0.1
	Hypothyroidism (10021114)	19	0.2	0.1	0.3	20	0.2	0.1	0.3
	Thyroiditis (10043778)	2	0.0	0.0	0.1	0	0.0	0.0	0.0
Eye disorders (10015919)	Blepharitis allergic (10005149)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Conjunctivitis allergic (10010744)	5	0.1	0.0	0.1	2	0.0	0.0	0.1
Gastrointestinal disorders (10017947)	Coeliac disease (10009839)	2	0.0	0.0	0.1	5	0.1	0.0	0.1
	Colitis ulcerative (10009900)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
	Crohn's disease (10011401)	2	0.0	0.0	0.1	2	0.0	0.0	0.1
	Inflammatory bowel disease (10021972)	1	0.0	0.0	0.1	1	0.0	0.0	0.1
	Proctitis ulcerative (10036783)	2	0.0	0.0	0.1	0	0.0	0.0	0.0
	Rectal haemorrhage (10038063)	3	0.0	0.0	0.1	3	0.0	0.0	0.1
General disorders and administration site conditions (10018065)	Injection site anaesthesia (10022046)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Injection site urticaria (10022107)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
Immune system disorders (10021428)	Allergy to animal (10001742)	2	0.0	0.0	0.1	2	0.0	0.0	0.1
	Allergy to arthropod bite (10058285)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
	Allergy to arthropod sting (10058284)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
	Anaphylactic reaction (10002198)	0	0.0	0.0	0.0	2	0.0	0.0	0.1
	Anaphylactic shock (10002199)	2	0.0	0.0	0.1	0	0.0	0.0	0.0
	Atopy (10003645)	1	0.0	0.0	0.1	4	0.0	0.0	0.1
	Drug hypersensitivity (10013700)	8	0.1	0.0	0.2	11	0.1	0.1	0.2
	Food allergy (10016946)	3	0.0	0.0	0.1	3	0.0	0.0	0.1
	Hypersensitivity (10020751)	20	0.2	0.1	0.3	28	0.3	0.2	0.4
	Latex allergy (10056435)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Multiple allergies (10028164)	0	0.0	0.0	0.0	4	0.0	0.0	0.1
	Reaction to drug excipients (10064787)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Seasonal allergy (10048908)	7	0.1	0.0	0.2	15	0.2	0.1	0.3
Infections and infestations (10021881)	Acquired immunodeficiency syndrome (10000565)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Hiv infection (10020161)	0	0.0	0.0	0.0	3	0.0	0.0	0.1
Investigations (10022891)	Blood creatinine increased (10005483)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
Metabolism and nutrition disorders (10027433)	Diabetes mellitus (10012601)	3	0.0	0.0	0.1	5	0.1	0.0	0.1
	Gestational diabetes (10018209)	1	0.0	0.0	0.1	1	0.0	0.0	0.1

Table 180-Study HPV-008: Percentage of subjects reporting New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term during the entire follow-up period (Total Vaccinated cohort) [CONT]

		HPV N = 9319				HAV N = 9325			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
	Glucose tolerance impaired (10018429)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Hypoglycaemia (10020993)	1	0.0	0.0	0.1	1	0.0	0.0	0.1
	Type 1 diabetes mellitus (10067584)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Type 2 diabetes mellitus (10067585)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
Musculoskeletal and connective tissue disorders (10028395)	Arthritis (10003246)	3	0.0	0.0	0.1	4	0.0	0.0	0.1
	Arthritis reactive (10003267)	3	0.0	0.0	0.1	0	0.0	0.0	0.0
	Psoriatic arthropathy (10037162)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Rheumatoid arthritis (10039073)	4	0.0	0.0	0.1	2	0.0	0.0	0.1
	Systemic lupus erythematosus (10042945)	2	0.0	0.0	0.1	2	0.0	0.0	0.1
Nervous system disorders (10029205)	Multiple sclerosis (10028245)	3	0.0	0.0	0.1	1	0.0	0.0	0.1
	Myelitis transverse (10028527)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Optic neuritis (10030942)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
	Optic neuritis retrobulbar (10030945)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Paraesthesia (10033775)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
Renal and urinary disorders (10038359)	Haematuria (10018867)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
	Proteinuria (10037032)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Urinary retention (10046555)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
Respiratory, thoracic and mediastinal disorders (10038738)	Allergic bronchitis (10052613)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Allergic cough (10053779)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Allergic sinusitis (10049153)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Asthma (10003553)	36	0.4	0.3	0.5	37	0.4	0.3	0.5
	Asthma exercise induced (10003557)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Asthmatic crisis (10064823)	1	0.0	0.0	0.1	2	0.0	0.0	0.1
	Bronchospasm (10006482)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
	Rhinitis allergic (10039085)	10	0.1	0.1	0.2	7	0.1	0.0	0.2
	Rhinitis seasonal (10039095)	1	0.0	0.0	0.1	1	0.0	0.0	0.1
Skin and subcutaneous tissue disorders (10040785)	Angioedema (10002424)	1	0.0	0.0	0.1	1	0.0	0.0	0.1
	Cutaneous lupus erythematosus (10056509)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Dermatitis allergic (10012434)	13	0.1	0.1	0.2	13	0.1	0.1	0.2
	Dermatitis atopic (10012438)	6	0.1	0.0	0.1	10	0.1	0.1	0.2
	Dermatitis contact (10012442)	3	0.0	0.0	0.1	9	0.1	0.0	0.2
	Dermatomyositis (10012503)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Drug eruption (10013687)	0	0.0	0.0	0.0	2	0.0	0.0	0.1
	Eczema (10014184)	5	0.1	0.0	0.1	0	0.0	0.0	0.0
	Erythema nodosum (10015226)	3	0.0	0.0	0.1	0	0.0	0.0	0.0
	Guttate psoriasis (10018797)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Henoch-schonlein purpura (10019617)	3	0.0	0.0	0.1	0	0.0	0.0	0.0
	Idiopathic urticaria (10021247)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Leukocytoclastic vasculitis (10024377)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Nail psoriasis (10028703)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Psoriasis (10037153)	7	0.1	0.0	0.2	6	0.1	0.0	0.1
	Skin reaction (10040914)	1	0.0	0.0	0.1	1	0.0	0.0	0.1

Table 180-Study HPV-008: Percentage of subjects reporting New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term during the entire follow-up period (Total Vaccinated cohort) [CONT]

		HPV N = 9319				HAV N = 9325			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
	Stevens-johnson syndrome (10042033)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Toxic skin eruption (10057970)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Urticaria (10046735)	28	0.3	0.2	0.4	22	0.2	0.1	0.4
	Urticaria cholinergic (10046740)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Urticaria chronic (10052568)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Urticaria physical (10046751)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Urticaria thermal (10061399)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Vitiligo (10047642)	1	0.0	0.0	0.1	2	0.0	0.0	0.1
Vascular disorders (10047065)	Raynaud's phenomenon (10037912)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Vasculitis (10047115)	0	0.0	0.0	0.0	3	0.0	0.0	0.1

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, CSR 008, Table 118, p. 408-410

The most common NOCDs were asthma, urticaria, hypersensitivity, hypothyroidism and seasonal allergy, all of which were reported with a similarly low incidence in both groups:

- Asthma was reported in 36 (0.4%) and 37 (0.4%) subjects in the HPV and HAV groups, respectively.
- Urticaria was reported in 28 (0.3%) and 22 (0.2%) subjects in the HPV and HAV groups, respectively.
- Hypersensitivity was reported in 20 (0.2%) and 28 (0.3%) subjects in the HPV and HAV groups, respectively.
- Hypothyroidism was reported in 19 and 20 subjects in the HPV and HAV groups, respectively (0.2% each).
- Seasonal allergy was reported in seven (0.1%) and 15 (0.2%) subjects in the HPV and HAV groups, respectively.

A similar incidence of NOCDs (as assessed by GSK) was observed for subjects who were seropositive and/or DNA positive for either HPV-16 or HPV-18 at baseline, seronegative and DNA negative for HPV-16 and HPV-18 at baseline, or DNA positive for either HPV-16 or HPV-18 at baseline.

Table 181-Study HPV-008: Overview of the incidence of New Onset Chronic Diseases (GSK assessment) reported during the entire follow-up period in subgroups by baseline seropositivity and/or DNA positivity status (Total Vaccinated cohort)

	HPV					HAV				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Total Vaccinated cohort	9319	251	2.7	2.4	3.0	9325	268	2.9	2.5	3.2
Vaccinated seropositive and/or DNA positive cohort	2409	67	2.8	2.2	3.5	2419	67	2.8	2.2	3.5
Vaccinated seronegative and DNA negative cohort	6802	180	2.6	2.3	3.1	6788	198	2.9	2.5	3.3
Vaccinated DNA positive cohort	690	21	3.0	1.9	4.6	649	21	3.2	2.0	4.9

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, CSR 008, Table 119, p. 411

Reviewer's Comment: The tables with preferred terms were reviewed and there was no apparent difference in the pattern of NOCDs. (Source: STN 125259.48, CSR 008, Supplement 340 and 341, p. 10678-10682)

New Onset Autoimmune Diseases: Overall, the number of subjects experiencing an NOAD (as assessed by GSK) was similar in the HPV and HAV groups: 78 (0.8%) and 77 (0.8%) subjects, respectively. The most frequently reported NOAD was hypothyroidism, reported in 19 and 20 subjects in the HPV and HAV groups, respectively (0.2% each). The other autoimmune disorders represented a range of disorders involving different body systems with no obvious pattern of events observed in either group.

Table 182-Study HPV-008: Percentage of subjects with New Onset Autoimmune Diseases classified by MedDRA Primary System Organ Class and Preferred Term during the entire follow-up period (Total Vaccinated cohort)

		HPV N = 9319				HAV N = 9325			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		78	0.8	0.7	1.0	77	0.8	0.7	1.0
Blood and lymphatic system disorders (10005329)	Idiopathic thrombocytopenic purpura (10021245)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Thrombocytopenia (10043554)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	4	0.0	0.0	0.1	3	0.0	0.0	0.1
	Basedow's disease (10004161)	3	0.0	0.0	0.1	2	0.0	0.0	0.1
	Goitre (10018498)	3	0.0	0.0	0.1	7	0.1	0.0	0.2
	Hyperthyroidism (10020850)	4	0.0	0.0	0.1	3	0.0	0.0	0.1
	Hypothyroidism (10021114)	19	0.2	0.1	0.3	20	0.2	0.1	0.3
	Thyroiditis (10043778)	2	0.0	0.0	0.1	0	0.0	0.0	0.0
Gastrointestinal disorders (10017947)	Coeliac disease (10009839)	2	0.0	0.0	0.1	5	0.1	0.0	0.1
	Colitis ulcerative (10009900)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
	Crohn's disease (10011401)	2	0.0	0.0	0.1	2	0.0	0.0	0.1
	Inflammatory bowel disease (10021972)	1	0.0	0.0	0.1	1	0.0	0.0	0.1
	Proctitis ulcerative (10036783)	2	0.0	0.0	0.1	0	0.0	0.0	0.0
Metabolism and nutrition disorders (10027433)	Diabetes mellitus (10012601)	3	0.0	0.0	0.1	5	0.1	0.0	0.1
	Type 1 diabetes mellitus (10067584)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
Musculoskeletal and connective tissue disorders (10028395)	Arthritis (10003246)	3	0.0	0.0	0.1	4	0.0	0.0	0.1
	Arthritis reactive (10003267)	3	0.0	0.0	0.1	0	0.0	0.0	0.0
	Psoriatic arthropathy (10037162)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Rheumatoid arthritis (10039073)	4	0.0	0.0	0.1	2	0.0	0.0	0.1
	Systemic lupus erythematosus (10042945)	2	0.0	0.0	0.1	2	0.0	0.0	0.1
Nervous system disorders (10029205)	Multiple sclerosis (10028245)	3	0.0	0.0	0.1	1	0.0	0.0	0.1
	Myelitis transverse (10028527)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Optic neuritis (10030942)	2	0.0	0.0	0.1	1	0.0	0.0	0.1
	Optic neuritis retrobulbar (10030945)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
Skin and subcutaneous tissue disorders (10040785)	Cutaneous lupus erythematosus (10056509)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Dermatomyositis (10012503)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Erythema nodosum (10015226)	3	0.0	0.0	0.1	0	0.0	0.0	0.0
	Guttate psoriasis (10018797)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Leukocytoclastic vasculitis (10024377)	1	0.0	0.0	0.1	0	0.0	0.0	0.0
	Nail psoriasis (10028703)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Psoriasis (10037153)	7	0.1	0.0	0.2	6	0.1	0.0	0.1
	Vitiligo (10047642)	1	0.0	0.0	0.1	2	0.0	0.0	0.1
Vascular disorders (10047065)	Raynaud's phenomenon (10037912)	0	0.0	0.0	0.0	1	0.0	0.0	0.1
	Vasculitis (10047115)	0	0.0	0.0	0.0	3	0.0	0.0	0.1

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, CSR 008, Table 120, p. 412

Reviewer's Comment: In review of the incidence of new onset autoimmune diseases, the overall numbers of cases and proportions of subjects with such a diagnosis in each group were

comparable. For some events (e.g., reactive arthritis and neuroinflammatory events), there was a slight imbalance. Given that this vaccine contains a novel adjuvant, CBER requested additional analyses and assessments be provided. These analyses and a full discussion of these events are included in the Overview of Safety in this review. These events will be studied in a large Managed Care Oragnization in the post-marketing period.

Medically significant conditions: Overall, medically significant conditions were reported in a similar percentage of subjects in the HPV and HAV groups: 31.8% and 32.4%, respectively. The most common medically significant conditions were gynecological Chlamydia infection, genito-urinary tract gonococcal infection and depression, all of which were reported in similar percentages of subjects in the HPV and HAV groups:

- Gynecological chlamydia infection was reported in 911 (9.8%) subjects in the HPV group and 957 (10.3%) subjects in the HAV group.
- Genito-urinary tract gonococcal infection was reported in 144 (1.5%) subjects in the HPV group and 162 (1.7%) subjects in the HAV group.
- Depression was reported in 142 (1.5%) subjects in the HPV group and 137 (1.5%) subjects in the HAV group.

The sponsor attributes the high incidence of gynecological chlamydia infection and genito-urinary tract gonococcal infection was expected as *Chlamydia trachomatis* and *Neisseria gonorrhea* testing was included in the study procedures on a yearly basis.

The incidence of other medically significant conditions was low (<1% of subjects in any group). The CIs for individual events were extremely narrow because of the large sample size. Although CIs did not overlap between the two groups for several events, these differences are not considered to be medically meaningful. The sponsor also provided these medically significant adverse events by high level term. In review of that table, 95% CIs around the incidence rates overlap (Source: STN 125259.0048, CSR 008, Supplement 344, p. 10687-10705, not shown here).

The observed incidence of medically significant conditions was lower for subjects who were seronegative and DNA negative for HPV-16 and HPV-18 at baseline compared to subjects who were DNA positive for either HPV-16 or HPV-18 at baseline. This trend was observed in both HPV and HAV groups. It appears that to a large degree, this higher rate of events in the group of subjects who were DNA positive for either HPV-16 or HPV-18 at baseline is related to the higher rates of gynecological chlamydia infection (15.2% in the HPV group and 14.6% in the HAV group in the vaccinated DNA positive cohort compared to 8.9% in the HPV group and 9.6% in the HAV group in the vaccinated seronegative and DNA negative cohort). No difference in the pattern of medically significant conditions was observed between the HPV and HAV groups in the vaccinated DNA positive cohort.

Table 183-Study HPV-008: Overview of the incidence of medically significant conditions reported during the entire follow-up period in subgroups by baseline seropositivity and/or DNA positivity status (Total Vaccinated cohort)

	HPV					HAV				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Total Vaccinated cohort	9319	2960	31.8	30.8	32.7	9325	3025	32.4	31.5	33.4
Vaccinated seropositive and/or DNA positive cohort	2409	877	36.4	34.5	38.4	2419	865	35.8	33.8	37.7
Vaccinated seronegative and DNA negative cohort	6802	2046	30.1	29.0	31.2	6788	2124	31.3	30.2	32.4
Vaccinated DNA positive cohort	690	274	39.7	36.0	43.5	649	261	40.2	36.4	44.1

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, CSR 008, Table 122, p. 439

Pregnancies

Data on overall reported pregnancies and pregnancy outcomes (Table 184): During the entire follow-up period, 3606 pregnancies were reported (1804 in the HPV group and 1802 in the HAV group) for 3091 subjects (1538 in the HPV group and 1553 in the HAV group). The mean age of subjects with pregnancies was 21.1 years. No differences between the HPV and HAV groups were observed for any of the characteristics, including smoking status, *Chlamydia trachomatis* infection or HPV-16/18 infection at baseline. While the majority of subjects in the Total Vaccinated cohort were of Caucasian or East/South East Asian origin, the majority of subjects with pregnancies were enrolled in the Asia Pacific and Latin American regions (49.9% and 19.5%, respectively). Also, when compared to the Total Vaccinated cohort, a higher percentage of subjects with pregnancies was positive for *Chlamydia trachomatis* (9.0% versus 5.5%) and was HPV-16/18 DNA negative and seropositive at baseline (17.2% versus 13.9% for HPV-16 and 12.5% versus 10.6% for HPV-18). During the entire follow-up period, no major differences in the rates of any specific pregnancy outcome were observed between the HPV and HAV groups. The overall rate of spontaneous abortion was 8.9%. The number of spontaneous abortions was 164 in the HPV group and 156 in the HAV group, corresponding to a proportion of pregnancies ending in abortion of 9.1% and 8.7%, respectively.

Table 184-Study HPV-008: Number of subjects with pregnancies (overall) and their outcome (Total Vaccinated cohort)

		HPV N = 1804		HAV N = 1802		Total N = 3606	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Outcome	Normal infant	1124	62.3	1136	63.0	2260	62.7
	Premature birth (healthy)	51	2.8	45	2.5	96	2.7
	Abnormal infant	21	1.2	19	1.1	40	1.1
	Elective termination	185	10.3	194	10.8	379	10.5
	Therapeutic abortion	2	0.1	1*	0.1	3	0.1
	Ectopic pregnancy	15	0.8	6	0.3	21	0.6
	Spontaneous abortion	164	9.1	156	8.7	320	8.9
	Still birth	14	0.8	9	0.5	23	0.6
	Lost to follow up	20	1.1	23	1.3	43	1.2
	Not applicable	4	0.2	1	0.1	5	0.1
	Pregnancy ongoing	204	11.3	212	11.8	416	11.5

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of pregnancies
n = number of pregnancies in a given category
% = (n / N) x 100
Abnormal infant includes congenital anomalies and/or other medically significant outcomes in offspring.
Therapeutic abortion: not due to congenital abnormalities
Spontaneous abortion includes missed abortion.
Twin pregnancies are counted as one pregnancy and the worst pregnancy outcomes have been considered.
Not applicable: e.g. mole, trophoblastic tumour
* One case of therapeutic abortion, which was reported in the interim analysis, has been re-classified as abnormal infant in the final analysis.
Source: STN 125259.48, CSR 008, Table 123, p. 441

The number of pregnancy outcomes defined as abnormal infants was 21 in the HPV group and 19 in the HAV group. Abnormal infant is defined as a pregnancy outcome that includes congenital anomalies and/or other medically significant outcomes in offspring. It does not include transient neonatal events such as transient tachypnea of the newborn. Of the abnormal infants, 21 cases were classified as congenital anomalies (12 cases in the HPV group and nine cases in the HAV group). All of the mothers (study subjects) of the 21 infants with congenital anomalies were exposed to the vaccine before conception. At the time of the final analysis, five fetal deaths (four in the HPV group and one in the HAV group), 15 neonatal deaths (six in the HPV group and nine in the HAV group) and two infant deaths (one in each group) were reported. The five fetal deaths included cystic lymphangioma, intra-uterine death, congenital cystic kidney disease, holoprosencephaly and encephalocele. Of the 15 neonatal deaths, seven deaths resulted from birth of a premature baby, while four deaths concerned conditions typically associated with prematurity, i.e. respiratory distress syndrome (three cases) and intracranial hemorrhage (one case). The remaining four neonatal deaths were related to sudden infant death (interstitial pneumonitis), Klinefelter's syndrome, asphyxia and gastroschisis. The two infant deaths were related to aspiration pneumonia and sepsis (pleural effusion, necrotizing colitis, short-bowel syndrome and respiratory distress).

Table 185-Study HPV-008: Listing of abnormal infants reported as pregnancy outcome (Total Vaccinated cohort)

PID	Age mother	LMP	Gestationsal age (weeks)	Events in mother (Preferred Term)	Serious events in child (Preferred Term)
HPV					
7896	16	7/10/05	25	Induced labor	Intra-uterine death and congenital hand malformation*,**
8383	22	3/5/07	22	Premature labor	Premature baby*
17066	27	8/18/06	39	Group B strep infection, normal delivery	Congenital laryngeal stridor**
18237	20	5/18/05	39	Normal delivery	Cerebral atrophy**
21047	22	Unkown	29	Abortion indiced	Holoprosencephaly**
21047	21	Unknown	26	PROM, oligohydramnios	(See above-medical TOP)
76586	21	3/16/05	28	Premature delivery	Premature baby*
620	22	4/9/06	24	Premture separation of placenta, premature labor	Respiratiry distress*
7673	22	9/8/06	37	Normal delivery	Jaundice neonatal, pyelocaliectasis
11588	19	11/25/05	22	Abortion induced	Congenital cystic kidney disease**, oligohydramnios*
17539	21	5/31/06	39	C-section	Talipes, hemangioma**
18838	23	12/1/06	30	PROM	Premature babies (both died)*
76134	21	1/21/07	40	Normal delivery	Neonatal asphyxia*
76421	26	11/25/06	28	Breech presentation, premature labor, diabetes mellitus	Premature babym Burkholderia cepacia infection, thrombocytopenia
8182	23	10/23/07	41	C-section	Diaphragmatic hernia**
8318	21	10/28/05	39	C-section	Meningomyelocoele, hydrocephalus**
15621	17	1/17/06	33	Premature delivery	Transposition of great vessels**
22379	24	8/24/06	11	Abotion missed	Klinefelter's syndrome*,**
76584	26	4/25/97	34	Induced labor, intrauterine growth retardation	Encephalocoele*,**
76832	23	9/16/05	26	Preterm labor	Premutre babies (twins) with RSDS (child alive) and one with sepsis, necrotizing colitis, short-bowel syndrome, RSDS (1 child died)*
91453	27	4/10/08	12	Therapeutic abortion	Conjoined twins**
HAV					
5380	22	12/14/06	38	C-section, cervical dystocia	Talipes**
7984	17	8/18/04	37	Normal delivery	Bacterial infection
8198	25	2/9/07	37	C-section, vaginal bleeding	Pyloric stenosis**
9309	25	4/05	23	Chorioamniotis	Premature babies*
11003	18	12/04	18	Abortion induced	Cystic lymphangioma, Turner's syndrome*,**
18597	24	Unknown	37	Premture delivery	Pneumonia aspiration*
76175	19	Unknown	40	Normal delivery	Teratoma
2920	24	Unknown	39	Normal delivery	VSD**
9342	24	10/6/07	12	Therapeutic abortion	Trisomy 18**
13904	18	9/14/05	41	Normal delivery	Congenital hand malformation**
17815	26	10/3/06	38	Normal delivery	Ankyloglossia**
18841	21	4/11/06	32	PROM	Premature baby*
19323	25	3/11/05	24	Eclampsia	RSDS, Death neonatal*
70886	21	8/1/05	37	C-section	Gastroschisis*, **
71598	21	9/14/05	24	Premature labor	Hemorrhage intracranial*
76058	25	3/17/05	34	Normal delivery	Clet lip**
76058	27	Unknown	28	Premature delivery	Premature baby, RSDS*
76413	24	3/23/07	30	Breech extraction	Premature baby*
86028	19	5/4/05	32	Premature delivery	Neonatal RSDS*

*Child case with fatal outcome

**Congenital anomaly

Note: One additional child case fatality (pregnancy outcome normal infant) was reported for a neonate who died two months after birth due to sudden infant death syndrome.

Source: STN 125259.48, CSR 008, Table 140, p. 485-488

Reviewer's Comment: Overall congenital anomalies and infant outcomes across trials is discussed in the Overall Safety section (with Tables in Appendix B).

The distribution of gestational age at which spontaneous abortions occurred, according to vaccine dose, is provided in Table 186.

Table 186-Study HPV-008: Distribution of gestational age at which the spontaneous abortions occurred per vaccine dose (Total Vaccinated cohort)

		HPV N = 164		HAV N = 156		Total N = 320	
Last dose	**Gestational age**	**n**	**%**	**n**	**%**	**n**	**%**
Dose 1	Up to 8 weeks	4	36.4	2	66.7	6	42.9
	9-12 weeks	4	36.4	1	33.3	5	35.7
	13-20 weeks	3	27.3	0	0.0	3	21.4
	Missing	4	-	1	-	5	-
	Total	15	-	4	-	19	-
Dose 2	Up to 8 weeks	8	44.4	7	50.0	15	46.9
	9-12 weeks	6	33.3	5	35.7	11	34.4
	13-20 weeks	4	22.2	2	14.3	6	18.8
	Missing	2	-	4	-	6	-
	Total	20	-	18	-	38	-
Dose 3	Up to 8 weeks	43	39.8	58	50.4	101	45.3
	9-12 weeks	46	42.6	40	34.8	86	38.6
	13-20 weeks	19	17.6	17	14.8	36	16.1
	Missing	14	-	10	-	24	-
	Total	122	-	125	-	247	-
Overall total	Up to 8 weeks	55	40.1	67	50.8	122	45.4
	9-12 weeks	56	40.9	46	34.8	102	37.9
	13-20 weeks	26	19.0	19	14.4	45	16.7
	Missing	27	-	24	-	51	-
	Total	164	-	156	-	320	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N = number of spontaneous abortions
n = number of spontaneous abortions in the given interval
% = (n / N) x 100
Source: STN 125259.48, CSR 008, Table 124, p. 442

Data in subjects with reported pregnancies around vaccination: An exploratory analysis on a subset of pregnancies and pregnancy outcomes was conducted with focus on pregnancies in women who had their LMP within 30 days prior to vaccination and up to 45 days after vaccination. These pregnancies occurred despite the fact that subjects were advised to take precautions to avoid pregnancy according to the protocol from 30 days before the first dose of study vaccine until two months after the last vaccination. A total of 369 pregnancies with an LMP around the time of vaccination were reported. An imbalance across treatment groups was observed (190 [51.1%] pregnancies in the HPV group versus 179 [48.5%] in the HAV group). The sponsor notes that the rate of elective terminations overall was equally distributed across treatment groups (10.3% in the HPV group versus 10.8% in the HAV group, but that a higher rate of elective terminations in the HPV group versus the HAV group was observed when restricting the analysis to pregnancies around vaccinations (18.9% versus 15.1%).

Table 187-Study HPV-008: Number of subjects with pregnancies around vaccinations and their outcome (Total Vaccinated cohort)

		HPV N = 190		HAV N = 179		Total N = 369	
Characteristics	Parameters or Categories	n	%	n	%	n	%
Outcome	Normal infant	116	61.1	127	70.9	243	65.9
	Premature birth (healthy)	8	4.2	5	2.8	13	3.5
	Abnormal infant	1	0.5	4*	2.2	5	1.4
	Elective termination	36	18.9	27	15.1	63	17.1
	Therapeutic abortion	0	0.0	1	0.6	1	0.3
	Ectopic pregnancy	2	1.1	1	0.6	3	0.8
	Spontaneous abortion	22**	11.6	9*	5.0	31	8.4
	Still birth	1	0.5	0	0.0	1	0.3
	Lost to follow up	4	2.1	5	2.8	9	2.4
	Not applicable	0	0.0	0	0.0	0	0.0
	Pregnancy ongoing	0	0.0	0	0.0	0	0.0

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of pregnancies around vaccination
n = number of pregnancies in a given category
% = (n / N) x 100
Pregnancies around vaccinations: Pregnancy in subjects for which last menstrual period occurred between 30 days before and 45 days after vaccination (subjects with missing date for last menstrual period are not included)
Abnormal infant includes congenital anomalies and/or other medically significant outcomes in offspring.
Therapeutic abortion: not due to congenital abnormalities
Spontaneous abortion includes missed abortion
Twin pregnancies are counted as one pregnancy and the worst pregnancy outcomes have been considered.
Not applicable: e.g. mole, trophoblastic tumour
* For one case of abnormal infant and spontaneous abortion included in the interim analysis, the date of LMP was changed to "unknown" based on follow-up information received after the interim analysis. These cases are therefore excluded from the final analysis of pregnancy outcomes around vaccination.
** One case of spontaneous abortion was reported for a pregnancy that was ongoing at the time of the interim analysis.
Source: STN 125259.48, CSR 008, Table 125, p. 443

A higher rate of abnormal infant pregnancy-related outcomes was observed in the HAV group compared to the HPV group (4 [2.2%] versus 1 [0.5%] cases), whereas a higher rate of spontaneous abortions was observed in the HPV group compared to the HAV group (22 [11.6%] versus 9 [5.0%] cases). To further describe the observed imbalance in spontaneous abortions, additional exploratory analyses were conducted including:

- A comparison between groups of the rates of spontaneous abortions per vaccine dose.
- A comparison between groups of the rates of spontaneous abortions according to the gestational age at which the abortion occurred.
- A comparison between groups of the mean gestational age at which the spontaneous abortions occurred.
- A comparison between groups of the rates of spontaneous abortions when distinguishing between women who had their LMP within 30 days before vaccination and women who had their LMP within 45 days after vaccination.

The distribution of cases of spontaneous abortion per dose and gestational age is presented, and the gestational age by treatment group and timing of vaccination is also presented. No major differences in gestational age were observed between the abortions reported in the HPV and HAV groups. There was no evidence of a higher number of events after the administration of any of the three vaccine doses, including the third dose, which was associated with the highest level of vaccine response. The mean gestational age at the time of abortion did not differ substantially between the HPV and HAV groups.

Table 188-Study HPV-008: Distribution of gestational age at which the spontaneous abortions with LMP date around vaccination (-30 to 45 days) occurred per vaccine dose (Total Vaccinated cohort)

		HPV N = 22		HAV N = 9		Total N = 31	
Last dose	**Gestational age**	**n**	**%**	**n**	**%**	**n**	**%**
Dose 1	Up to 8 weeks	3	50.0	1	50.0	4	50.0
	9-12 weeks	2	33.3	1	50.0	3	37.5
	13-20 weeks	1	16.7	0	0.0	1	12.5
	Missing	1	-	0	0.0	1	-
	Total	7	-	2	-	9	-
Dose 2	Up to 8 weeks	2	40.0	1	33.3	3	37.5
	9-12 weeks	1	20.0	1	33.3	2	25.0
	13-20 weeks	2	40.0	1	33.3	3	37.5
	Missing	0	0.0	1	-	1	-
	Total	5	-	4	-	9	-
Dose 3	Up to 8 weeks	3	30.0	1	33.3	4	30.8
	9-12 weeks	4	40.0	2	66.7	6	46.2
	13-20 weeks	3	30.0	0	0.0	3	23.1
	Total	10	-	3	-	13	-
Overall total	Up to 8 weeks	8	38.1	3	37.5	11	37.9
	9-12 weeks	7	33.3	4	50.0	11	37.9
	13-20 weeks	6	28.6	1	12.5	7	24.1
	Missing	1	-	1	-	2	-
	Total	22	-	9	-	31	-

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of spontaneous abortions with LMP date around vaccination (-30 to 45 days)
n = number of spontaneous abortions in the given interval; % = (n / N) x 100
Spontaneous abortion includes missed abortion
Source: STN 125259.48, CSR 008, Table 126, p. 445

Table 189-Study HPV-008: Gestational age (weeks) at the time of abortion (for spontaneous abortions with LMP date around vaccination) (Total Vaccinated cohort)

	HPV N = 22	HAV N = 9	Total N = 31
Parameters	**Value**	**Value**	**Value**
Mean	10.0	9.9	10.0
Median	9.0	12.0	9.0
Minimum	4.0	6.0	4.0
Maximum	18.0	13.0	18.0

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of spontaneous abortions with LMP date around vaccination (-30 to 45 days)
Value = value of the considered parameter
Source: STN 125259.48, CSR 008, Table 28, p. 445

A total of 183 subjects (103 in the HPV group and 80 in the HAV group) had their LMP within 30 days prior to vaccination. The observed imbalance in spontaneous abortions by treatment group appears to have mostly occurred in the group of women who had their LMP within 30 days before vaccination.

Table 190-Study HV-008: Number of spontaneous abortions per timing of exposure over the total number of pregnancies around vaccinations (Total Vaccinated cohort)

		HPV N = 190		HAV N = 179		Total N = 369	
Interval	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
LMP within 30 days prior to vaccination	Spontaneous abortions	12	11.7	3	3.8	15	8.2
	All other pregnancies	91	88.3	77	96.3	168	91.8
LMP within 45 days after vaccination	Spontaneous abortions	10	11.5	6	6.1	16	8.6
	All other pregnancies	77	88.5	93	93.9	170	91.4
Total	Spontaneous abortions	22	11.6	9	5.0	31	8.4
	All other pregnancies	168	88.4	170	95.0	338	91.6

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of pregnancies around vaccination
n = number of pregnancies with the specified outcome
% = (n / N) x 100
Pregnancies around vaccinations: Pregnancy in subjects for which last menstrual period occurred between 30 days before and 45 days after vaccination (subjects with missing date for last menstrual period are not included)
Spontaneous abortion includes missed abortion
Source: STN 125259.48, CSR 008, Table 128, p. 446

Reviewer's Comment: The imbalance in the proportion of women who experienced a spontaneous abortion was noted in women who were vaccinated around the time of estimated date of conception. This was also noted at the time of the original BLA submission. CBER required additional information about these events. A full discussion regarding these events is in the Overview of Safety section. This finding was discussed at VRBPAC. The obstetricians on the committee noted that the rates of expected pregnancy loss in the population are higher than those noted in this analysis. However, this finding could not be ignored. This will be studied in the post-marketing period (required study). Please see the Overview of Safety section for a full discussion regarding this finding.

The sponsor also compared pregnancy outcomes for subjects who were seropositive and/or PCR positive for HPV 16 and/or 18 as well as subjects who were initially seronegative and PCR negative. The same relative proportions were noted as reported for the Total Vaccinated Cohort.

(Source: STN 125259.48, CSR 0080, Supplements 350, 351, 353 and 354, p. 10750-10752, not shown here).

Safety conclusions: Overall, the reactogenicity and safety profile of the HPV group was similar to that of the HAV group with the exception of solicited symptoms, which were more frequently reported in the HPV group (Table 191).

Table 191-Study HPV-008: Summary of solicited and unsolicited symptoms

		HPV			HAV		
Solicited symptoms: percentage of doses with events within 7 days after vaccination in the safety diary card subset (Interim Total Vaccinated cohort)							
			95% CI			95% CI	
		%	LL	UL	%	LL	UL
Pain	All	80.2	79.3	81.0	58.9	57.8	59.9
	Grade 3	7.3	6.8	7.9	1.8	1.5	2.1
Redness	All	28.1	27.2	29.1	16.0	15.2	16.8
	> 50.0 mm	0.4	0.3	0.6	0.0	0.0	0.1
Swelling	All	25.4	24.5	26.3	10.1	9.5	10.8
	> 50.0 mm	1.0	0.8	1.2	0.2	0.1	0.3
Arthralgia	All	10.7	10.0	11.3	8.6	8.0	9.2
	Grade 3	0.4	0.3	0.5	0.3	0.2	0.4
Fatigue	All	38.8	37.8	39.9	35.3	34.3	36.3
	Grade 3	1.6	1.4	1.9	1.3	1.1	1.6
Fever	All	5.3	4.8	5.8	4.6	4.1	5.0
	> 39.0°C	0.2	0.1	0.3	0.1	0.1	0.2
Gastrointestinal	All	14.3	13.6	15.1	14.0	13.3	14.7
	Grade 3	0.7	0.6	0.9	0.7	0.5	0.9
Headache	All	32.9	31.9	33.9	30.8	29.8	31.8
	Grade 3	1.7	1.4	2.0	1.4	1.1	1.6
Myalgia	All	34.3	33.3	35.3	26.5	25.6	27.5
	Grade 3	1.8	1.5	2.1	0.6	0.4	0.8
Rash	All	4.4	4.0	4.9	3.6	3.2	4.0
	Grade 3	0.1	0.0	0.2	0.1	0.0	0.1
Urticaria	All	4.6	4.2	5.1	3.7	3.3	4.1
	Grade 3	0.3	0.2	0.5	0.4	0.2	0.5
Percentage of subjects with at least one event (Total Vaccinated cohort)*							
			95% CI			95% CI	
		%	LL	UL	%	LL	UL
Unsolicited symptom (day 0-29)		42.5	40.8	44.3	43.6	41.9	45.3
SAE		7.5	7.0	8.1	7.5	7.0	8.0
Medically significant condition		31.8	30.8	32.7	32.4	31.5	33.4
NOCD		2.7	2.4	3.0	2.9	2.5	3.2
NOAD		0.8	0.7	1.0	0.8	0.7	1.0

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
%= percentage of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
* Events were reported during the entire follow-up period (based on Final Total Vaccinated cohort), except for unsolicited symptoms (30-day post-vaccination period, based on Interim Total Vaccinated cohort)
Note: Data from interim analysis for solicited and unsolicited (day 0-29) symptoms
Source: STN 125259.48, CSR 008, Table 29, p. 447

The sponsor notes that The IDMC met in Geneva on February 11, 2009 to discuss and review the HPV-008 final study results. Based on data reviewed, the IDMC concluded at that time that there was no serious safety concern.

IMMUNOGENICITY RESULTS

Data sets analyzed: Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and the Total Vaccinated cohort. In addition, analysis of antibody kinetics was performed on subjects in the ATP cohort for immunogenicity who had an ELISA/PBNA result available at all timepoints. At the time of the final analysis, results from the anti-HPV-16 and anti-HPV-18 ELISA and PBNA (neutralizing antibodies) testing were available. The anti-hepatitis A ELISA will be performed at the end of the study.

Immune response induced by natural infection measured by ELISA (Total Vaccinated cohort): The antibody titers associated with naturally acquired HPV-16 or HPV-18 infection and successful immunological clearance of infection are presented. The calculation of GMTs was done on subjects who were seropositive for HPV-16 or HPV-18 at Month 0 and who were HPV DNA negative for the antigen considered (i.e. who had successfully "cleared" the infection and mounted an immune response). Selection of this population was considered to be the most relevant to indicate GMTs that may reflect protective immune responses against natural infection. Subjects who had cleared HPV-16 infection had GMTs of 29.8 EL.U/ml [28.6; 31.0]. Subjects who had cleared HPV-18 infection had GMTs of 22.6 EL.U/ml [21.6; 23.6].

Table 192-Study HPV-008: GMTs for anti-HPV-16 and anti-HPV-18 antibodies in seropositive and HPV DNA negative subjects at Month 0 (Total Vaccinated cohort)

		GMT				
			95% CI			
Antibody	N	Value	LL	UL	Min	Max
HPV-16	2560	29.8	28.6	31.0	8.0	2805.0
HPV-18	1956	22.6	21.6	23.6	7.0	2282.0

GMT = geometric mean antibody titre calculated on subjects seropositive and HPV DNA negative for the corresponding HPV type
N = number of subjects with available results
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
Source: STN 125259.48, CSR 008, Table 130, p. 451

Immune response induced by vaccine: The immunogenicity subset includes a subset of subjects from study sites selected to collect blood samples at Months 0, 6, 7, 12, 24, 36 and 48. The ATP cohort for immunogenicity includes subjects from this immunogenicity subset with at least one ELISA result available after completion of the full three-dose vaccination course (N=1933). At the time of the final analysis, anti-HPV-16 and anti- HPV-18 ELISA results were available for Months 0, 6, 7, 12, 24 and 36. A further subset of 100 subjects had their blood samples taken at Months 0, 7, 12 and 24 tested for anti- HPV-16 and anti-HPV-18 PBNA. The anti-HPV-16/18 seropositivity status at baseline (as measured by ELISA) was comparable between the HPV and HAV groups. The majority of subjects in the two groups were seronegative for both anti-HPV-16 and anti-HPV-18 antibodies at baseline (79.6% and 76.2%, respectively).

Table 193-Study HPV-008: Seropositivity status at baseline (ATP cohort for immunogenicity)

		HPV (N = 1035)		HAV (N = 898)		Total (N = 1933)	
HPV-16	HPV-18	n	%	n	%	n	%
Seropositive	Seropositive	47	4.6	40	4.5	87	4.5
Seropositive	Seronegative	114	11.1	105	11.8	219	11.4
Seropositive	Missing	0	-	1	-	1	-
Seronegative	Seropositive	48	4.7	67	7.5	115	6
Seronegative	Seronegative	817	79.6	680	76.2	1497	78.1
Seronegative	Missing	3	-	1	-	4	-
Missing	Seropositive	1	-	1	-	2	-
Missing	Seronegative	2	-	2	-	4	-
Missing	Missing	3	-	1	-	4	-

HPV = HPV-16/18 L1 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
Missing = Result not available
Source: STN 125259.48, CSR 008, Table 131, p. 452

Similar results were seen in the TVC. (Source: STN 125259.48, CSR 008, Supplement 401, p. 10920, not shown here).

Anti-HPV-16 and anti-HPV-18 ELISA (According-to-protocol): One month post Dose 3 (at Month 7), 99.5% of the subjects in the HPV group had seroconverted for anti-HPV-16 and anti-HPV-18 antibodies and at least 99.4% of the subjects remained seropositive up to Month 36, i.e. up to 30 months after completion of the full vaccination course. There was an approximately 10-fold increase in GMTs for both antibodies observed from Month 6 (post Dose 2) to Month 7 (post Dose 3). After a gradual decline from Month 7 through Month 24, GMTs reached a plateau between Month 24 and Month 36. This is also illustrated by the reverse cumulative distribution curves for anti-HPV-16 and anti-HPV-18 antibodies, which shift to the left from Month 7 to Month 24 without substantial evidence of a further decline between Month 24 and Month 36.

Overall, the immune responses after vaccination were comparable for subjects initially seronegative for HPV-16 and subjects initially seropositive for HPV-16. At Month 7, GMTs were higher in initially seronegative subjects, but at Month 12 GMTs were comparable between subjects initially seronegative and initially seropositive for HPV-16. For HPV-18, the immune responses were similar between subjects initially seronegative for HPV-18 and subjects initially seropositive for HPV-18 at all assessed time points. Similar immune responses were also observed between subjects initially seronegative for both antigens and subjects initially seropositive for either antigen. (Source: STN 125259.48, CSR 008, Supplements 393-396, p. 10982-10987, not shown here)

The HPV vaccine lots administered in this study were consistency lots, for which lot-to-lot consistency in terms of immunogenicity was demonstrated in study HPV-012. The present analysis, which shows similar seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies for subjects vaccinated with the three different vaccine lots. (Source: STN 125259.48, CSR 008, Supplements 397-398, p. 10898-10905, not shown here).

An overview of the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies by ethnicity reveals that the vaccine was similarly immunogenic in terms of seropositivity rates at all post-vaccination timepoints in subgroups by ethnicity. GMT assessments for both HPV-16 and HPV-18, however, demonstrated that subjects of Hispanic origin tended to have lower titers at Months 24 and 36 than subjects of Caucasian, Black or Asian origin. As vaccine efficacy for the primary endpoint was further assessed by region and was shown to be consistent with the overall efficacy results, this difference was not considered as clinically relevant. Anti-HPV-16 and anti-HPV-18 ELISA results obtained in the Total Vaccinated cohort were consistent with those obtained in the ATP cohort for immunogenicity.

Reviewer's Comment: The results of the GMTs for subjects who received HPV vaccine at Month 24 and Month 36 are provided in Table 194. All seropositivity rates were very high (nearly 100% in all groups, so are not reproduced in this table). As noted by the sponsor, Hispanic subjects tended to have lower GMTs at Months 24 and 36 (non-overlapping GMTs as compared to White/Caucasians). As noted in the efficacy section, no difference in efficacy was noted when assessed by ethnic group.

Table 194-Study HPV-008: GMTs at Months 24 and 36 by Ethnic Group in HPV vaccine recipients

Antibody	Ethnic group	Timing	GMT	95% CI	Min, Max
HPV-16	Black	M24	1550.6	1151.5, 2087.9	240.0, 8822.0
		M36	1247.8	948.1, 1642.3	183.0, 6784.0
	White	M24	2022.5	1862.5, 2196.4	69.0, 36310.0
		M36	1640.6	1506.6, 1785.4	70.0, 223557.0
	Asian	M24	1351.9	1201.6, 1521.1	<8.0, 7233.0
		M36	1094.9	983.6, 1218.8	145.0, 7116.0
	Hispanic	M24	1065.3	945.2, 1200.6	166.0, 30339.0
		M36	822.5	726.6, 931.0	25.0, 22363.0
	Other*	M24	1131.0	650.7, 1965.9	267.0, 14351.0
		M36	1001.7	552.1, 1817.4	175.0, 10172.0
HPV-18	Black	M24	799.6	608.9, 1050.1	142.0, 4094.0
		M36	648.4	498.2, 843.9	72.0, 2898.0
	White	M24	876.2	801.8, 957.4	53.0, 30567.0
		M36	671.8	612.3, 737.1	34.0, 20621.0
	Asian	M24	694.8	611.9, 788.9	<7.0, 3959.0
		M36	551.1	487.6, 622.8	56.0, 3319.0
	Hispanic	M24	426.6	374.4, 486.1	48.0, 12856.0
		M36	317.4	278.7, 361.5	28.0, 9508.0
	Other*	M24	565.4	376.3, 849.6	204.0, 1583.0
		M36	432.1	288.8, 646.5	139.0, 1257.0

Source: STN 125259.48, CSR 008, Supplements 399 and 400, p. 10906-10919

The tables below provide seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibody titers by baseline serostatus (Tables 195 and 196) through Month 36 in the ATP cohort for immunogenicity. As noted, 100% of tested subjects in this subset were seropositive for anti-HPV-16 and for anti-HPV-18.

Table 195-Study HPV-008: Seropositivity rates and GMTs for anti-HPV-16 antibody titers (ATP cohort for immunogenicity)

					≥ 8 EL.U/ml				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-16	HPV	S-	PRE	868	0	0.0	0.0	0.4	4.0	4.0	4.0	<8.0	<8.0
			PII(M6)	861	860	99.9	99.4	100	627.9	589.0	669.5	<8.0	13291.0
			PIII(M7)	861	857	99.5	98.8	99.9	9206.4	8607.2	9847.2	<8.0	187703.0
			PIII(M12)	835	833	99.8	99.1	100	3282.6	3065.3	3515.3	<8.0	87534.0
			PIII(M24)	793	792	99.9	99.3	100	1590.4	1490.0	1697.6	<8.0	36310.0
			PIII(M36)	780	780	100	99.5	100	1264.6	1184.1	1350.5	25.0	23557.0
		S+	PRE	161	161	100	97.7	100	28.6	24.4	33.6	8.0	502.0
			PII(M6)	159	158	99.4	96.5	100	1247.4	1019.3	1526.6	<8.0	38767.0
			PIII(M7)	160	159	99.4	96.6	100	6408.3	5459.7	7521.6	<8.0	67959.0
			PIII(M12)	151	151	100	97.6	100	2923.8	2511.1	3404.3	210.0	26849.0
			PIII(M24)	143	143	100	97.5	100	1574.9	1354.4	1831.4	193.0	12965.0
			PIII(M36)	139	139	100	97.4	100	1238.4	1060.5	1446.1	182.0	10346.0
		Total	PRE	1029	161	15.6	13.5	18.0	5.4	5.2	5.7	<8.0	502.0
			PII(M6)	1020	1018	99.8	99.3	100	698.9	655.4	745.2	<8.0	38767.0
			PIII(M7)	1021	1016	99.5	98.9	99.8	8698.2	8171.5	9259.0	<8.0	187703.0
			PIII(M12)	986	984	99.8	99.3	100	3224.9	3029.6	3432.8	<8.0	87534.0
			PIII(M24)	936	935	99.9	99.4	100	1588.1	1495.9	1685.9	<8.0	36310.0
			PIII(M36)	919	919	100	99.6	100	1260.6	1186.7	1339.1	25.0	23557.0
	HAV	S-	PRE	748	0	0.0	0.0	0.5	4.0	4.0	4.0	<8.0	<8.0
			PII(M6)	736	41	5.6	4.0	7.5	4.4	4.2	4.5	<8.0	2929.0
			PIII(M7)	738	34	4.6	3.2	6.4	4.4	4.2	4.6	<8.0	21663.0
			PIII(M12)	717	30	4.2	2.8	5.9	4.3	4.2	4.4	<8.0	2032.0
			PIII(M24)	670	32	4.8	3.3	6.7	4.3	4.2	4.5	<8.0	339.0
			PIII(M36)	663	35	5.3	3.7	7.3	4.4	4.2	4.5	<8.0	286.0
		S+	PRE	146	146	100	97.5	100	29.4	24.7	35.0	8.0	1055.0
			PII(M6)	138	118	85.5	78.5	90.9	24.1	19.7	29.5	<8.0	714.0
			PIII(M7)	138	105	76.1	68.1	82.9	21.3	17.2	26.5	<8.0	640.0
			PIII(M12)	133	100	75.2	67.0	82.3	20.0	16.1	24.8	<8.0	664.0
			PIII(M24)	137	95	69.3	60.9	76.9	18.5	14.8	23.0	<8.0	1295.0
			PIII(M36)	126	87	69.0	60.2	77.0	17.5	13.9	22.0	<8.0	1388.0
		Total	PRE	894	146	16.3	14.0	18.9	5.5	5.2	5.9	<8.0	1055.0
			PII(M6)	874	159	18.2	15.7	20.9	5.7	5.4	6.1	<8.0	2929.0
			PIII(M7)	876	139	15.9	13.5	18.5	5.6	5.3	6.0	<8.0	21663.0
			PIII(M12)	850	130	15.3	12.9	17.9	5.4	5.1	5.8	<8.0	2032.0
			PIII(M24)	807	127	15.7	13.3	18.4	5.6	5.2	5.9	<8.0	1295.0
			PIII(M36)	789	122	15.5	13.0	18.2	5.4	5.1	5.8	<8.0	1388.0

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
S- = seronegative subjects (antibody titre < 8 EL.U/ML) prior to vaccination
S+ = seropositive subjects (antibody titre ≥ 8 EL.U/ML) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination; PII(M6) = Post Dose II (Month 6)
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12)
PIII(M24) = Post Dose III (Month 24); PIII(M36) = Post Dose III (Month 36)
Source: STN 125259.48, CSR 008, Table 132, p. 454-455

Table 196-Study HPV-008: Seropositivity rates and GMTs for anti-HPV-18 antibody titres (ATP cohort for immunogenicity)

					≥ 7 EL.U/ml				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-18	HPV	S-	PRE	933	0	0.0	0.0	0.4	3.5	3.5	3.5	<7.0	<7.0
			PII(M6)	924	921	99.7	99.1	99.9	540.1	507.9	574.5	<7.0	23874.0
			PIII(M7)	924	919	99.5	98.7	99.8	4744.6	4454.1	5053.9	<7.0	142964.0
			PIII(M12)	895	895	100	99.6	100	1522.8	1431.7	1619.8	79.0	62477.0
			PIII(M24)	848	847	99.9	99.3	100	703.8	657.7	753.2	<7.0	30567.0
			PIII(M36)	835	835	100	99.6	100	534.0	498.6	572.0	28.0	20621.0
		S+	PRE	96	96	100	96.2	100	24.4	19.8	30.2	7.0	1397.0
			PII(M6)	96	95	99.0	94.3	100	892.5	704.2	1131.2	<7.0	30703.0
			PIII(M7)	96	96	100	96.2	100	4131.3	3539.2	4822.6	658.0	31432.0
			PIII(M12)	91	91	100	96.0	100	1505.7	1265.8	1791.1	241.0	18730.0
			PIII(M24)	88	88	100	95.9	100	742.9	616.6	895.1	148.0	16554.0
			PIII(M36)	85	85	100	95.8	100	577.5	471.2	707.7	124.0	12798.0
		Total	PRE	1029	96	9.3	7.6	11.3	4.2	4.0	4.4	<7.0	1397.0
			PII(M6)	1020	1016	99.6	99.0	99.9	566.3	533.0	601.7	<7.0	30703.0
			PIII(M7)	1020	1015	99.5	98.9	99.8	4683.2	4414.7	4967.9	<7.0	142964.0
			PIII(M12)	986	986	100	99.6	100	1521.3	1435.3	1612.4	79.0	62477.0
			PIII(M24)	936	935	99.9	99.4	100	707.4	663.7	754.0	<7.0	30567.0
			PIII(M36)	920	920	100	99.6	100	537.9	504.0	574.1	28.0	20621.0
	HAV	S-	PRE	787	0	0.0	0.0	0.5	3.5	3.5	3.5	<7.0	<7.0
			PII(M6)	768	29	3.8	2.5	5.4	3.7	3.6	3.8	<7.0	4271.0
			PIII(M7)	769	31	4.0	2.8	5.7	3.8	3.6	3.9	<7.0	9564.0
			PIII(M12)	745	34	4.6	3.2	6.3	3.8	3.6	3.9	<7.0	4060.0
			PIII(M24)	695	35	5.0	3.5	6.9	3.8	3.7	3.9	<7.0	235.0
			PIII(M36)	689	31	4.5	3.1	6.3	3.7	3.6	3.8	<7.0	295.0
		S+	PRE	108	108	100	96.6	100	23.4	18.9	29.1	7.0	745.0
			PII(M6)	105	90	85.7	77.5	91.8	19.6	15.2	25.4	<7.0	1706.0
			PIII(M7)	105	90	85.7	77.5	91.8	20.8	16.2	26.8	<7.0	1363.0
			PIII(M12)	106	89	84.0	75.6	90.4	19.9	15.5	25.5	<7.0	822.0
			PIII(M24)	102	84	82.4	73.6	89.2	18.9	14.6	24.4	<7.0	722.0
			PIII(M36)	98	73	74.5	64.7	82.8	16.8	12.8	22.1	<7.0	467.0
		[illegible]											
		Total	PRE	895	108	12.1	10.0	14.4	4.4	4.2	4.6	<7.0	745.0
			PII(M6)	873	119	13.6	11.4	16.1	4.5	4.3	4.8	<7.0	4271.0
			PIII(M7)	874	121	13.8	11.6	16.3	4.6	4.4	4.9	<7.0	9564.0
			PIII(M12)	851	123	14.5	12.2	17.0	4.6	4.4	4.9	<7.0	4060.0
			PIII(M24)	797	119	14.9	12.5	17.6	4.6	4.4	4.9	<7.0	722.0
			PIII(M36)	787	104	13.2	10.9	15.8	4.5	4.3	4.8	<7.0	467.0

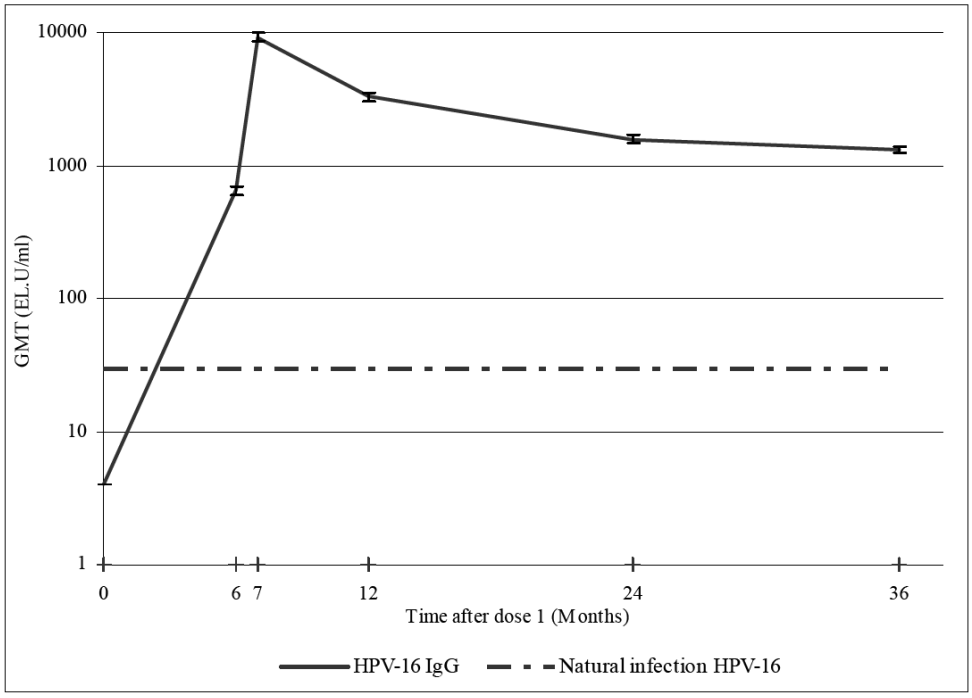
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
S- = seronegative subjects (antibody titre < 7 EL.U/ML) prior to vaccination
S+ = seropositive subjects (antibody titre ≥ 7 EL.U/ML) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination; PII(M6) = Post Dose II (Month 6)
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12)
PIII(M24) = Post Dose III (Month 24); PIII(M36) = Post Dose III (Month 36)
STN 125259.48, CSR 008, Table 133, p. 456-457

Comparison of post-vaccination anti-HPV-16 and anti-HPV-18 ELISA titers to natural infection titers: The kinetics of anti-HPV-16 and anti-HPV-18 antibody responses compared to antibody levels associated with clearance of natural infection are presented in Figures 22 and 23 below. Vaccine-induced GMTs were above levels elicited after naturally acquired infection at each timepoint post-vaccination. After a peak antibody response at Month 7, GMTs gradually declined up to approximately Month 24, after which timepoint a plateau level was reached until Month 36.

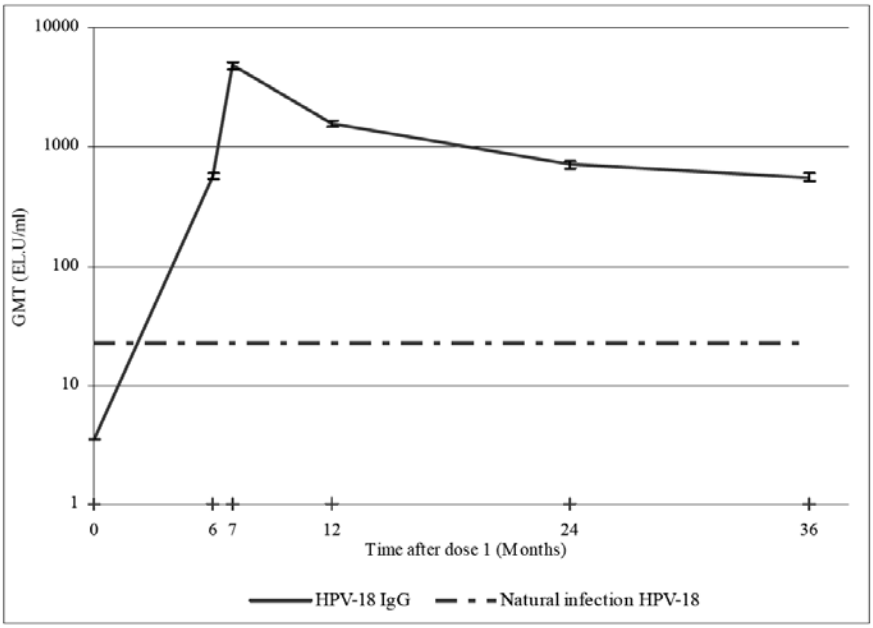
Reviewer's Comment: The actual seropositivity rates and GMTs are provided for all subjects with immunogenicity results available at all time points, and these results are similar to those reported for the ATP cohort for immunogenicity. (Source: STN 125259.48, CSR 008, Supplements 408-409, p. 10934-10937, not shown here).

Figure 22-Study HPV-008: Kinetics for anti-HPV-16 antibodies in initially seronegative subjects with anti-HPV-16 ELISA results available at all time-points (ATP cohort for immunogenicity - HPV group)



Source: STN 125259.48, CSR 008, Figure 7, p. 459

Figure 23-Study HPV-008: Kinetics for anti-HPV-18 antibodies in initially seronegative subjects with anti-HPV-18 ELISA results available at all time-points (ATP cohort for immunogenicity - HPV group)



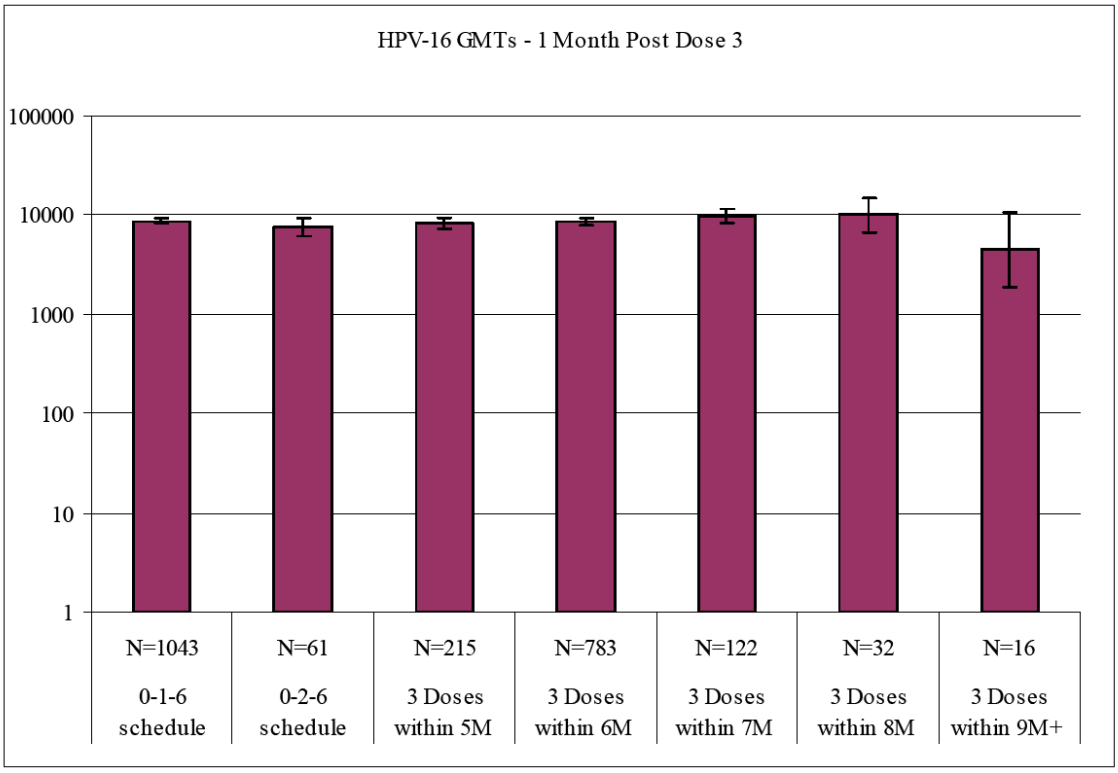
Source: STN 125259.48, CSR 008, Figure 8, p. 460

Immune response in subjects with varied vaccination schedules (Total Vaccinated cohort): An additional analysis was performed to evaluate the immune response elicited by the vaccine in subjects vaccinated according to different schedules as follows:

- A flexible schedule for Dose 2 was evaluated based on subjects vaccinated according to a 0, 1, 6-month or a 0, 2, 6-month schedule.
- A flexible schedule for Dose 3 was evaluated based on subjects who received the three vaccine doses within a period of 5, 6, 7, 8 or 9 or more months.

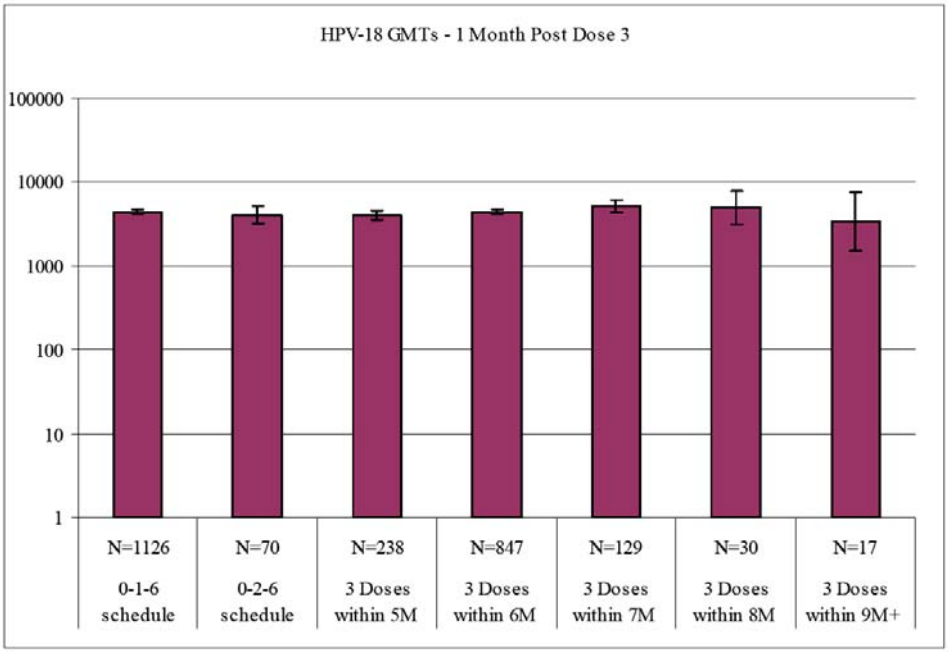
An overview of the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies by schedule for subjects vaccinated according to the different schedules is presented. As shown in Figures 24 and 25 below, similar immune responses against HPV-16 and HPV-18 were elicited in subjects receiving the vaccine according to a 0, 1, 6-month schedule or a 0, 2, 6-month schedule. Also, similar immune responses against both antigens were observed for subjects receiving the three doses within a period of either 5, 6, 7, 8 or 9 or more months. **Note that only a small number of subjects were available for the analysis of three doses within 9 or more months.**

Figure 24-Study HPV-008: GMTs for anti-HPV-16 antibodies one month after the third dose in initially seronegative subjects by schedule – HPV group (Total Vaccinated cohort – Subset of subjects who received three doses)



0-1-6 = 0, 1, 6-month schedule: Dose 1-Dose 2 interval equals 1 Month (30 ± 15 Days) and Dose 1-Dose 3 interval equals [161; 216] days
0-2-6 = 0, 2, 6-month schedule: Dose 1-Dose 2 interval equals 2 Months (60 ± 15 Days) and Dose 1-Dose 3 interval equals [161; 216] days
3 Doses within 5M = Dose 1-Dose 3 interval equals 5 months (150 ± 15 Days)
3 Doses within 6M = Dose 1-Dose 3 interval equals 6 months (180 ± 15 Days)
3 Doses within 7M = Dose 1-Dose 3 interval equals 7 months (210 ± 15 Days)
3 Doses within 8M = Dose 1-Dose 3 interval equals 8 months (240 ± 15 Days)
3 Doses within 9M+ = Dose 1-Dose 3 interval equals 9 months and more (≥ 255 Days)
Source: STN 125259.48, CSR 008, Figure 9, p. 461

Figure 25-Study HPV-008: GMTs for anti-HPV-18 antibodies one month after the third dose in initially seronegative subjects by schedule – HPV group (Total Vaccinated cohort – Subset of subjects who received three doses)



0-1-6 = 0, 1, 6-month schedule: Dose 1-Dose 2 interval equals 1 Month (30 ± 15 Days) and Dose 1-Dose 3 interval equals [161; 216] days
0-2-6 = 0, 2, 6-month schedule: Dose 1-Dose 2 interval equals 2 Months (60 ± 15 Days) and Dose 1-Dose 3 interval equals [161; 216] days
3 Doses within 5M = Dose 1-Dose 3 interval equals 5 months (150 ± 15 Days)
3 Doses within 6M = Dose 1-Dose 3 interval equals 6 months (180 ± 15 Days)
3 Doses within 7M = Dose 1-Dose 3 interval equals 7 months (210 ± 15 Days)
3 Doses within 8M = Dose 1-Dose 3 interval equals 8 months (240 ± 15 Days)
3 Doses within 9M+ = Dose 1-Dose 3 interval equals 9 months and more (≥ 255 Days)
Source: STN 125259.48, CSR 008, Figure 10, p. 462

Reviewer's Comment: Any ability to make a recommendation for advising on alternative schedules is limited by the small number of subjects who received vaccine according to these alternative schedules, although the vast majority of subjects (≥ 98.2% for anti-HPV 16 and ≥98.5% for anti-HPV 18) who received vaccine according to alterative schedules became seropositive by Month 7. For subjects who received 3 doses within 8 months and 9 months, 100% of these subjects were seropositive for anti-HPV 16 and HPV 18 by Month 6. (Source: STN 125259.48, CSR 008, Supplements 410-411, p. 10938-10947, not shown here)

Anti-HPV-16 and anti-HPV-18 PBNA (According-to-protocol): In line with the results obtained for ELISA, all subjects were seropositive for anti-HPV-16 and anti-HPV-18 neutralizing antibodies at Month 24 and high GMT levels were observed for both antibodies at Month 7 (27364.8 and 9052.7 ED50, respectively) (Table 197). GMTs for anti-HPV-16 neutralizing antibodies declined from Month 7 to Month 12 and further to Month 24. Between Month 12 and Month 24, the decline in anti-HPV-16 GMTs was less pronounced than between Month 7 and Month 12. GMTs for anti-HPV-18 neutralizing antibodies, however, already reached a plateau at Month 12 that was maintained up to Month 24. Anti-HPV-16 and anti-HPV-18 PBNA results obtained in the Total Vaccinated cohort were consistent with those obtained for the ATP cohort for immunogenicity.

Table 197-Study HPV-008: Seropositivity rates and GMTs for anti-HPV-16 titers using PBNA (ATP cohort for immunogenicity)

					≥ 40 ED50				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-16 PBNA	HPV	S-	PRE	46	0	0.0	0.0	7.7	20.0	20.0	20.0	<40.0	<40.0
			PIII(M7)	46	46	100	92.3	100	27364.8	19780.1	37857.9	1416.0	343855.0
			PIII(M12)	45	45	100	92.1	100	8385.9	5857.3	12006.0	881.0	129002.0
			PIII(M24)	46	46	100	92.3	100	3647.4	2586.5	5143.4	261.0	30246.0
	HAV	S-	PRE	44	0	0.0	0.0	8.0	20.0	20.0	20.0	<40.0	<40.0
			PIII(M7)	44	0	0.0	0.0	8.0	20.0	20.0	20.0	<40.0	<40.0
			PIII(M12)	43	0	0.0	0.0	8.2	20.0	20.0	20.0	<40.0	<40.0
			PIII(M24)	40	0	0.0	0.0	8.8	20.0	20.0	20.0	<40.0	<40.0

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
PBNA = pseudovirion based neutralizing assay
S- = seronegative subjects (antibody titre < 40 ED50) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination; PIII(M7) = Post Dose III (Month 7)
PIII(M12) = Post Dose III (Month 12); PIII(M24) = Post Dose III (Month 24)
Source: STN 125259.48, CSR 008, Table 134, p. 464

Table 198-Study HPV-008: Seropositivity rates and GMTs for anti-HPV-18 titers using PBNA (ATP cohort for immunogenicity)

					≥ 40 ED50				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-18 PBNA	HPV	S-	PRE	48	0	0.0	0.0	7.4	20.0	20.0	20.0	<40.0	<40.0
			PIII(M7)	46	46	100	92.3	100	9052.7	6851.8	11960.5	1161.0	55863.0
			PIII(M12)	45	44	97.8	88.2	99.9	1889.9	1316.0	2714.1	<40.0	25047.0
			PIII(M24)	46	46	100	92.3	100	1695.6	1200.7	2394.4	67.0	20814.0
	HAV	S-	PRE	47	0	0.0	0.0	7.5	20.0	20.0	20.0	<40.0	<40.0
			PIII(M7)	44	0	0.0	0.0	8.0	20.0	20.0	20.0	<40.0	<40.0
			PIII(M12)	43	0	0.0	0.0	8.2	20.0	20.0	20.0	<40.0	<40.0
			PIII(M24)	40	0	0.0	0.0	8.8	20.0	20.0	20.0	<40.0	<40.0

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
PBNA = pseudovirion based neutralizing assay
S- = seronegative subjects (antibody titre < 40 ED50) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination; PIII(M7) = Post Dose III (Month 7)
PIII(M12) = Post Dose III (Month 12); PIII(M24) = Post Dose III (Month 24)
Source: STN 125259.48, CSR 008, Table 135, p. 465

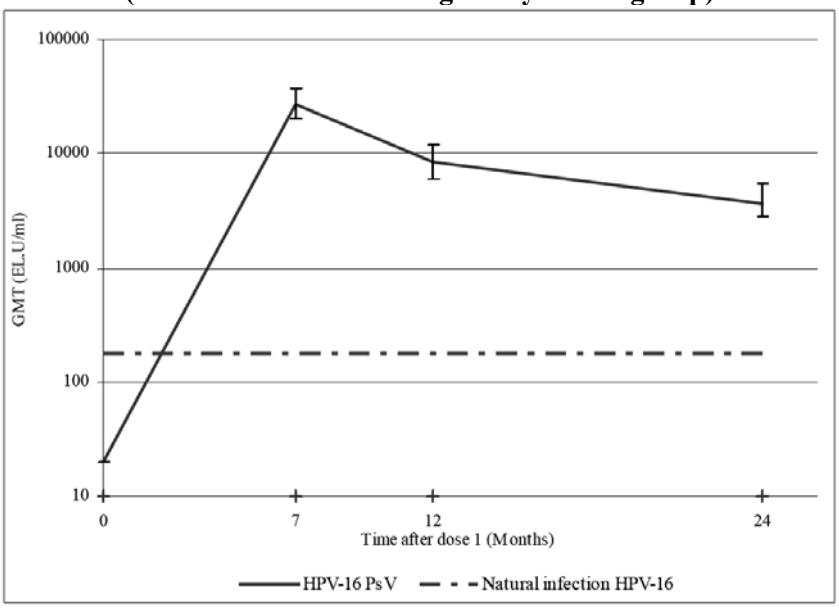
Results for the TVC were very similar to those reported for the ATP cohort for immunogenicity. (Source: STN 125259.48, CSR 008, Supplements 412-415, p. 10948-10950, not shown here).

Comparison of post-vaccination anti-HPV-16 and anti-HPV-18 titers by PBNA to natural infection titers by PBNA from study HPV-010: GMT values associated with clearance of natural infection were obtained from subjects in study HPV-010 (study not submitted to BLA), who were seropositive as measured by PBNA for HPV-16 or HPV-18 at Month 0 and HPV DNA negative for the antigen considered. In study HPV-010, subjects who had cleared HPV-16 infection had GMTs of 180.1 ED50 [153.3, 211.4] and subjects who had cleared HPV-18 infection had GMTs of 137.3 ED50 [112.2, 168.0] when evaluated by PBNA.

Reviewer's Comment: Although subjects who were seropositive but DNA negative presumably had cleared infection, one cannot definitively determine if those subjects had sustained a "hit" to their cells that would later progress to cervical cancer. Although there was evidence of reduction of 12-month persistent infection with HPV-16 and/or HPV-18 in Cervarix recipients in the ATP cohort, there were few cases of CIN2+ related to HPV-16 and/or HPV-18 (6 in the control group and 2 in the Cervarix group).

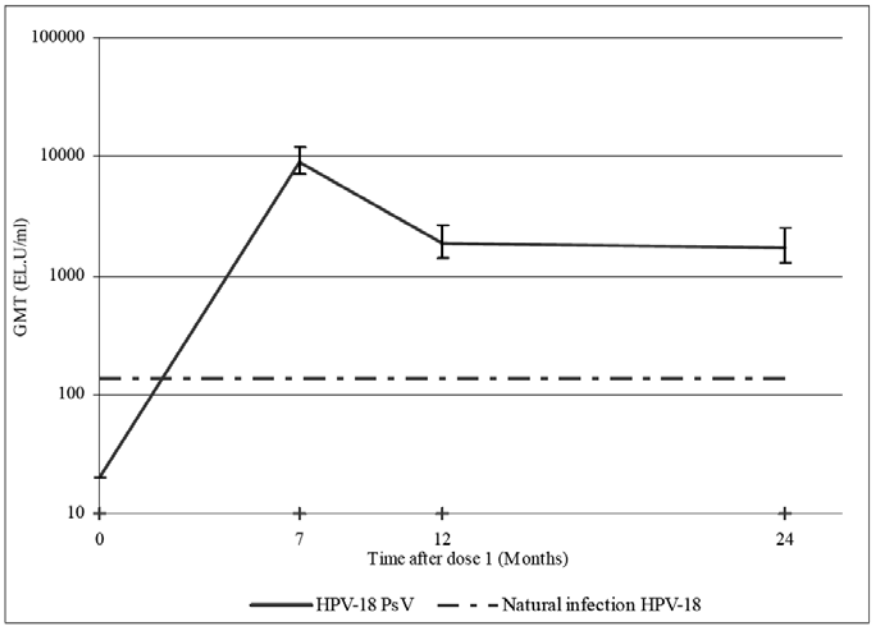
Vaccine-induced GMTs were above levels elicited after naturally acquired infection at each time-point post-vaccination. At Month 24, GMTs for anti-HPV-16 and anti-HPV-18 neutralizing antibodies were higher than those elicited after natural infection. As observed for ELISA, the kinetics of anti-HPV-16 and anti-HPV-18 antibodies by PBNA confirm the results obtained in the ATP cohort for immunogenicity. After a peak response at Month 7, GMTs for anti-HPV-16 neutralizing antibodies gradually declined up to Month 24. Between Month 12 and Month 24, the decline in anti-HPV-16 GMTs was however less pronounced than between Month 7 and Month 12. GMTs for anti-HPV-18 neutralizing antibodies already reached a plateau at Month 12 that was maintained up to Month 24 (Figure 26).

Figure 26-Study HPV-008: Kinetics for anti-HPV-16 antibodies using PBNA in initially seronegative subjects with anti-HPV-16 PBNA results available at all timepoints (ATP cohort for immunogenicity - HPV group)



Source: STN 125259.48, CSR 008, Figure 13, p. 468

Figure 27-Study HPV-008: Kinetics for anti-HPV-18 antibodies using PBNA in initially seronegative subjects with anti-HPV-18 PBNA results available at all timepoints (ATP cohort for immunogenicity - HPV group)



Source: STN 125259.48, CSR 008, Figure 14, p. 468

Immune correlates of protection: Anti-HPV-16 and anti-HPV-18 ELISA and PBNA titers assessed in vaccine recipients with breakthrough CIN2+ associated with HPV-16 or HPV-18 infection are presented. In the TVC-1, eight cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected, of which three cases were also identified as associated with HPV-16 or HPV-18 based on the HPV type assignment algorithm. Four of the eight CIN2+ cases were included in the analysis of HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy. Due to this low number of cases at the time of the final analysis, no correlate of protection could be identified.

Table 199-Study HPV-008: Anti-HPV-16 and anti-HPV-18 ELISA and PBNA titers at Month 0 and Month 7 for vaccine recipients with breakthrough CIN2+ (TVC-1)

Case #	Protocol defined case	Type assignment case	ELISA titres (cut-off)				PBNA titres (cut-off)			
			HPV-16 (8 EL.U/mL)		HPV-18 (7 EL.U/mL)		HPV-16 (40 ED50)		HPV-18 (40 ED50)	
			PRE	PIII(M7)	PRE	PIII(M7)	PRE	PIII(M7)	PRE	PIII(M7)
1*	HPV-16	NO	<8	4945	<7	1179	<40	15783	<40	1929
2*	HPV-18	NO	<8	29564	<7	14383	<40	150256	<40	82284
26*	HPV-18	HPV-18	73	3461	<7	4096	<40	1844	<40	12841
42	HPV-16	HPV-16	96	7336	<7	2357	100	22843	<40	27462
44	HPV-16	NO	15	8926	<7	4078	<40	59359	<40	44703
63	HPV-16	HPV-16	<8	22974	<7	14049	<40	177305	<40	44166
91	HPV-16	NO	13	28241	<7	13033	<40	37734	<40	251218
109*	HPV-16	NO	<8	8243	76	2609	<40	25728	<40	9562

PRE = Pre-vaccination
PIII(M7) = Post Dose III (Month 7)
PBNA = pseudovirion based neutralizing assay
Case numbers were assigned by GSK.
Protocol defined case = CIN2+ case with HPV-16/18 detected in the lesion in subjects that were HPV DNA negative at Month 0, regardless of serostatus, for the corresponding type found in the lesion.
Type assignment case = Protocol defined cases were further evaluated using the HPV type assignment algorithm in which the association with HPV-16 and/or HPV-18 was based not only on the detection of HPV DNA in the lesion, but also considered the presence of HPV types in the two immediately preceding cytology samples when more than one HPV type was found in the lesion.
*Cases in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy.
Source: STN 125259.48, CSR 008, Table 136, p. 469

Immunogenicity conclusions: In this final analysis, the immune response elicited by the HPV vaccine was evaluated by ELISA and PBNA. When measured by ELISA, high seropositivity rates (≥ 99.4%) were observed for anti-HPV-16 and anti-HPV-18 antibodies up to Month 36 (up to 30 months after completion of the full vaccination course). After a peak response at Month 7, GMTs for anti-HPV-16 and anti-HPV-18 antibodies gradually declined until approximately Month 24 and then reached a plateau level. GMTs were above levels elicited after naturally acquired infection at each time-point post-vaccination.

Overall, the immune responses for subjects who were seronegative for HPV-16 or HPV-18 at baseline and subjects who were seropositive for HPV-16 or HPV-18 at baseline were comparable. Also, no clinically relevant differences in immune responses were observed between subgroups by ethnicity.

Analysis of subjects vaccinated according to varied schedules showed similar immune responses for subjects vaccinated according to a flexible Dose 2 schedule (0, 2, 6-month versus 0, 1, 6-month schedule) and subjects vaccinated according to a flexible Dose 3 schedule (three doses administered within a period of 5, 6, 7, 8 or 9 or more months).

The analysis of anti-HPV-16 and anti-HPV-18 neutralizing antibodies by PBNA, in a subset of "naïve" subjects (i.e. DNA negative for HPV-16, 18, 31, 33 and 45 and seronegative for HPV-16 and HPV-18 at Month 0), showed similar results than those obtained by ELISA. All evaluated subjects were seropositive for anti-HPV-16 and anti- HPV-18 neutralizing antibodies at Month 24, i.e. up to 18 months after completion of the full vaccination course. After a peak response at Month 7, GMTs for anti-HPV-18 neutralizing antibodies already reached a plateau at Month 12, while GMTs for anti- HPV-16 neutralizing antibodies gradually declined up to Month 24 (with a smaller decline between the Month 12 and 24 timepoints). GMTs by PBNA were well above levels elicited after naturally acquired infection at each timepoint post-vaccination (20.3-fold higher for HPV-16 and 12.3-fold higher for HPV-18 at Month 24).

CONCLUSIONS FOR STUDY HPV-008
EFFICACY CONCLUSIONS

For prevention of CIN2+ lesions associated with HPV-16 and/or HPV-18 (HPV-16/18), vaccine efficacy was 92.9% [96.1% CI: 79.9, 98.3] in subjects who were seronegative at baseline and HPV DNA negative at baseline and Month 6, with 4 cases in the HPV group and 56 in the HAV group in the ATP cohort for efficacy. Statistically significant vaccine efficacy also was observed for HPV-16 or HPV-18, with high point estimates and the lower limits of the 95% CI well above 30% for each type. All other histopathological (CIN3+, CIN1+, ASC-US+ and VIN/VaIN1+) and virological (incident, 6-month and 12-month persistent infection) efficacy endpoints associated with HPV-16/18 were statistically significant in the ATP cohort for efficacy in subjects who were seronegative at baseline and HPV DNA negative at baseline and Month 6. With this final analysis, efficacy was demonstrated individually for HPV-016 and HPV-018 (item in complete response letter 12/14/07). There were several statistical issues which were discussed (as measured in the complete response letter 12/14/07). Please see statistical review.

At the final analysis, the average follow-up time for the primary endpoint evaluation was approximately 2 years longer than at interim, with a mean follow-up of 2.9 years in the ATP cohort for efficacy and 3.3 years in TVC 1. At final analysis the results in TVC-1, also demonstrated statistically significant vaccine efficacy for the primary and secondary endpoints associated with HPV-16/18 and supported the results in the ATP cohort for efficacy. These results were in a population of women aged 15-25 years, many of whom had prevalent infections with oncogenic HPV types other than HPV-16/18 at study entry. Vaccine efficacy levels evaluated in subjects without considering their initial HPV-16/18 serostatus at study entry were comparable to those in HPV-16/18 seronegative subjects, in both the ATP cohort for efficacy and TVC 1.

Overall vaccine efficacy was assessed in an analysis that included all lesions, irrespective of the HPV type present, which avoided the limitation of detection of multiple HPV DNA types by the PCR algorithm used in the trial and indicated a broad prophylactic overall vaccine efficacy. Results for overall vaccine efficacy against CIN2+, CIN1+ and ASC-US+, irrespective of HPV DNA type present in the lesion, were statistically significant in subjects irrespective of their baseline HPV DNA status in TVC-1. The results in the broader Total Vaccinated cohort for CIN2+ and CIN3+, were also statistically significant. The proportion of all CIN2+ lesions in the HAV group associated with HPV-16/18 ranged from 30.7% to 58.4%, depending on whether only HPV-16/18 were present or if other HPV types were also present, which was consistent with rates in the literature. In an exploratory analysis, an impact of the vaccine was also observed for cervical therapy and was consistent with a reduction in the number of CIN2+ lesions.

At final analysis, additional data was available prevention of other oncogenic HPV types. There was evidence of prevention of CIN2+ associated with non-vaccine HPV types (combined analysis) even when excluding lesions which also contain HPV 16 and/or 18. In *post-hoc* analyses in which lesions which contained HPV 16 and/or 18, there was evidence of impact on prevention of CIN2+ lesions associated with HPV-31. However, it is not clear if the duration of protection for this HPV type will be as robust as the protection against HPV-16 and HPV-18.

Vaccination did not protect against histopathological lesions caused by HPV-16/18 infections present at the time of vaccination and did not influence clearance of HPV. In addition, there was no evidence that the vaccine enhanced cervical disease caused by a HPV-16/18 infection or increased the duration of HPV infection if already present at the time of vaccination.

SAFETY CONCLUSIONS
Cervarix induced a higher rate of local and general solicited symptoms compared to the HAV group. This increased reactogenicity did not appear to impact on the subjects' completion of the vaccination course. There were no apparent differences in overall safety outcomes, including SAEs, medically significant events, NOCDs and NOADs following HPV-16/18 vaccination.

The proportions of spontaneous abortions was higher in subjects who received Cervarix around the time of estimated date of conception. This issue is discussed in additional detail in the overall safety section. The distribution of other pregnancy outcomes was generally balanced between treatment groups.

Compliance with the full vaccination course was equally high in both HPV and HAV groups, confirming that the higher rates of local and general solicited symptoms following HPV-16/18 vaccination did not negatively impact tolerability or acceptance of the vaccination. The analysis of this large dataset confirms that the safety profile of the vaccine is satisfactory and clinically acceptable.

IMMOGENICITY CONCLUSIONS
The immunogenicity results of this final analysis confirm the strong immune response induced by the HPV vaccine compared to the immune response elicited after natural infection, with 99.4% or more of the vaccinees remaining seropositive for anti-HPV-16 and anti-HPV-18 antibodies (by ELISA) up to 30 months after completion of the three-dose vaccination course. The antibody kinetics for HPV-16 and HPV-18 are in line with those observed in other HPV studies, i.e. a peak response at Month 7, followed by a gradual decline in GMTs until approximately Month 24, after which timepoint a plateau level is reached. Vaccine-induced GMTs were well above titers associated with clearance of natural infection when analyzed by ELISA and PBNA (neutralizing titers).

As noted in study HPV-001/007, the seropositivity rates in subjects initially seronegative for the specific vaccine HPV type as measured by IgG by ELISA and by pseudovirion neutralizing assay were near or at 100% for both HPV types. The peak antibody response was 1 month after dose 3, declined between Month 12-18, and then plateaued between Month 18-24. No immune correlate of protection was identified.

8.7: Trial # 7: A Phase III, double-blind, randomized, controlled study to evaluate the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a 0, 1, 6 month schedule in healthy female subjects aged 10-14 years.
Study Dates: 6/30/04-8/4/05
Study Site: This study was conducted by 52 investigators in 12 countries at 57 centers (Australia, Colombia, Czech Republic, France, Germany, Honduras, Korea, Norway, Panama, Spain, Sweden and Taiwan).

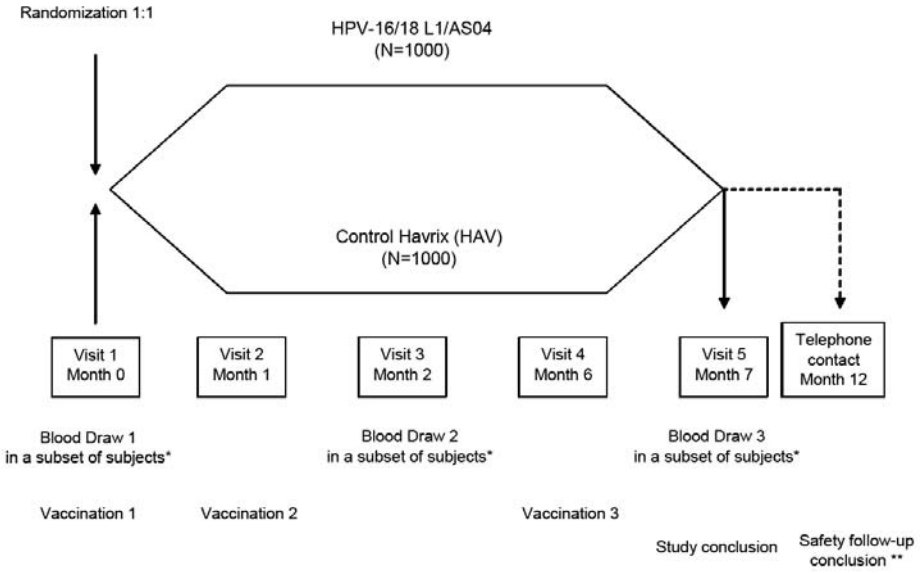
Study Objectives
The **primary objective** was to compare the occurrence of serious adverse events (SAEs) between the HPV-16/18 vaccine group and the hepatitis A vaccine (HAV) control group throughout the study period (up to Month 7).

The **secondary objectives** of the study were as follows:
- Evaluate in both groups the solicited local and general symptoms reported during the 7-day period (Days 0 – 6) following each and any vaccination.

- Evaluate in both groups the occurrence of unsolicited symptoms reported during the 30-day period (Days 0 – 29) following any vaccination.
- Evaluate between the HPV-16/18 vaccine group and the HAV control group the occurrence of new onset of chronic diseases (NOCD) and other medically significant conditions, e.g. autoimmune disorders, asthma, type I diabetes and conditions prompting emergency room visits or physician visits that are not related to common diseases, throughout the study period (up to Month 7) regardless of causal relationship to vaccination and intensity.
- Evaluate in all subjects from pre-specified sites the effect of vaccination on biochemical and hematological parameters at Months 0, 2 and 7.
- Evaluate in all HPV-16/18 vaccine recipients from pre-specified sites antibody responses against HPV-16 and HPV-18 (by enzyme-linked immunosorbent assay [ELISA]) at Months 0, 2 and 7.
- Evaluate in all subjects from pre-specified sites antibody responses against MPL (by ELISA) at Months 0, 2 and 7.
- Compare, 1 month after the third dose (i.e. at Month 7), the immune responses to the candidate HPV-16/18 vaccine (as determined by anti-HPV-16/18 ELISA) in healthy female subjects aged 10 – 14 year old in this study with responses measured in sera from adults of the efficacy study 580299/001 (HPV-001).
- Compare the occurrence of SAEs, NOCD and other medically significant conditions between the HPV-16/18 vaccine group and the HAV control group through the Month 12 follow-up telephone call. This objective will be presented in a separate annex report.

Study Design: This study was a phase III, multicentric, double-blinded, randomized and controlled trial with two groups (Cervarix vaccine [HPV] and Havrix control vaccine [HAV] groups). All subjects were to receive either the HPV vaccine or HAV control vaccine according to a 0, 1, 6 month schedule. Five visits were scheduled at Months 0, 1, 2, 6 and 7, and a telephone contact at Month 12. Blood samples were to be collected at visits 1, 3, 5 (i.e. at Months 0, 2, and 7). A diagram of the study is shown below in Figure 28.

Figure 28 –Study HPV-013: Overall Study Design



N = planned number of subjects.
* All subjects from a number of pre-specified sites across the three geographic regions (a minimum of 600 subjects comprising HPV vaccine recipients and HAV recipients was planned in the protocol).
** This safety follow-up is still ongoing and will be presented in an annex report.

- Experimental design: multi-center, double-blinded, randomized (1:1), controlled study with two parallel groups.
- Treatment allocation: subjects received either the candidate HPV-16/18 vaccine or the hepatitis A virus (HAV) control vaccine (GSK Biologicals' HAV vaccine containing 360 EU of hepatitis A antigen per 0.5 mL dose).

Reviewer's Comment: GSK indicated that this dose was previously licensed for use in pediatric subjects.

- Vaccination schedule: three doses of vaccine administered intramuscularly according to a 0, 1, 6 month schedule.
- Blood sampling schedule: blood samples were collected at Months 0, 2 and 7 in 35 pre-defined centers.
- Blinding: Due to differences in the appearance of the HPV-16/18 vaccine and the HAV control vaccine, the study was conducted double-blinded (observer-blinded, i.e., syringes were prepared and administered by qualified medical personnel not otherwise involved in the conduct of the study or in the assessment of symptoms, whereas study staff involved in the assessment of subjects remained blinded).
- This study was conducted in 12 countries in Asia Pacific, Europe and Latin America (Australia, Colombia, Czech Republic, France, Germany, Honduras, Korea, Norway, Panama, Spain, Sweden and Taiwan).
- Treatments were allocated to subjects using an internet based randomization system (--b(4)--). Enrolment was age-stratified (10 - 12 year olds and 13 - 14 year olds). The protocol was amended to ensure that no more than 50% and no fewer than 40% of subjects were in the 13 - 14 year olds stratum.
- There were five scheduled visits per subject at Months 0, 1, 2, 6 and 7.
- The safety and the reactogenicity of the HPV-16/18 vaccine and the HAV vaccine were monitored as follows:
  - Biochemical and hematological parameters at Months 0, 2 and 7 in the subset of subjects who were bled.
  - Solicited signs and symptoms were self-reported in all subjects, using a diary card, within 7 days (Days 0 - 6) after each vaccination.
  - Unsolicited signs and symptoms were reported in all subjects within 30 days (Days 0 - 29) after each vaccination.
  - SAEs were reported in all subjects throughout the study period (up to Month 7).
  - NOCD and other medically significant conditions were reported in all subjects throughout the study period (up to Month 12) regardless of causal relationship to vaccination and intensity.
  - Antibody responses against HPV-16 and HPV-18 were evaluated in HPV vaccine recipients.
  - Antibody responses against HAV were to be evaluated in HAV vaccine recipients.

These data will be provided in an annex report.

- Antibody responses against MPL were evaluated in a limited number of subjects (only subjects enrolled in German centers. The final data of the complete immunogenicity subset (the 35 pre-defined centers in the immunogenicity subset) will be provided in an annex report.
- An annex report was prepared to describe additional safety data collected through the Month 12 follow-up telephone contact.

Table 200-Study HPV-013: Outline of study procedures

Visit Timing Sampling time point	Visit 1 Day 0 Pre-vacc	Visit 2 Month 1 Post vacc I	Visit 3 Month 2 Post vacc II	Visit 4 Month 6 Post vacc II	Visit 5 Month 7 Post vacc III	Telephone contact Month 12†
Informed consent/assent	●					
Check inclusion criteria	●					
Check exclusion criteria	●					
Check elimination criteria		●	●	●	●	
Check contraindications		●		●		
Record any concomitant medication/vaccination	●	●	●	●	●	
Medical history	●					
History-directed physical examination	●					
Collect demographic data	●					
Urine sample for pre-vaccination pregnancy test	●	●		●		
Pre-vaccination body temperature	●	●		●		
Blood sampling - 5 mL for biochemical and haematological analysis - 5 mL for HPV/MPL®/HAV antibody determination	● ●		● ●		● ●	
Internet randomization	●					
Vaccination	●	●		●		
Distribution of diary cards for post-vaccination recording of solicited symptoms (Days 0 - 6) and unsolicited symptoms (Days 0 - 29)	○	○		○		
Counselling	●	●	●	●	●	
Return of diary cards		○	○		○	
Diary card transcription		●	●		●	
Reporting of SAEs, new onset chronic diseases and other medically significant conditions	●	●	●	●	●	●
Reporting of pregnancies (and outcome)		●	●	●	●	●
Safety follow-up contact						●
Study Conclusion					●	
Safety follow-up conclusion						●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
† The results of the Month 12 follow-up telephone contact will be reported in annex report.
Source: STN 125259/0, CSR HPV-013, Table 1, p. 30

All subjects/subjects' parents/guardians received diary cards to record solicited adverse events within 7 days (Day 0 – 6) following vaccination and any unsolicited adverse events within 30 days (Day 0 – 29) following vaccination. Subjects were instructed to return the diary cards at the next visit, for transcription. Follow-up data through Month 24 are included in this review.

Selection of study population: This study was conducted in healthy female subjects between 10 and 14 years of age. The target was to enroll 2000 subjects in multiple centers located in Australia, Colombia, Czech Republic, France, Germany, Honduras, Korea, Norway, Panama, Spain, Sweden and Taiwan.

Inclusion criteria
All subjects were to satisfy the following criteria at study entry:

- Subjects able to comply with requirements of the protocol.
- A female between, and including, 10 and 14 years of age at the time of the first vaccination.
- Written informed assent obtained from the subject and written informed consent obtained from a parent or legally acceptable representative.

- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Subjects were to have a negative urine pregnancy test.
- Subjects of childbearing potential at the time of study entry were to be abstinent (and if so, this was to be documented in the source documents at each vaccination visit) or using an effective method of birth control for 30 days prior to vaccination and to have agreed to continue such precautions for 2 months after completion of the vaccination series. Subjects who reached menarche during the study and therefore were of childbearing potential had to agree to follow the same precautions.

Exclusion criteria
The following criteria were to be checked at the time of study entry. If any applied, the subject was not to be included in the study:
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Pregnant or breastfeeding.
- Planning to become pregnant or likely to become pregnant (as determined by the investigator).
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccine dose.
- Planned administration/administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after (i.e. Days 0 – 29) the first dose of vaccine. Administration of routine vaccines specified).
- Previous administration of MPL or AS04 adjuvant.
- Previous vaccination against HPV.
- History of vaccination against hepatitis A or a known clinical history of hepatitis A infection.
- Any medically diagnosed or suspected immunodeficient condition based on medical history and physical examination (no lab testing required).
- History of allergic disease, suspected allergy or reactions likely to be exacerbated by any component of the study vaccines, e.g. aluminum, MPL®, hepatitis A antigen, 2-phenoxyethanol or neomycin.
- Hypersensitivity to latex (found in syringe-tip cap and plunger).
- Known acute or chronic, clinically significant neurologic, hepatic or renal functional abnormality, as determined by previous physical examination or laboratory tests.
- History of chronic condition(s) requiring treatment such as cancer, chronic hepatic or kidney disease(s), diabetes, or autoimmune disease.
- Administration of immunoglobulins and/or any blood product within 3 months preceding the first dose of study vaccine or planned administration during the study period. Enrolment warranted deferral until the subject was outside of specified window.
- Acute disease at the time of enrollment. Acute disease was defined as the presence of a moderate or severe illness with or without fever. Enrollment warranted deferral until condition was resolved. All vaccines could have been administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-Grade febrile illness, i.e. oral temperature <37.5°C (99.5°F)/axillary temperature <37.5°C (99.5°F).

Elimination criteria
The following criteria were to be checked at each visit subsequent to the first visit. If any became applicable during the study, it was not required to withdraw the subject from the study but it determined a subject's evaluability in the ATP analysis.
- Pregnancy.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids were allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before each dose of study vaccines and ending 30 days after (i.e. Days 0 – 29). Administration of routine meningococcal, hepatitis B, inactivated influenza, diphtheria/tetanus and/or diphtheria/tetanus-containing vaccine up to 8 days before each dose of study vaccine was allowed if the subject was outside of the 30 days follow-up period of the previous dose.
- Administration of immunoglobulins and/or any blood products during the study period.
- Newly diagnosed immunosuppressive condition, including human immunodeficiency virus (HIV) infection.

Contraindications to subsequent doses of vaccine

The following adverse events (AEs) constituted absolute contraindications to further administration of any study vaccine; if any of these AEs occurred during the study, the subject was not to receive additional doses of vaccine but was allowed to continue other study procedures at the discretion of the investigator. The subject was to be followed until resolution of the event, as with any AE:

- Clinically significant decreased liver or renal function which in the opinion of the investigator (or designate) precluded further administration of vaccine to the subject.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Pregnancy.
- Hypersensitivity reaction following vaccine administration (including urticaria within 30 minutes of vaccine administration).
- Anaphylactic reaction following the administration of study vaccines.
- Any SAE judged to be related to study vaccines.
- Other significant reactions which in the opinion of the investigator (or designate) precluded further administration of the study vaccine (may have included severe pain, severe swelling, severe limitation of motion, persistent high fever, severe headache or other systemic or local reactions).

The following AEs constituted contraindications to administration of any study vaccine at that point in time. If any one of these AEs occurred at the time scheduled for vaccination, the subject could be vaccinated at a later date, within the time window specified in the Protocol or withdrawn at the discretion of the investigator. The subject was to be followed until resolution of the event, as with any AE.

- Acute disease at the time of vaccination. Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines could be administered to persons with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile illness, i.e. oral/axillary temperature <37.5°C (99.5°F).
- Oral/axillary temperature ≥37.5°C (99.5°F) at the time of vaccination.

Subject completion and withdrawal from study

Subject withdrawal from the study: A subject who returned for the concluding visit at Month 7 was considered to have completed the active phase of the study. The following possible reasons were considered as responsible for withdrawal of the subject from the study: Serious adverse event; Non-serious adverse event; Protocol violation (to be specified); Consent withdrawal, not due to an AE; Moved from the study area; Lost to follow-up; Other (to be specified).

Subject withdrawal from administration of the investigational product: A 'withdrawal' from administration of the investigational product was defined as any subject who did not receive the complete treatment, i.e. when no further planned dose was administered from the date of withdrawal. A subject withdrawn from administration of the investigational product may not necessarily be withdrawn from the study, and could participate as to further assessments for safety and immunogenicity if planned in the study protocol. Possible reasons for withdrawal: Serious adverse event; Non-serious adverse event; Other (to be specified).

Vaccine Products Used

Table 201-Study HPV-013: Vaccines, formulation, lot numbers and allocation

Vaccine	Formulation Each dose (0.5 mL) contains:	Presentation	Lot number	Group
Candidate Vaccine: HPV-16/18 L1/AS04	20 μg HPV-16 L1 protein 20 μg HPV-18 L1 protein 50 μg MPL® 500 μg aluminium as $Al(OH)_3$	Liquid in pre-filled syringes	DHPV007A 9	HPV
Control vaccine: Havrix®	360 E.U. inactivated hepatitis A viral antigen 250 μg aluminium as $Al(OH)_3$ 2.5 mg 2-phenoxyethanol 1.5 mg amino acid supplement 25 μg polysorbate 20 residual MRC-5 cellular proteins trace of neomycin sulfate (<20 ng/dose) trace of formalin	Liquid in pre-filled syringes	DHAVA001 A	HAV

Source: STN 125259/0, CSR HPV-013, Table 3, p. 36

Vaccines were to be stored in the refrigerator at + 2°C to +8°C/ 36°F to 46°C and were not to be frozen.

Dosage and administration: The HPV vaccine and the HAV control vaccine were supplied as liquid in individual pre-filled syringes (0.5 mL) to be administered intramuscularly into the deltoid of the non-dominant arm on a 0, 1, 6 month schedule. The vaccinees were observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a reaction.

Randomization of subjects: 2000 subjects were to be enrolled to reach approximately 1900 subjects evaluable for the final ATP analysis of safety. The enrollment was to be performed to provide approximately equal distribution of the population across the age ranges (10 – 12 and 13 – 14 year olds). The protocol was amended to ensure that no more than 50% and no fewer than 40% of subjects were in the 13 - 14 year old stratum. The treatment allocation at the investigator site was performed using --b(4)--.

Blinding: Study HPV-HPV-013 was conducted as observer-blinded. Due to the different appearance of the HPV vaccine and the HAV control vaccine (both vaccines contain different quantities of aluminum, which results in a different turbidity of the vaccines which may allow identification), individuals involved in preparation of the vaccine doses were not involved in any safety assessments. All subjects and study personnel not involved in preparation and administration of study vaccines were blinded to the individual subject treatment. Blinding was to be maintained for the subjects and the investigators until the telephone contact at Month 12. An extended follow-up study was conducted and results reported to Month 24 in the BLA.

GSK Biologicals' personnel involved in laboratory testing were provided with the individual subject treatment group assignments so that appropriate laboratory tests could be performed

(testing of sera from the HPV vaccine group for anti-HPV antibodies and testing of sera from the HAV group for anti-HAV antibodies). Laboratory personnel were not involved in safety assessments. GSK personnel directly involved in the conduct of the study and the review of study listings were blinded to individual subject treatment group assignments. Blinding was maintained until the last subject enrolled completed the last visit at Month 7 and during cleaning activities. After that point, GSK staff were to be unblinded. To maintain blinding of investigators and other study site personnel until all assessments were complete, this report would only be distributed outside GSK Biologicals to regulatory authorities (as needed) and to the HPV IDMC.

Prior and concomitant medication/ vaccinations: All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine and ending 1 month (minimum 30 days) after each dose of study vaccine were to be recorded.

Adverse events and serious adverse events: All AEs occurring within 30 days following administration of each dose of vaccine were to be recorded on the Adverse Event form in the subject's electronic Clinical Report Form (eCRF), irrespective of severity or whether or not they were considered vaccination-related.

AEs related to new onset chronic diseases and other medically significant conditions prompting emergency room visits or physician visits that were not related to common diseases or routine visits occurring throughout the study period (up to Month 7) were to be recorded on the Adverse Event form in the subject's eCRF, irrespective of severity or whether or not they were considered vaccination-related. The following did not require reporting as long as they were not considered SAEs and occurred more than 30 days after each vaccination: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities, injury, visits for routine physical examination or visits for vaccination.

SAEs that were related to study participation (e.g. procedures, first vaccination, invasive tests) began at the time the consent to participate in the study was obtained and ended one month following administration of the last dose of study vaccine (i.e. at Month 7) for each subject. SAEs and AEs related to NOCD and other medically significant conditions were to be collected up to the Month 12 telephone contact and recorded in the eCRF.

The investigator inquired about the occurrence of AEs/SAEs at every visit/contact during the study.

Solicited and unsolicited adverse events: The solicited local and general adverse events were as described for study HPV-001. In addition, the intensity was also graded as noted in study HPV-001. Fever was reported in 0.5 deg C increments.

The causality was assessed by the investigator.

Follow-up and reporting of serious adverse events were as noted in study HPV-001.

Pregnancy was to be followed as noted in study HPV-001.

New Onset Chronic Diseases were also assessed as noted in study HPV-007.

Clinical laboratory evaluations: Urine samples (10 mL) were collected before each vaccination (Month 0, 1 and 6) to perform pregnancy tests. In case the test was positive, the vaccine was not to be administered.

Blood samples were collected at Months 0, 2 and 7 in 35 pre-defined centers to evaluate changes in subjects' biochemical and hematological values. These blood tests included creatinine, alanine amino transferase, white blood cells and differential, red blood cells, platelets, and hematocrit. In case of insufficient blood sample volume to perform all assays, the analysis of biochemical and hematological parameters was to take priority over serology testing.

Laboratory assays and time points: Blood samples were collected at Months 0, 2 and 7 in 35 pre-defined centers:

- Antibody responses against HPV-16 and HPV-18 were evaluated in HPV vaccine recipients.
- Antibody responses against HAV were to be evaluated in HAV vaccine recipients.
- Antibody responses against MPL were evaluated in a limited subset of subjects (only subjects enrolled in German centers)

The serological assays performed in this study are described in Table 202. All assays were run in GSK Biologicals laboratory.

Table 202-Study HPV-013: Serological assays

Assay type	Marker	Assay method	Test Kit / Manufacturer	Assay unit	Assay cut-off	Laboratory
Quantitative	anti-HPV-16	ELISA	(b)(4) methodology modified by GSK Biologicals	El. U/mL	8 EU/mL	GSK Biologicals
	anti-HPV-18				7 EU/mL	
Quantitative	anti-MPL	ELISA	In-house assay	El. U/mL	—*	GSK Biologicals

* There was no cut-off value for this assay. The anti-MPL antibodies were evaluated using a limit of quantification of --b(4)-- EU/mL.
Source: STN 125259/0, CSR HPV-013, Table 8, p. 49

In case of insufficient blood sample volume to perform assays for all antibodies in HPV-16/18 vaccine recipients, samples were analyzed according to the following priority ranking: 1. anti-HPV-16; 2. anti-HPV-18; 3. anti-MPL

STATISTICAL CONSIDERATIONS

Primary endpoint: Occurrence of SAEs throughout the study period (up to Month 7).

Secondary endpoints

- Occurrence, intensity and relationship to vaccination of solicited general symptoms, and occurrence and intensity of solicited local symptoms within 7 days (Days 0 – 6) after each and any vaccination.
- Occurrence, intensity and causal relationship to vaccination of unsolicited symptoms within 30 days (Days 0 – 29) after any vaccination.
- Occurrence of NOCD and other medically significant conditions prompting emergency room visits or physician visits that are not related to common diseases throughout the study period (up to Month 7) regardless of causal relationship to vaccination and intensity.
- Occurrence of clinically relevant abnormalities in biochemical and hematological parameters assessed at Months 0, 2 and 7.
- Anti-HPV-16/18 antibody titers (by ELISA) assessed at Months 0, 2 and 7.
- Anti-MPL antibody titers (by ELISA) assessed at Months 0, 2 and 7.

- Comparison of anti-HPV-16/18 antibody titers (by ELISA) assessed in sera from 10 - 14 year olds in this study (HPV-HPV-013) with sera from adults in study 580299/001 at Month 7.
- Occurrence of SAEs, NOCDs and other medically significant conditions up to Month 12 (extended safety follow-up).

Determination of sample size: The primary objective of this study was to compare the occurrence of SAEs between the HPV-16/18 vaccine group and the HAV control group throughout the study period (up to Month 7).

SAE rates in the HPV-16/18 vaccine group and in the HAV control group were expected to be the same. The rate of SAEs observed in a HPV-001 at 18 months was about 3.9%. Since the active phase of this study (HPV-HPV-013) was to last 7 months, it was assumed that the SAE rate during the study would vary from 0% to 3%.

With 950 evaluable subjects in the HPV vaccine group and 950 subjects in the HAV control group, the study was calculated to have 70% power to rule out an increase of 1.5% in the rate of SAEs in the HPV vaccine group and 91% power to rule out an increase of 2%, if the reference rate in the HAV control group was 1.5%. If the HAV control group had a SAE rate of 1%, the study would have 84% power to rule out an increase of 1.5% and 97% power to rule out an increase of 2% in the HPV-16/18 vaccine group. The study would have 80% power to detect a statistically significant difference between the two groups if the SAE rate was 3.9% in the HPV-16/18 vaccine group as compared to 2% in the HAV control group (approximately a 2-fold increase).

With 1000 subjects enrolled in the HPV vaccine group and 1000 in the HAV control group, and assuming 5% may be non-evaluable subjects for the analysis of safety, the two groups to be compared in the primary objective (HPV vaccine versus HAV control vaccine) should each have 950 evaluable subjects.

Study cohorts/data sets analyzed
Total Vaccinated cohort: The Total Vaccinated cohort included all vaccinated subjects for whom data were available.
- **Total analysis of safety** included all subjects with at least one vaccine administration documented. This cohort was considered the primary cohort for analysis of safety.
- **Total analysis of immunogenicity** included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.
- **Total Vaccinated cohort analysis** was performed per treatment actually administered.

According-To-Protocol (ATP) cohort for analysis of safety: The ATP cohort for analysis of safety included all subjects with the following:
- received at least one dose of study vaccine/control according to their random assignment
- sufficient data to perform an analysis of safety (at least one dose with safety follow-up)
- administration site of study vaccine/control was known
- not received a vaccine not specified or forbidden in the protocol
- randomization code had not been broken.

According To Protocol (ATP) cohort for analysis of immunogenicity: The **ATP cohort for analysis of immunogenicity** was considered the primary cohort for analysis of immunogenicity and included all evaluable subjects as follows:
- meeting all eligibility criteria

- complying with the procedures defined in the protocol
- with no elimination criteria during the study
- data concerning immunogenicity endpoint measures were available (included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.)

Derived and transformed data
Reactogenicity
- The analysis of solicited symptoms was based on the Total vaccinated cohort and included only subjects/doses with documented safety data.
- For the analysis of unsolicited AEs/SAE/concomitant medication, all vaccinated subjects were considered and subjects who did not report the event were considered as subjects without the event.

Immunogenicity
- The cut-off values of the assay were defined by the laboratory before the analysis.
- A seronegative subject was a subject whose titer was below the cut-off value.
- A seropositive subject was a subject whose titer was greater than or equal to the cutoff value.
- In the evaluation of anti-MPL antibodies, a seropositive subject was a subject whose titer was greater than or equal to the limit of quantification value (-b(4)- EU/mL).
- Seroconversion was defined as the appearance of antibodies with a titer ≥ cut-off value in subjects seronegative before vaccination.
- Geometric Mean Titers (GMTs) calculations were performed by taking the antilog of the mean of the log titer transformations. Antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation. For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced.

Analysis of demographics: Demographic characteristics (age, region and race) of each study cohort were reported and mean age (plus range and standard deviation) of the enrolled subjects, as a whole and per group, was calculated.

Analysis of safety: The primary analysis of safety was based on the Total vaccinated cohort. A second analysis based on this ATP cohort was also performed.

Primary objective: The primary objective was to compare the occurrence of SAEs between the HPV vaccine group and the HAV control group throughout the study period (up to Month 7). The two-sided standardized asymptotic 95% CI for the difference of SAE rates (SAE rate in HAV vaccine group minus SAE rate in HPV vaccine control group) were computed. The SAE rate was defined as the proportion of subjects in both groups who experienced at least one SAE.

The other safety objectives were reported as well.
- Solicited AEs and unsolicited AEs were reported per subject and per dose, as well as the proportion assessed as Grade 3 in intensity and relationship to vaccine as assessed by the investigator.
- Unsolicited AEs in the 30 days after vaccination were reported per subject, along with proportions assessed as Grade 3 in intensity and relationship to vaccination as assessed by the investigator.
- Occurrence of fever was reported per 0.5°C increments
- Duration of solicited symptoms was presented.

- The proportion of subjects with at least one report of NOCD during the entire study period, classified by MedDRA was reported. GSK presented these NOCDs as assessed by GSK physicians and investigator's assessments.
- The proportion of subjects with at least one report of a medically significant AE up to 30 days after vaccination and starting at 30 days after vaccination classified by MedDRA was reported.
- Withdrawal due to adverse events was described.

Analysis of immunogenicity: The primary analysis of immunogenicity was based on the ATP cohort. A second analysis based on the Total Vaccinated cohort was performed to supplement the primary analysis.
Reviewer's Comment: Only subjects at specific centers were to be included in the ATP cohort for immunogenicity.

For the HPV vaccine group, the range and distribution of anti-HPV-16, anti-HPV-18 and anti-MPL antibody titers measured by ELISA were tabulated by GMTs with their 95% CI at each time point that a blood sample result was available, along with seroconversion rates. The range and distribution of anti-HPV-16 and anti-HPV-18 antibody titers measured by ELISA in the HPV-001 reference group (study HPV-001 group) were tabulated by GMTs with their 95% CI before vaccination and at Month 7, along with seroconversion rates. The distribution of anti-HPV-16 and anti-HPV-18 antibody titers was displayed using reverse cumulative curves. For the HPV vaccine group and the HAV vaccine group, the range and distribution of anti-MPL antibody titers measured by ELISA were tabulated by GMTs with their 95% CI at each time point that a blood sample result was available, along with seroconversion rates.

Interim analysis: No interim analysis was performed.

Changes in the conduct of the study or planned analyses
Protocol amendments/modifications: There were two amendments to the study protocol. The rationale for each amendment and major changes to the conduct of the study is described below:
- The protocol was amended on December 21, 2004 during the enrollment period. The original protocol planned an equally balanced enrollment in each age stratum (10-12 year olds and 13-14 year olds). The amendment modified the balance between age groups to allow for no more than 50% and no fewer than 40% of subjects in the 13-14 year olds age stratum. The amendment also clarified the period for collection of information on concomitant medication and/or treatment, or 30 days before and 30 days after (Days 0-29) each dose of study vaccine. The amendment gave instructions to record administration of oral contraceptives and provided clarification on routine vaccines, not foreseen by the protocol that could be administered before each dose of study vaccine, and on the definition of an adverse event. The presence or absence of urticaria/rash within 30 minutes of vaccine administration following each vaccine dose was to be documented by the investigator. In addition, reference was made to publication of data from the HPV-001 efficacy study in The Lancet. Prior to the second amendment to the protocol, an additional IRB approval was requested by letter (dated April 19th, 2005) in order to evaluate the anti-MPL antibody levels in HAV vaccine recipients' blood samples. This request was then formalized in the second amendment to the protocol (please see paragraph below for further details).
- The protocol was further amended on August 05, 2005 before the end of the extended safety follow-up (telephone contact Month 12). The amendment provided the design of a 3-year long-term follow-up extension to study HPV-HPV-013. This long-term follow-up study was designed to assess the persistence of vaccine-induced immune responses (anti-HPV-16, anti-

HPV-18 and anti-MPL) and long-term vaccine safety in subjects from the immunogenicity subset in the HPV-HPV-013 study. All subjects in the immunogenicity subset completing the HPV-HPV-013 study were invited to participate to the current study. Once the HPV-HPV-013 study Month 12 telephone contact has been reported, the treatment allocation was to be unblinded and only subjects who received the HPV vaccine were to continue in the extension study, whereas subjects who received the HAV vaccine would attend one further visit as their study conclusion visit. The amendment also planned the assessment of anti-MPL antibodies in all study subjects enrolled in the follow-up study (for all available time points) such that the subjects who received the HAV vaccine in the primary study would provide a control for the subjects that received HPV vaccine.

Other Changes: This study was conducted according to the protocol. Analyses were performed as planned in the protocol and in the RAP with the following exceptions:

- The analyses of the solicited symptoms were done using documented doses (i.e., doses for which information on the solicited local/general symptom sheet was available).
- The duration of solicited symptoms was presented.
- The seropositivity status at study entry before vaccination (pre-vaccination) was presented for both the ATP cohort for immunogenicity analysis and the Total Vaccinated cohort.
- Anti-MPL antibodies were presented in an annex report.
- Per-country analyses were performed for safety and immunogenicity but were to be reported in an annex report.
- Analysis of anti-HAV antibodies were to be presented in an annex report.

RESULTS

Study Population Results

Study dates: The first subject was enrolled in the study on the 6/30/04 and the last study visit (Month 7) took place on the 8/4/05.

Number and distribution of subjects: A total of 2067 subjects were enrolled and vaccinated in the study. The Total vaccinated cohort therefore included 2067 subjects (1035 subjects received the HPV vaccine and 1032 received the HAV control vaccine).The ATP safety cohort included 2031 subjects (1019 in the HPV group and 1012 in the HAV group). The ATP immunogenicity cohort included 1341 subjects (675 subjects in the HPV group and 666 subjects in the HAV group). 383 subjects were selected from the HPV-001 study to constitute the HPV-001 reference group that was compared to the HPV-HPV-013 vaccine group.

Table 203 – Study HPV-013: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

	Total			HPV		HAV	
	n	s	%	n	s	n	s
Total enrolled cohort	**2067**						
Total vaccinated cohort	**2067**		**100**	**1035**		**1032**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	25	25		13	13	12	12
Randomisation code broken at the investigator site (code 1060)†	1	1		0	0	1	1
Study vaccine dose not administered according to protocol (code 1070)	10	10		3	3	7	7
ATP safety cohort	**2031**		**98.3**	**1019**		**1012**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	1	1		1	1	0	0
Administration of any medication forbidden by the protocol (code 2040)	7	9		3	3	4	6
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	21	21		7	7	14	14
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	18	21		10	12	8	9
Essential serological data missing (code 2100)	18	22		7	9	11	13
Obvious incoherence or abnormality or error in data (code 2120)	3	3		3	3	0	0
Subject not included in the pre-defined subset for blood sampling (code 2130)*	622	655		313	327	309	328
ATP immunogenicity cohort	**1341**		**64.9**	**675**		**666**	

HPV = HPV-16/18 L1/AS04
HAV = Hepatitis A vaccine group
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
† The treatment allocation of this subject was unblinded because of an unexpected AE considered by the investigator as related to vaccination.
*This elimination code was given to subjects enrolled from centers not selected for inclusion in the immunogenicity subset and were therefore not bled. Those centers were in Australia, Czech Republic, France, Norway, Spain and Sweden
Source: STN 125259/0, CSR HPV-013, Table 11, p. 58

The distribution of subjects by country is presented in Table 204.

Table 204-Study HPV-013: Number of subjects by country (Total Vaccinated Cohort)

Country	HPV	HAV	Total	
	n	n	n	%
Australia	56	57	113	5.5
Colombia*	100	100	200	9.7
Czech Republic	60	59	119	5.8
France	19	20	39	1.9
Germany*	253	251	504	24.4
Honduras*	135	133	268	13.0
Korea*	27	27	54	2.6
Norway	36	36	72	3.5
Panama*	84	84	168	8.1
Spain	76	77	153	7.4
Sweden	80	79	159	7.7
Taiwan*	109	109	218	10.5

HPV = HPV-16/18 L1/AS04
HAV = Hepatitis A vaccine group
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
* All centers from these countries are part of the immunogenicity subset (a total of 1412 subjects).
Source: STN 125259/0, CSR HPV-013, Table 12, p. 59

Study completion and withdrawal from study: Overall, 2027 subjects completed the Month 7 visit (visit 5): 1017 subjects in the HPV group and 1010 subjects in the HAV group. A total of 40 subjects withdrew from the study: 18 subjects in the HPV group and 22 subjects in the HAV group. In the HPV group, 12subjects withdrew their consent and 4 subjects moved from the study

area. Two subjects with incomplete vaccination course were lost to follow-up. There were no withdrawals in the HPV group due to AEs or SAEs.

In the HAV group, 12 subjects withdrew their consent and 3 subjects moved from the study area. Three subjects were lost to follow-up: 2 with vaccination course completed and 1 with incomplete vaccination course. 2 subjects (subjects no. 2782 and 3218) reported a non-serious adverse event which led to their withdrawal from the study. Subject no. 2782 experienced pain at the injection site and subject no. 3218 joint swelling. One subject (subject no. 1507) was withdrawn because of a SAE (anorexia nervosa) which was still ongoing at study conclusion. These are shown in Table 205.

Table 205-Study HPV-013: Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total Vaccinated Cohort)

	Group		
	HPV	HAV	Total
Number of subjects vaccinated	1035	1032	2067
Number of subjects completed	1017	1010	2027
Number of subjects withdrawn	18	22	40
Reasons for withdrawal :			
Serious Adverse Event	0	1	1
Non-serious adverse event	0	2	2
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	12	12	24
Migrated/moved from study area	4	3	7
Lost to follow-up (subjects with incomplete vaccination course)	2	1	3
Lost to follow-up (subjects with complete vaccination course)	0	2	2
Others	0	1	1

HPV = HPV-16/18 L1/AS04
HAV = Hepatitis A vaccine group
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Source: STN 125259/0, CSR HPV-013, Table 13, p. 60

The number and percentage of subjects who received the study vaccine doses per group are presented in Table 206. Compliance with completion of the 3-dose vaccination schedule was high in both groups (98.2 %).

Table 206-Study HPV-013: Number and percentage of subjects who received study vaccine doses by group (Total Vaccinated Cohort)

Total number of doses received	HPV (N = 1035)		HAV (N = 1032)	
	n	%	n	%
1	10	1.0	9	0.9
2	9	0.9	10	1.0
3	1016	98.2	1013	98.2
Any	1035	100	1032	100

HPV = HPV-16/18 L1/AS04
HAV = Hepatitis A vaccine group
N = number of subjects in each group included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose
Source: STN 125259/0, CSR HPV-013, Table 16, p. 62

Protocol deviations which led to exclusion from analyses cohorts are provided.

Total Vaccinated Cohort = 2067 subjects enrolled and vaccinated (1035 HPV, 1032 HAV) Subjects eliminated from Total Vaccinated Cohort = 36 [a subject may have had more than one reason for exclusion]), so ATP cohort for safety included 2031 subjects.

- 10 subjects (3 subjects in the HPV group and 7 subjects in the HAV group) did not receive the study vaccine according to protocol. Among these 10 subjects, 8 subjects (2 subjects in the HPV group and 6 in the HAV group) did not receive the full vaccination course.
- Two subjects, one in each treatment group, received the wrong vaccine vial.
- Twenty-five subjects (13 subjects in the HPV group and 12 subjects in the HAV group) were administered vaccines other than study vaccine in the period forbidden by the protocol.
- One subject in the HAV group who experienced an unexpected SAE (an aminotransferases increase) that was considered as related to vaccination by the investigator had her treatment allocation unblinded.

ATP safety cohort = 2031 subjects. Of these 2031 subjects included in the ATP safety:

- 7 subjects received medication forbidden by the protocol
- 21 subjects were non compliant with vaccination schedule
- 18 subjects were non compliant with the blood sampling schedule.
- 1 subject was 15 years old when administered the first study vaccine dose
- 18 subjects had essential serological data missing.
- 3 subjects in the HPV group had incoherent data. For these three subjects, they were seronegative for both anti-HPV-16 and anti-HPV-18 antibodies at Day 0, all had a substantial increases in GMTs at Month 2, and then were reported to return to seronegativity or nearly seronegative by Month 7.
- 622 subjects were enrolled at centers not planned for the immunogenicity subset so were not included in the ATP cohort for immunogenicity.

ATP immunogenicity cohort = 1341 subjects. Only subjects enrolled from six countries in Asia Pacific (Korea and Taiwan), Europe (Germany) and Latin America (Colombia, Honduras and Panama) had blood samples collected, leading to a total of 1412 subjects in the Total vaccinated cohort for the immunogenicity subset.

Protocol deviations not leading to exclusion of subjects from an analysis were also provided. In the **Total vaccinated cohort:**

- 10 subjects received at least one study vaccine dose in the dominant arm instead of the non-dominant arm, thus not according to protocol (six subjects in the HPV group and four subjects in the HAV group). These subjects were not eliminated from the ATP safety cohort.
- Visit intervals were adapted so as to avoid eliminating subjects for irrelevant clinical reasons. Subjects outside the protocol intervals but within the adapted intervals were not eliminated from any of the analyses.

Reviewer's Comment: The majority of interval adaptations were made in a small proportion of subjects in both treatment groups. According to the protocol, the interval between informed consent and visit 1 was supposed to be 0 days, but in both treatment groups, approximately 22% of subjects started the protocol up to 68 days after signing the informed consent. In this generally sexually inexperienced group, in which blood tests were conducted at visit 1, this would have little or no impact the immunogenicity results. For the other intervals, the proportions of subjects with a deviation from the scheduled time points were ≤ 3.3%. (Source: STN 125259/0, CSR HPV-013, Supplement 5, p. 97, not shown here).

Demographic characteristics

Total Vaccinated cohort: The demographic characteristics of the HPV group and the HAV group were comparable with respect to mean age and racial distribution. The mean age at first vaccination was 12.1 years. In accordance with the regional distribution of the study, the population was predominantly White/Caucasian (54.9%), Hispanic (30.4%) or Chinese (10.5%). The demographic characteristics of the Total Vaccinated Cohort are presented in Table 207.

Table 207-Study HPV-013: Summary of demographic characteristics (Total Vaccinated Cohort)

		HPV N=1035	HAV N=1032	Total N=2067
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	12.1	12.1	12.1
	SD	1.4	1.4	1.4
	Median	12.0	12.0	12.0
	Min-Max	10-15	10-14	10-15
Region	Asia Pacific	192 (18.6%)	193 (18.7%)	385 (18.6%)
	Europe	524 (50.6%)	522 (50.6%)	1046 (50.6%)
	Latin America	319 (30.8%)	317 (30.7%)	636 (30.8%)
Race	Black	6 (0.6%)	10 (1.0%)	16 (0.8%)
	White/Caucasian	571 (55.2%)	564 (54.7%)	1135 (54.9%)
	Arabic/North African	5 (0.5%)	1 (0.1%)	6 (0.3%)
	East/South East Asia	0 (0.0%)	3 (0.3%)	3 (0.1%)
	South Asian	0 (0.0%)	1 (0.1%)	1 (0.0%)
	Hispanic	315 (30.4%)	313 (30.0%)	628 (30.4%)
	Chinese	109 (10.5%)	109 (10.6%)	218 (10.5%)
	Other	29 (2.8%)	31 (3.0%)	60 (2.9%)

HPV = HPV-16/18 L1/AS04
HAV = Hepatitis A vaccine group
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = standard deviation
Source: STN 125259/0, CSR HPV-013, Table 17, p. 64

ATP safety cohort: The demographic characteristics of the ATP safety cohort were also presented and are comparable to those of the Total vaccinated cohort. (Source: STN 125259/0, CSR HPV-013, Supplement 6, p. 98, not shown here).

ATP immunogenicity cohort: The demographic profiles of the ATP cohort for immunogenicity were comparable for both groups (HPV and HAV) with respect to mean age and racial distribution. As for the Total vaccinated cohort, the mean age at first vaccination was 12.1 years. In accordance with the center distribution in the different regions for the immunogenicity subset, the population was predominantly Hispanic (44.3%), White/Caucasian (34.3%) and Chinese (16.1%). All Latin American centers were part of the immunogenicity subset, whereas among the European centers, only German centers were included. In the HPV-001 reference group, the mean age at first vaccination was 20.2 years and the population was principally White/Caucasian (66.8%). As noted earlier in this review, the HPV-001 trial was conducted in Brazil and North America (USA and Canada).

Table 208-Study HPV-013: Summary of demographic characteristics (ATP cohort for immunogenicity)

		HPV N=675	HAV N=666	Total N=1341	HPV-001 N=383
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	12.1	12.0	12.1	20.2
	SD	1.4	1.4	1.4	2.9
	Median	12.0	12.0	12.0	20.0
	Min-Max	10-14	10-14	10-15	15-26
Region	Asia Pacific	134 (19.9%)	136 (20.4%)	270 (20.1%)	0 (0.0%)
	Europe	236 (35.0%)	232 (34.8%)	468 (34.9%)	0 (0.0%)
	Latin America	305 (45.2%)	298 (44.7%)	603 (45.0%)	195 (50.9%)
	North America	0 (0.0%)	0 (0.0%)	0 (0.0%)	188 (49.1%)
Country	Colombia	98 (14.5%)	98 (14.7%)	196 (14.6%)	-
	Germany	236 (35.0%)	232 (34.8%)	468 (34.9%)	-
	Honduras	131 (19.4%)	128 (19.2%)	259 (19.3%)	-
	Korea	27 (4.0%)	27 (4.1%)	54 (4.0%)	-
	Panama	76 (11.3%)	72 (10.8%)	148 (11.0%)	-
	Taiwan	107 (15.9%)	109 (16.4%)	216 (16.1%)	-
Race	Black	5 ().7%)	5 (0.8%)	10 (0.7%)	32 (8.4%)
	White/Caucasian	232 (34.3%)	228 (34.2%)	460 (34.3%)	256 (66.8%)
	Arabic/North African	3 (0.4%)	1 (0.2%)	4 (0.3%)	0 (0.0%)
	East/South East Asia	0 (0.0%)	1 (0.2%)	1 (0.1%)	0 (0.0%)
	Hispanic	300 (44.4%)	294 (44.1%)	594 (44.3%)	0 (0.0%)
	Chinese	107 (15.9%)	109 (16.4%)	216 (16.1%)	0 (0.0%)
	Other	28 (4.1%)	28 (4.2%)	56 (4.2%)	86 (22.5%)

HPV = HPV-16/18 L1/AS04
HAV = Hepatitis A vaccine group
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = standard deviation
Source: STN 125259/0, CSR HPV-013, Table 18, p. 65 and Supplement 7, p. 99

SAFETY RESULTS

Compliance in terms of returning local and general symptom sheets and safety data capture in the Total Vaccinated Cohort was very high in the two treatment groups (> 99%) after all doses. (Source: STN 125259/0, CSR HPV-013, Table 19, p. 66 and Supplement 9, p.100, not shown here).

Reviewer's Comment: The analyses in the ATP cohort for safety and the Total vaccinated cohort were comparable. (Source: STN 125259/0, CSR HPV-013, Supplements 35-69, p. 158-219, not shown here).

Total vaccinated cohort analysis

Serious adverse events: The primary objective was to compare the occurrence of SAEs between the HPV vaccine group and the HAV vaccine control group throughout the study period (up to Month 7). The difference of SAE rates (SAE rate in the HAV vaccine control group minus SAE rate in the HPV-16/18 vaccine group) was calculated with the two-sided standardized asymptotic 95% CI.

Overall, 24 subjects reported at least one SAE: 11 subjects in the HPV group and 13 subjects in the HAV group. The percentage of subjects reporting at least one SAE classified by MedDRA System Organ Class and Preferred Term during the entire follow-up period is presented in Table 209. The SAE rates in the two groups were similar: the difference in SAE rates for subjects reporting at least one SAE between the HAV group and the HPV group was equal to 0.20% (95% CI [-0.78; 1.20]) (Amended June 2006). Similarly, the SAE rates reported by Preferred Term between the two groups were similar (overlapping 95% CIs) except for appendicitis, which was only reported in the HAV group with an incidence of 0.5% of subjects. None of the reports of

appendicitis were considered as related to study vaccination by the investigator. The difference was not considered to be clinically significant.

Table 209-Study HPV-013: Percentage of subjects reporting the occurrence of Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, up to Month 7 (Total Vaccinated Cohort)

		HPV (N = 1035)				HAV (N = 1032)				Difference between HAV - HPV		
				95% CI				95% CI			95% CI*	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL
At least one SAE		***11***	***1.1***	***0.5***	***1.9***	13	1.3	0.7	2.1	***0.20***	***-0.78***	***1.20***
Blood and lymphatic system disorders (10005329)	Lymphadenitis (10025188)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	2	0.2	0.0	0.7	0	0.0	0.0	0.4	-0.19	-0.70	0.18
	Constipation (10010774)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
	Gastritis (10017853)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
Infections and infestations (10021881)	Appendicitis (10003011)	0	0.0	0.0	0.4	5	0.5	0.2	1.1	0.48	0.11	1.13
	Enterobiasis (10014881)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Gastroenteritis (10017888)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Herpangina (10019936)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Ludwig angina (10048806)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
	Pneumonia bacterial (10060946)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Pseudocroup (10050187)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Upper respiratory tract infection (10046306)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Urinary tract infection (10046571)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
Injury, poisoning and procedural complications (10022117)	Concussion (10010254)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
	Drug toxicity (10013746)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Gun shot wound (10018794)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Injury (10022116)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
	Ulna fracture (10045375)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
Investigations (10022891)	Transaminases increased (10054889)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
Metabolism and nutrition disorders (10027433)	Dehydration (10012174)	1	0.1	0.0	0.5	0	0.0	0.0	0.4	-0.10	-0.55	0.27
Nervous system disorders (10029205)	Headache (10019211)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
	Syncope (10042772)	***1***	***0.1***	***0.0***	***0.5***	***0***	***0.0***	***0.0***	***0.4***	***-0.10***	***-0.55***	***0.27***
Psychiatric disorders (10037175)	Anorexia nervosa (10002649)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55
Reproductive system and breast disorders (10038604)	Ovarian cyst ruptured (10033136)	0	0.0	0.0	0.4	1	0.1	0.0	0.5	0.10	-0.27	0.55

HPV = HPV-16/18 L1/AS04
HAV = Hepatitis A vaccine group
At least one SAE = at least one SAE experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the SAE
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
Source: STN 125259/0, CSR HPV-013, Table 20, p. 67

Reviewer's Comment: There was no apparent difference in proportions of subjects with any SAE. There were comparable rates of syncope between the two treatment groups. The reason for the difference in appendicitis rates (higher in HAV as compared to HPV) is unclear, but this difference was not seen in the 15-25 year old age group. None of the appendicitis events were

considered related to HAV vaccine. It has been reported that appendicitis is one of the most common pediatric surgical illnesses, and the peak incidence is reported in children ages 10-12. The incidence rises from infants, peaks in teen years, and then slowly decreases with age.

Fatal events: There were no fatalities reported during the study.

SAEs: Overall, 24 subjects reported 29 SAEs: 14 SAEs reported by 11 subjects in the HPV group and 15 SAEs reported by 13 subjects in the HAV group. One subject in the HAV group (anorexia nervosa) was withdrawn due to the SAE, and one subject had an SAE assessed as possibly related to HAV (increased transaminases). Tables of SAEs (Table 210-HPV and Table 211-HAV) were constructed to show the time to event, duration, outcome, and assessment of relationship to vaccination as per investigator.

Table 210-Study HPV-013, Annex 3: Subjects with SAE (Month 7-12) [HPV group] (CBER generated)

Case number, age (years)	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to Vaccination (investigator)
00592, 13 year old	Abdominal pain with bacturia (uncertain etiology)	4 days after dose 1	11 days	Resolved	Unrelated (no sx with dose 2 or 3)
01325, 11 year old	Gun shot wound	41 days after dose 2	18 days	Resolved	Unrelated
01376, 13 year old	Injury to face and shoulder after fall with LOC	7 days after dose 2	9 days	Resolved	Unrelated
01838, 10 year old	Herpangina (viral infection)	16 days after dose 3	21 days	Resolved	Unrelated
01855, 14 year old	Dehydration, gastroenteritis, URI	15 days after dose 3	33 days	Resolved	Unrelated
02525, 15 year old	Syncope (aortic insufficiency, + tilt test)	26 days after dose 3	3 days	Resolved	Unrelated
02594, 13 year old	Abdominal pain and fever (possible intercurrent illness)	54 days after dose 2	4 days	Resolved	Unrelated
03098, 10 year old	Enterobiasis (pin worm)	61 days after dose 2	7 days	Resolved	Unrelated
03149, 10 year old	Pneumonia bacterial	32 days after dose 2	9 days	Resolved	Unrelated
03650, 11 year old	Peudocroup	88 days after dose 2	2 days	Resolved	Unrelated
04212, 13 year old	Drug intoxication (pills) ulna fracture	51 days after dose 2 27 days after dose 3	2 days 73 days	Resolved Resolved	Unrelated Unrelated

Table 211-Study HPV-013, Annex 3: Subjects with SAE (Month 7-12) [HAV group] (CBER generated)

Case number, age (years)	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to Vaccination (investigator)
00549, 13 year old	Constipation (possible incidental illness)	12 days after dose 2	20 days	Resolved	Unrelated
00594, 11 year old	Gastritis (hx GE reflux for years)	10 days after dose 1	20 days	Resolved	Unrelated
01507, 14 year old	Anorexia nervosa (first had calorie restriction and over-exercise the same month she received dose 1)	Same month as dose 1 3 months after dose 2	Ongoing	Withdrawn from study	Unrelated
02539, 11 year old	Appendicitis	21 days after dose 3	12 days	Resolved	Unrelated
03034, 13 year old	Appendicitis	5 days after dose 2	9 days	Resolved	Unrelated
03127, 14 year old	Appendicitis	18 days after dose 2	22 days	Resolved	Unrelated
03637, 14 year old	Appendicitis	47 days after dose 2	27 days	Resolved	Unrelated
04217, 11 year old	Appendicitis	30 days after dose 1	11 days	Resolved	Unrelated
03109, 14 year old	Ludwig angina, lymphadenitis (Group A strep)	47 days after dose 2	11 days	Resolved	Unrelated
03117, 11 year old	Headache (negative work-up)	7 days after dose 1 (received dose 2 during the time of event)	84 days	Resolved	Unrelated
03647, 15 year old	Concussion (snowboarding accident)	49 days after dose 2	82 days	Resolved	Unrelated
04113, 13 year old	Ovarian cyst ruptured	39 days after dose 2	3 days	Resolved	Unrelated
04283, 11 year old	Transaminases increased, UTI	2 days after dose 3	82 days	Resolved	Related (↑LFTs) Unrelated (UTI)

Solicited and unsolicited symptoms: During the 30-day post-vaccination period, the percentage of any solicited and unsolicited symptoms, solicited and unsolicited local symptoms and solicited and unsolicited general symptoms reported after each dose was higher in the HPV group than the HAV group. Any solicited and unsolicited symptoms were reported after 81.9% of doses in the HPV group and after 66.0% of doses in the HAV group. This observation was primarily related to a higher incidence of local symptoms in the HPV group than in the HAV group, but a somewhat higher proportion of subjects with general symptoms in the 30 days post-vaccination was observed in the HPV group as compared to the HAV group. There was no increase in general symptoms noted with subsequent doses.

Reviewer's Comment: For local symptoms, a higher proportion of HPV recipients reported local symptoms (after dose 1, after dose 2, after dose 3, when calculated per dose, and when calculated per subject). None of the 95% CIs for these proportions overlapped between the HPV and HAV recipients. For general symptoms, a higher proportion of subjects in the HPV group reported a general symptom after dose 1, after dose 2, after dose 3, when calculated by dose, and when calculated by subject. The 95% CIs for these proportions did not overlap between the 2 treatment groups except for after dose 1 and when calculated by subject.

Table 212-Study HPV-013: Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Dose 1	HPV	1029	903	87.8% (85.6, 89.7%)	1029	689	67.0% (64.0, 69.8%)	1028	824	80.2% (77.6, 82.6%)
	HAV	1027	782	76.1% (73.4, 78.7%)	1027	638	62.1% (59.1, 65.1%)	1027	562	54.7% (51.6, 57.8%)
Dose 2	HPV	1021	818	80.1% (77.5, 82.5%)	1021	608	59.5% (56.5, 62.6%)	1021	716	70.1% (67.2, 72.9%)
	HAV	1021	643	63.0% (59.9, 65.9%)	1021	506	49.6% (46.4, 52.7%)	1021	442	43.3% (40.2, 46.4%)
Dose 3	HPV	1016	791	77.9% (75.2, 80.4%)	1016	595	58.6% (55.5, 61.6%)	1016	701	69.0% (66.1, 71.8%)
	HAV	1010	592	58.6% (55.5, 61.7%)	1009	467	46.3% (43.2, 49.4%)	1010	403	39.9% (36.9, 43.0%)
Overall/dose	HPV	3066	2512	81.9% (80.5, 83.3%)	3066	1892	61.7% (60.0, 63.4%)	3065	2241	73.1% (71.5, 74.7%)
	HAV	3058	2017	66.0% (64.2, 67,6%)	3057	1611	52.7% (50.9, 54.5%)	3058	1407	46.0% (44.2, 47.8%)
Overall/subject	HPV	1029	967	94.0% (92.3, 95.3%)	1029	859	83.5% (81.1, 85.7%)	1028	901	87.6% (85.5, 89.6%)
	HAV	1027	893	87.0% (84.7, 89.0%)	1027	807	78.6% (75.9, 81.1%)	1027	703	68.5% (65.5, 71.3%)

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Table 22, p. 69

Reporting of solicited and unsolicited Grade 3 symptoms followed a similar pattern. Any solicited and unsolicited Grade 3 symptoms were reported after 11.3% of doses in the HPV group versus 5.7% of doses in the HAV group.

Table 213-Study HPV-013: Incidence and nature of Grade 3 symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Dose 1	HPV	1029	120	11.7% (9.8, 13.8%)	1029	74	7.2% (5.7, 8.9%)	1028	66	6.4% (5.0, 8.1%)
	HAV	1027	63	6.1% (4.7, 7.8%)	1027	53	5.2% (3.9, 6.7%)	1027	13	1.3% (0.7, 2.2%)
Dose 2	HPV	1021	97	9.5% (7.8, 11.5%)	1021	70	6.9% (5.4, 8.6%)	1021	52	5.1% (3.8, 6.6%)
	HAV	1021	56	5.5% (4.2, 7.1%)	1021	50	4.9% (3.7, 6.4%)	1021	7	0.7% (0.3, 1.4%)
Dose 3	HPV	1016	128	12.6% (10.6, 12.4%)	1016	79	7.8% (6.2, 9.6%)	1016	75	7.4% (5.9, 9.2%)
	HAV	1010	55	5.4% (4.1, 7.0%)	1009	47	4.7% (3.4, 6.1%)	1010	17	1.7% (1.0, 2.7%)
Overall/dose	HPV	3066	345	11.3% 910.2, 12.4%)	3066	223	7.3% (6.4, 8.3%)	3065	193	6.3% (5.5, 7.2%)
	HAV	3058	174	5.7% (4.9, 6.6%)	3057	150	4.9% (4.2, 5.7%)	3058	37	1.2% (0.9, 1.7%)
Overall/subject	HPV	1029	251	24.4% (21.8, 27.1%)	1029	173	16.8% (14.6. 19.2%)	1028	148	14.4% (12.3, 16.7%)
	HAV	1027	138	13.4% (11.4, 15.7%)	1027	124	12.1% (10.1, 14.2%)	1027	31	3.0% (2.1, 4.3%)

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Table 23, p. 70

Reviewer's Comment: A higher proportion of HPV vaccine recipients experienced a grade 3 local symptom as compared to HAV recipients, and 95% CIs for the proportions did not overlap after any dose, when calculated per dose, and when calculated per subject. A slightly higher proportion of HPV recipients experienced a grade 3 general symptom as compared to HAV recipients, and 95% CIs did not overlap in comparisons after dose 3 or when calculated per dose or per subject, but did overlap in comparisons of doses 1 and 2.

Solicited adverse events are also presented for the 7-day period after each dose and per dose and per subject.

Table 214-Study HPV-013: Incidence and nature of symptoms (solicited only) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Dose 1	HPV	1029	890	86.5% (84.3, 88.5%)	1029	649	63.1% (60.0, 66.0%)	1028	822	80.0% (77.4, 82.4%)
	HAV	1027	734	71,5% (68.6, 74.2%)	1027	574	55.9% (52.8, 59.0%)	1027	559	54.4% (51.3, 57.5%)
Dose 2	HPV	1021	800	78,4% (75.7, 80.8%)	1021	555	54.4% (51.2, 57.4%)	1021	715	70.0% (67.1, 72.8%)
	HAV	1021	600	58.8% (55.7, 61.8%)	1021	447	43.8% (40.7. 46.9%)	1021	441	43.2% (40.1, 46.3%)
Dose 3	HPV	1016	766	75.4% (72.6, 78.0%)	1016	546	53.7% (50.6, 56.8%)	1016	699	68.8% (65.8, 71.6%)
	HAV	1010	540	53.5% (50.3, 56.6%)	1009	403	39.9% 36.9, 43.0%)	1010	402	39.8% (36.8, 42.9%)
Overall/dose	HPV	3066	2456	80.1% (78.6, 81.5%)	3066	1750	57.1% (55.3, 58.8%)	3065	2236	73.0% (71.3, 74.5%)
	HAV	3058	1874	61.3% (59.5, 63.0%)	3057	1424	46.6% (44.8, 48.4%)	3058	1402	45.8% (44.1, 47.6%)
Overall/subject	HPV	1029	954	92.7% (90.9, 94.2%)	1029	820	79.7% (77.1, 82.1%)	1028	900	87.5% (85.4, 89.5%)
	HAV	1027	844	82.2% (79.7, 84.5%)	1027	730	71.1% (68.2, 73.8%)	1027	699	68.1% (65.1, 70.9%)

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Supplement 11, p. 103

Reviewer's Comment: A higher proportion of HPV recipients reported solicited local and unsolicited adverse events as compared to the HAV recipients after each dose, and when calculated per dose and per subject for both local and general symptoms, and none of the 95% CIs for proportions overlap between HPV and HAV subjects. The majority of solicited adverse events were reported in the 7 days after vaccination.

Table 215-Study HPV-013: Incidence and nature of Grade 3 symptoms (solicited only) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall
(Total Vaccinated Cohort)

		Any Symptoms			General Symptoms			Local Symptoms		
		N	n	% (95% CI)	N	n	% (95% CI)	N	n	% (95% CI)
Dose 1	HPV	1029	113	11.0% (9.1, 13.1%)	1029	65	6.3% (4.9, 8.0%)	1028	66	6.4% (5.0, 8.1%)
	HAV	1027	45	4.4% (3.2, 5.8%)	1027	35	3.4% (2.4, 4.7%)	1027	13	1.3% (0.7, 2.2%)
Dose 2	HPV	1021	84	8.2% (6.6, 10.1%)	1021	56	5.5% (4.2, 7.1%)	1021	52	5.1% (3.8, 6.6%)
	HAV	1021	41	4.0% (2.9, 5.4%)	1021	35	3.4% (2.4, 4.7%)	1021	7	0.7% (0.3, 1.4%)
Dose 3	HPV	1016	118	11.6% (9.7, 13.7%)	1016	69	6.8% (5.3, 8.5%)	1016	75	7.4% (5.9, 9.2%)
	HAV	1010	44	4.4% (3.2, 5.8%)	1009	36	3.6% (2.5, 4.9%)	1010	17	1.7% (1.0, 2.7%)
Overall/dose	HPV	3066	315	10.3% (9.2, 11.4%)	3066	190	6.2% (5.4, 7.1%)	3065	193	6.3% (5.5, 7.2%)
	HAV	3058	130	4.3% (3.6, 5.0%)	3057	106	3.5% (2.8, 4.2%)	3058	37	1.2% (0.9, 1.7%)
Overall/subject	HPV	1029	226	22.0% (19.5, 24.6%)	1029	146	14.2% (12.1, 16.5%)	1028	148	14.4% (12.3, 16.7%)
	HAV	1027	103	10.0% (8.3, 12.0%)	1027	88	8.6% (6.9, 10.5%)	1027	31	3.0% (2.1%. 4.2%)

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Supplement 12, p. 104

Reviewer's Comment: A higher proportion of HPV recipients reported both Grade 3 local and general symptoms as compared to the HAV recipients after each dose, and when calculated per dose and per subject for both local and general symptoms. none of the 95% CIs for proportions overlap between HPV and HAV subjects for the grade 3 local symptoms, although for general symptoms, there is overlap after dose 2. The majority of grade 3 solicited adverse events were reported in the 7 days after vaccination.

Solicited local symptoms: Overall, the number of subjects experiencing solicited local symptoms during the 7-day follow-up period after each dose was higher in the HPV group. In both groups, the most frequently reported solicited local symptom during the 7-day post-vaccination period was pain at injection site, followed by redness, and swelling.

The sponsor also notes that Grade 3 pain was reported more frequently in the HPV group than in the HAV group. Redness and swelling greater than 50 mm was rare in both groups. The proportions of solicited local symptoms per dose and per subject are presented in Table 216 below.

Table 216-Study HPV-013: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period overall per subject (Total Vaccinated Cohort)

		HPV			HAV		
Overall/dose							
Symptom	Type	N	n	% (95% CI)	N	n	% (95% CI)
Pain	All	3065	2150	70.1% (68.5, 71.8%)	3058	1263	41.3% (39.5, 43.1%)
	Grade 3	3065	154	5.0% (4.3, 5.9%)	3058	26	0.9% (0.6, 1.2%)
Redness (mm)	All	3065	850	27.7% (26.2, 29.4%)	3058	418	13.7% (12.5, 14.9%)
	>50	3065	11	0.4% (0.2, 0.6%)	3058	4	0.1% (0.0, 0.3%)
Swelling (mm)	All	3065	721	23.5% (22.0, 25.1%)	3058	261	8.5% (7.6, 9.6%)
	Grade 3	3065	36	1.2% (0.8, 1.6%)	3058	7	0.2% (0.1, 0.5%)
Overall/subject							
Pain	All	1028	888	86.4% (84.1, 88.4%)	1027	659	64.2% (61.1, 67.1%)
	Grade 3	1028	116	11.3% (9.4, 13.4%)	1027	24	2.3% (1.5, 3.5%)
Redness (mm)	All	1028	466	45.3% (42.3, 48.4%)	1027	259	25.2% (22.6, 28.0%)
	>50	1028	11	1.1% (0.5, 1.9%)	1027	2	0.2% (0.0, 0.7%)
Swelling (mm)	All	1028	430	41.8% (38.8, 44.9%)	1027	178	17.3% (15.1, 19.8%)
	Grade 3	1028	30	2.9% (2.0, 4.1%)	1027	5	0.5% (0.2, 1.1%)

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
For Overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
For overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Table 24, p. 71

Reviewer's Comment: When considered per subject or per dose, HPV vaccine recipients had higher proportions of the solicited local adverse reactions, and the 95% CIs for the proportions did not overlap with those around the HAV proportions. Grade 3 pain and swelling was also higher in HPV recipients as compared to HAV recipients when presented by dose and by subject, and 95% CIs did not overlap.

Table 217-Study HPV-013: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

		HPV					HAV				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Pain	All	1028	800	77.8	75.2	80.3	1027	498	48.5	45.4	51.6
	Grade 3	1028	53	5.2	3.9	6.7	1027	8	0.8	0.3	1.5
Redness (mm)	All	1028	287	27.9	25.2	30.8	1027	160	15.6	13.4	17.9
	> 50	1028	4	0.4	0.1	1.0	1027	1	0.1	0.0	0.5
Swelling (mm)	All	1028	215	20.9	18.5	23.5	1027	97	9.4	7.7	11.4
	> 50	1028	12	1.2	0.6	2.0	1027	4	0.4	0.1	1.0
Dose 2											
Pain	All	1021	680	66.6	63.6	69.5	1021	393	38.5	35.5	41.6
	Grade 3	1021	45	4.4	3.2	5.9	1021	2	0.2	0.0	0.7
Redness (mm)	All	1021	258	25.3	22.6	28.1	1021	136	13.3	11.3	15.6
	> 50	1021	2	0.2	0.0	0.7	1021	2	0.2	0.0	0.7
Swelling (mm)	All	1021	217	21.3	18.8	23.9	1021	88	8.6	7.0	10.5
	> 50	1021	6	0.6	0.2	1.3	1021	3	0.3	0.1	0.9
Dose 3											
Pain	All	1016	670	65.9	62.9	68.9	1010	372	36.8	33.8	39.9
	Grade 3	1016	56	5.5	4.2	7.1	1010	16	1.6	0.9	2.6
Redness (mm)	All	1016	305	30.0	27.2	32.9	1010	122	12.1	10.1	14.2
	> 50	1016	5	0.5	0.2	1.1	1010	1	0.1	0.0	0.6
Swelling (mm)	All	1016	289	28.4	25.7	31.3	1010	76	7.5	6.0	9.3
	> 50	1016	18	1.8	1.1	2.8	1010	0	0.0	0.0	0.4

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
Source: STN 125259/0, CSR HPV-013, Supplement 15, p. 107

Reviewer's Note: There is an increase in the proportion of subjects with swelling with progressive doses of HPV vaccine (20.9% to 28.4%). There is a lower proportion of subjects with pain after doses 2 and 3 (66.6% and 65.9%, respectively) as compared to dose 1 (77.8%).

Duration of solicited local adverse events was also presented. Pain (3.0 days in the HPV group and 2.0 days in the HAV group), redness and swelling (2.0 days for both symptoms) duration during the 7-day post-vaccination period were similar in the two groups. In addition, duration of Grade 3 symptoms was also generally of short duration. (Source: STN 125259/0, CSR 13, Supplements 17 and 18, p. 109-112, not shown here).

The number of solicited local symptoms ongoing beyond the 7-day reporting period (Days 0-6) was low and similar in both groups. (Source: STN 125259/0, CSR HPV-013, Supplement 16, p. 108, not shown here).

Solicited general symptoms: The incidence of solicited general symptoms was higher in the HPV vaccine group as compared to the HAV vaccine group. The pattern of adverse events was

very similar between both study groups with respect to the relative incidence, severity, and duration.

In both groups, the most frequently reported solicited general symptoms during the 7-day post-vaccination period were headache, fatigue and myalgia; followed by gastrointestinal symptoms, arthralgia and fever. The observed small differences in incidence of fever and gastrointestinal symptoms between groups were considered as not clinically relevant. Incidence of rash and urticaria was low after both vaccines. The incidence of grade 3 solicited general symptoms followed the same pattern. These general solicited symptoms are presented per subject in Table 218 below.

Table 218-Study HPV-HPV-013: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period overall per subject (Total Vaccinated Cohort)

	HPV		HAV	
	Overall/subject			
Symptom	n/N	%	n/N	%
Arthralgia				
All	259/1029	**25.2%**	204/1027	**19.9%**
Grade 3	21/1029	**2.0%**	5/1027	**0.5%**
Fatigue				
All	499/1029	**48.5%**	434/1027	**42.3%**
Grade 3	40/1029	3.9%	30/1027	2.9%
Fever (° C) Axilla				
All	193/1029	18.8%	164/1027	16.0%
>39.0	19/1029	1.8%	14/1027	1.4%
Gastrointestinal				
All	265/1029	25.8%	253/1027	24.6%
Grade 3	26/1029	2.5%	22/1027	2.1%
Headache				
All	516/1029	50.1%	464/1027	45.2%
Grade 3	68/1029	6.6%	40/1027	3.9%
Myalgia				
All	509/1029	**49.5%**	340/1027	**33.1%**
Grade 3	57/1029	**5.5%**	13/1027	**1.3%**
Rash				
All	98/1029	9.5%	69/1027	6.7%
Grade 3	8/1029	0.8%	3/1027	0.3%
Urticaria				
All	70/1029	6.8%	55/1027	5.4%
Grade 3	9/1029	0.9%	6/1027	0.6%

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
Rel* = causally related to vaccination according to the investigator.
For overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
bolded percentages – 95% CIs do not overlap
For overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR HPV-013, Table 25, p. 72-74

Reviewer's Comment: A higher proportion of HPV recipients reported a solicited general adverse event as compared to HAV recipients. The 95% CIs do not overlap for all and grade 3 arthralgia; all fatigue; all and grade 3 myalgia. These are bolded in Table 218 above.

The duration (median number of days) of fever, headache, arthralgia, urticaria, myalgia, fatigue and rash during the 7-day post-vaccination period was similar in both groups. Besides fever (which lasted a median of one day in both groups), the other symptoms lasted a median of two

days in both groups. Grade 3 general symptoms were also of short duration in both treatment groups (Source: STN 125259/0, CSR 13, Supplements 17 and 18, p. 109-112, not shown here).

The incidence of solicited general symptoms reported during the 7-day (Days 0-6) period following each dose and overall was presented.
Reviewer's Comment: This table was reviewed and there was no increase in the incidence of events noted with consecutive doses. (Source: STN 125259/0, CSR 13, Supplement 19, p. 113-115, not shown here).

The number of solicited general symptoms ongoing beyond the 7-day reporting period (Days 0-6) post-vaccination period was similar in both groups. (Source: STN 125259/0, CSR 13, Supplement 20, p. 116-118, not shown here). The maximum temperature experienced by the subjects in both groups is also presented. No differences in patterns were identified between the HPV and the HAV group.
Reviewer's Comment: The table containing this information was reviewed and no apparent difference was noted in severity of temperature between treatment groups. (Source: STN 125259/0, CSR 13, Supplement 21, p. 119, not shown here).

Unsolicited symptoms: Overall, 386 subjects reported 685 unsolicited symptoms after 535 doses of HPV-16/18 vaccine, and 427 subjects reported 698 unsolicited symptoms after 565 doses of HAV vaccine within the 30-day post-vaccination period.

The percentages of doses with at least one unsolicited symptom (classified by MedDRA Primary System Organ Class and Preferred Term) within the 30-day post-vaccination period between the two groups were similar (17.4% in the HPV group versus 18.4% in the HAV group). The number of subjects with at least one unsolicited symptom was also similar.
Reviewer's Comment: The proportions of subjects with an event in the specific SOC are presented in Table 219 below. All the 95% CIs overlap between different treatment groups.

Table 219-Study HPV-013: Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEdDRA Primary System Organ Class, within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated Cohort)

	HPV N-1035	HAV N=1032
Primary System Organ Class	**n(%)**	**n(%)**
At least one symptom	**386 (37,3%)**	**427 (41.4%)**
Blood and lymphatic system disorders	3 (0.3%)	4 (0.4%)
Cardiac disorders	2 (0.2%)	1 (0.1%)
Ear and labyrinth disorders	10 (1.0%)	10 (1.0%)
Endocrine disorders	1 (0.1%)	3 (0.3%)
Gastrointestinal disorders	28 (2.7%)	38 (3.7%)
General disorders and administration site conditions	51 (4.9%)	39 (3.8%)
Hepatobiliary disorders	0 (0.0%)	1 (0.1%)
Immune system disorders	5 (0.5%)	7 (0.7%)
Infections and infestations	226 (21.8%)	240 (23.3%)
Injury, poisoning and procedural complications	21 (2.0%)	28 (2.7%)
Investigations	1 (0.1%)	3 (0.3%)
Metabolism and nutrition disorders	7 (0.7%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	22 (1.3%)	16 (1.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps	0 (0.0%)	1 (0.1%)
Nervous system disorders	54 (5.2%)	62 (6.0%)
Psychiatric disorders	2 (0.2%)	4 (0.4%)
Renal and urinary disorders	1 (0.1%)	1 (0.1%)
Reproductive system and breast disorders	23 (2.2%)	26 (2.5%)
Respiratory, thoracic and mediastinal disorders	67 (6.5%)	54 (5.2%)
Skin and subcutaneous tissue disorders	28 (2.7%)	27 (2.6%)
Surgical and medical procedures	5 (0.5%)	7 (0.7%)
Vascular disorders	4 (0.4%)	2 (0.2%)

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary SOC)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR HPV-013, Supplement 23, p. 121

The most frequently reported unsolicited symptoms by Preferred Term were: upper respiratory tract infection, nasopharyngitis, pharyngolaryngeal pain, cough, headache, and dizziness. Reporting rates were comparable in each treatment group. No differences in incidence were identified between groups for any unsolicited symptoms classified by either Preferred Term or Primary System Organ Class. It is noted that there were equal proportions of syncope or vasovagal syncope (0.4%) in each treatment group days 0-29 after vaccination. Unsolicited adverse events which occurred $\geq$ 1% of subjects in either treatment group are presented in Table 220 below.

Overall, 99 subjects reported 127 Grade 3 unsolicited symptoms within the 30-day (Days 0-29) post-vaccination period. The number of Grade 3 unsolicited symptoms were similar in the two groups (61symptoms in 46 HPV recipients and 66 symptoms in 53 subjects in the HAV group). The most frequently reported Grade 3 unsolicited symptoms classified by Preferred Term were: nasopharyngitis, pharyngolaryngeal pain, and headache after 0.1% of doses in the HPV group and after 0.2% of doses in the HAV group.

Table 220-Study HPV-013: Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEdDRA Preferred Term > 1% in either group, within the 30-day (Days 0-29) postvaccination period (Total Vaccinated Cohort)

Primary System Organ Class	Preferred Term	HPV N=1035	HAV N=1032
		n (%)	n (%)
At least one symptom		**386 (37.3%)**	**427 (41.4%)**
General disorders and administration site conditions	Injection site hemorrhage	10 (1.0%)	11 (1.1%)
Infections and Infestations	Influenza	6 (0.6%)	13 (1.3%)
	Nasopharyngitis	56 (5.4%0	61 (5.9%)
	Pharyngitis	22 (2.1%)	23 (2.2%)
	Tonsillitis	24 (2.3%)	13 (1.3%)
	URI	60 (5.8%)	69 (6.7%)
Injury, poisoning and procedural complications	Injury	4 (0.4%)	10 (1.0%)
Nervous system disorders	Dizziness	14 (1.4%)	15 (1.5%)
	Headache	27 (2.6%)	34 (3.3%)
Reproductive system and breast disorders	Dysmenorrhea	17 (1.6%)	20 (1.9%)
Respiratory, thoracic and mediastinal disorders	Cough	20 (1.9%)	15 (1.5%)
	Pharyngolaryngeal pain	28 (2.7%)	22 (2.1%)

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Supplement 25, p. 129-135

Adverse Events Leading to Premature Discontinuation of StudyVaccine and/or Study:
There were no withdrawals due to AEs in the HPV group. Two subjects in the HAV group withdrew from the study due to non-serious adverse events.

- One subject discontinued the study before the second vaccine dose due to pain at the injection site following the first vaccination.
- One subject discontinued the study before receiving the third vaccine dose because of joint swelling.

Other Significant Adverse Events

New onset of chronic diseases: Based on GSK assessment, 47 reports of NOCD were identified. Three additional subjects were reported as having a NOCD as per the investigator. 46 subjects reported 47 AEs classified as NOCD according to GSK assessment. In the HPV group 25 subjects reported 26 events (2.4% of subjects) and in the HAV group 21 subjects reported 21 events (2.0% of subjects). The most frequently identified were rhinitis allergic (reported by 8 subjects in the HPV group and by 5 subjects in the HAV group), asthma (reported by 4 subjects in the HPV group and by 3 subjects in the HAV group), hypersensitivity (reported by 4 subjects in the HPV group and by 3 subjects in the HAV group) and chronic urticaria (reported by 4 subjects in the HPV group and by 1 subject in the HAV group). The additional NOCD reports based on the investigator's assessments included localized infection; back pain and mental disorder.

Table 221-Study HPV-013: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK and investigator assessment) classified by MEdDRA Primary System Organ Class and Preferred Term, Month 0-7 (Total Vaccinated Cohort)

	Preferred Term	HPV N=1035	HAV N=1032
Primary System Organ Class		**n (%)**	**n (%)**
At least one NOCD		**27 (2.6%)**	**22 (2.1%)**
Endocrine disorders	Goiter	1 (0.1%)	0 (0.0%
	Hypothyroidism	0 (0.0%)	2 (0.2%)
Eye disorders	Conjunctivitis allergic	1 (0.1%)	2 (0.2%)
Immune system disorders	Food allergy	1 (0.1%)	0 (0.0%)
	Hypersensivity	4 (0.4%)	3 (0.3%)
	Seasonal allergy	0 (0.0%)	2 (0.2%)
Infections and Infestations	Localized infection	1 (0.1%)	0 (0.0%)
Musculoskelatal and connective tissue disorders	Back pain	1 (0.1%)	0 (0.0%)
Psychiatric disorders	Mental disorder	0 (0.0%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	Asthma	4 (0.4%)	3 (0.3%)
	Rhinitis allergic	8 (0.8%)	5 (0.5%)
Skin and subcutaneous tissue disorders	Dermatitis allergic	2 (0.2%)	2 (0.2%)
	Dermatitis atopic	1 (0.1%)	1 (0.1%)
	Urticaria	4 (0.4%)	1 (0.1%)

HPV = HPV-16/18 L1/AS04.
HAV = Hepatitis A vaccine group.
At least one NOCD = at least one NOCD experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOCD
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR HPV-013, Table 30, p. 79 and Supplement 30, p. 143

Medically significant conditions prompting emergency room visits or physician visits: The percentages of subjects reporting at least one medically significant AE prompting emergency room visits or physician visits (classified by MedDRA Primary System Organ Class and Preferred Term) within the 30-day follow-up period post vaccination were similar in the two groups (12.6% of subjects in the HPV group and 15.5% of subjects in the HAV group).

The percentages of subjects reporting at least one medically significant AE prompting emergency room visits or physician visits (classified by MedDRA Primary System Organ Class and Preferred Term) starting from Day 30 post-vaccination were similar in the two groups (8.3% of subjects in the HPV group and 8.4% of subjects in the HAV group).
Reviewer's Comment: This table was reviewed for specific events, and all proportions were low in frequency in both groups (≤1.1% for preferred term) and comparable in occurrence between the two groups. The most common event identified was influenza (1.1% HAV group and 0.4% HPV group). (Source: STN 125259/0, CSR HPV-013, Supplement 32, p. 148-150, not shown here).

In an annex report to study HPV-013, additional analyses were presented which included analysis of medically significant adverse events (using a revised definition of these adverse events) reported from Month 0 to Month 7 in all subjects. The definition of medically significant AEs was slightly modified in that it was updated to include serious adverse events (SAEs) that are not related to common diseases, and the category 'Vulvitis' was no longer considered as a separate category. The results were reported for the entire period (Month 0-7). This revised methodology was implemented following comments received from regulatory authorities.

Based on the revised definition, in the Total Vaccinated Cohort, overall, 197 (19%) subjects reported 271 medically significant AEs after 231 doses of HPV vaccine, and 223 (21.6%) subjects reported 303 medically significant AEs after 256 doses of Hepatitis (HAV) vaccine during the entire follow-up period, from Month 0 to Month 7.

Reviewer's Comment: The number of subjects with specific medically significant AEs was low for a variety of Preferred Terms and comparable for the two treatment groups. The most commonly reported events in each group were influenza (0.7% HPV group and 1.6% HAV group), bronchitis (1.0% in each group), and rhinitis allergic (1.0% in each group). Other events were < 1% in each group and generally comparable between the 2 groups. There were 3 subjects (0.3%) with hypersensitivity in the HPV group and 0 in the HAV group in the 7 months after vaccination. There were 2 subjects (0.2%) with arthralgia in the HPV group and 0 in the HAV group. In addition, there were 2 subjects (0.2%) with urticaria in the HPV group and 0 in the HAV group in this time period. The number of subjects overall with such symptoms are also reported. (Source: STN 125259/0, CSR HPV-013, Annex 2, table 2, p. 10-14, not shown here)

Concomitant medications/vaccinations: The percentage of doses after which concomitant medication was taken was similar in both groups. Overall, subjects received concomitant medication after 18.7% of doses in the HPV group and after 18.1% of doses in the HAV group. Only three subjects (two subjects in the HPV group and one subject in the HAV group) received antipyretics prophylactically.

Reviewer's Comment: The proportions of subjects who were administered any medication, any antipyretic, or any antibiotic were comparable in each treatment group. Overall, 39.1% HPV recipients and 40.2% of HAV recipients were administered any medication in the 30 days after vaccination. There was no increase in use of concomitant medications with progressive doses of either vaccine. (Source: STN 125259/0, CSR HPV-013, Supplement 33, p. 151, not shown here)

Clinical Laboratory Evaluations: At study entry and at Months 2 and 7, the hematological and biochemical parameters were evaluated in all subjects. For one subject who had laboratory tests done following a urinary tract infection that was reported as an SAE, the ALT levels were above the normal range (one of the SAEs). For most of the subjects in both groups the hematological and biochemical parameters were within the normal ranges at study entry and remained as such after each vaccine dose. Post Dose 3, the majority of subjects had lab values in the normal range, and percentages were comparable in the two treatment groups. For each parameter, the percentage of subjects outside normal ranges was low and similar in the two groups. (Source: STN 125259/0, CSR HPV-013, Supplement 34, p. 152-157, not shown here).

Pregnancy: During the active phase of the study (up to Month 7), three pregnancies were reported (two subjects in the HAV group and one subject in the HPV group). None of these pregnancies were reported as an SAE or AE and none of the subjects were withdrawn from the study. Their outcomes are detailed in Table 222. The one subject with an elective abortion had this procedure for social reasons.

Table 222-Study HPV-013: Outcome of reported pregnancies (Months 0 to 7) Total Vaccinated Cohort)

Outcome	HPV	HAV
Healthy baby	1	1
Elective abortion	0	1
Total	1	2

HPV = HPV-16/18; HAV = Hepatitis A vaccine group.
Source: STN 125259/0, CSR HPV-013, Table, p. 81

According-to-protocol cohort analysis: The analyses based on the ATP safety cohort are consistent with those obtained for the Total Vaccinated cohort. (Source: STN 125259/0, CSR HPV-013, Supplements 35-69, p. 158-219, not shown here.)

GSK also presented solicited and unsolicited adverse events Months 0-7 in the Total Vaccinated Cohort by ethnicity in a separate annex report. There was no apparent difference in reported local adverse reaction rates among the ethnic groups, except for higher reporting rates of Grade 3 pain in Hispanic subjects. Higher proportions of Hispanic subjects reported solicited general adverse events (days 0-7) and unsolicited adverse events (days 0-29) as compared to white and Asian subjects. Small numbers of black subjects precluded assessment of these events Overall, the sponsor concluded that there were minor ethnically-determined variations between the rates of adverse events reported following administration of HPV vaccine.

IMMUNOGENICITY RESULTS

Data sets analyzed: The analysis of immunogenicity was performed on the ATP cohort (primary analysis) and the Total vaccinated cohort. In addition, the immunogenicity analyses were stratified by serostatus at baseline.

According-To-Protocol analysis: Seropositivity rates and Geometric mean titers (GMTs) for anti-HPV-16 and anti-HPV-18 antibodies

Seropositivity status before vaccination: Of the 675 subjects receiving HPV-16/18 vaccine, 90.6% were seronegative for both HPV-16 and HPV-18 antigens before vaccination. These are presented in Table 223. It is noted that subjects who received HPV vaccine had anti-HPV-16 and anti-HPV-18 antibodies reported.

Table 223-Study HPV-013: Seropositivity status before vaccination (ATP cohort for immunogenicity)

Anti-HPV-16	Anti-HPV-18	HPV (N = 675)	
		n	%
Pos	Pos	5	0.7
Pos	Neg	34	5.1
Pos	MISSING	1	-
Neg	Pos	24	3.6
Neg	Neg	604	90.6
Neg	MISSING	2	-
MISSING	Neg	1	-
MISSING	MISSING	4	-

Source: STN 125259/0, CSR HPV-013, Supplement 70, p. 220

Seropositivity rates and geometric mean titers at each time point: All initially seronegative subjects in the HPV group had seroconverted for both HPV-16 and HPV-18 antigens one month after the third dose of HPV-16/18 vaccine, with high GMT values (19882.0 EU/mL for anti-HPV-16 antibodies and 8262.0 EU/mL for anti-HPV-18 antibodies). The third HPV vaccine dose led to a 4-fold increase in GMT values. One month after the second dose, most initially seronegative subjects had already seroconverted for both antigens (> 99%). Initially seropositive subjects for HPV-16 and/or HPV-18 antigens also demonstrated an immune response to the HPV-16/18 vaccine that was similar in terms of GMT values to the immune response in initially seronegative subjects.

Table 224-Study HPV-013: Seropositivity rates and GMTs for Anti-HPV-16 antibodies by prevaccination status (ATP cohort for immunogenicity)

					≥ 8 EU/ML				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-HPV-16	HPV	S-	PRE	630	0	0.0	0.0	0.6	4.0	4.0	4.0	<8.0	<8.0
			PII(M2)	625	622	99.5	98.6	99.9	4696.9	4388.6	5026.8	<8.0	49477.0
			PIII(M7)	619	619	100	99.4	100	19882.0	18626.7	21221.9	706.0	244471.0
		S+	PRE	40	40	100	91.2	100	15.1	11.8	19.3	8.0	141.0
			PII(M2)	37	37	100	90.5	100	5402.9	4162.4	7013.1	1028.0	26626.0
			PIII(M7)	37	37	100	90.5	100	22437.5	17807.6	28271.1	3631.0	67566.0
		Total	PRE	670	40	6.0	4.3	8.0	4.3	4.2	4.5	<8.0	141.0
			PII(M2)	662	659	99.5	98.7	99.9	4733.8	4433.1	5054.9	<8.0	49477.0
			PIII(M7)	656	656	100	99.4	100	20018.1	18799.3	21315.9	706.0	244471.0

HPV = HPV-16/18 L1/AS04
S- = seronegative subjects (antibody titer < 8 EU/ML) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 8 EU/ML) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval
MIN/MAX = Minimum/Maximum
Pre-vacc status = Pre-vaccination status; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR HPV-013, Table 32, p. 84

Table 225-Study HPV-013: Seropositivity rates and GMTs for Anti-HPV-18 antibodies by prevaccination status (ATP cohort for immunogenicity)

					≥ 7 EU/ML				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-HPV-18	HPV	S-	PRE	639	0	0.0	0.0	0.6	3.5	3.5	3.5	<7.0	<7.0
			PII(M2)	633	631	99.7	98.9	100	3741.7	3499.3	4000.9	<7.0	47111.0
			PIII(M7)	628	628	100	99.4	100	8262.0	7725.0	8836.2	567.0	187560.0
		S+	PRE	29	29	100	88.1	100	19.7	15.0	25.8	7.0	89.0
			PII(M2)	28	28	100	87.7	100	3825.9	2840.4	5153.3	1124.0	14514.0
			PIII(M7)	27	27	100	87.2	100	10981.1	7202.5	16742.0	2244.0	200687.0
		Total	PRE	668	29	4.3	2.9	6.2	3.8	3.7	3.9	<7.0	89.0
			PII(M2)	661	659	99.7	98.9	100	3745.2	3508.8	3997.7	<7.0	47111.0
			PIII(M7)	655	655	100	99.4	100	8359.4	7820.8	8935.1	567.0	200687.0

HPV = HPV-16/18 L1/AS04
S- = seronegative subjects (antibody titer < 7 EU/ML) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 7 EU/ML) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
Pre-vacc status = Pre-vaccination status; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR HPV-013, Table 32, p. 84

Comparison of seroconversion rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies between HPV-HPV-013 subjects (10-14 year olds) and HPV-001 subjects (15-25 year olds): The majority (84.9%) of the 383 subjects selected from the HPV-001 study (HPV-001 group) were seronegative for both HPV-16 and HPV-18 antigens before vaccination. In both groups, all initially seronegative subjects had seroconverted for both antigens after the third vaccine dose. The GMT values in the HPV-HPV-013 HPV vaccine group (preteen and adolescent subjects) were nominally higher for both anti-HPV-16 antibodies and for anti-HPV-18 antibodies than those in the HPV-001 vaccine group (adult subjects): 19882.0 EU/mL versus 4415.9 EU/mL for anti-HPV-16 antibodies, and, 8262.0 EU/mL versus 3471.8 EU/mL for anti-HPV-18 antibodies. The reverse cumulative distribution curves for anti-HPV-16 and anti-HPV-18

antibodies show that all subjects in the two studies had seroconverted at Month 7 but with higher antibody titers achieved by subjects enrolled in the study HPV-HPV-013.

The baseline seropositivity rates of subjects in each study are compared in Table 226 and are noted to be comparable.

Table 226-Study HPV- HPV-013 and Study HPV-001: Seropositivity status before vaccination (ATP cohort for immunogenicity and HPV-001 reference group)

		HPV-013 (N = 675)		HPV-001 (N = 383)	
HPV 16 IGG ELISA	HPV 18 IGG ELISA	n	%	n	%
Pos	Pos	5	0.7	3	0.8
Pos	Neg	34	5.1	21	5.8
Pos	MISSING	1	-	0	-
Neg	Pos	24	3.6	31	8.5
Neg	Neg	604	90.6	310	84.9
Neg	MISSING	2	-	6	-
MISSING	Pos	0	-	3	-
MISSING	Neg	1	-	3	-
MISSING	MISSING	4	-	6	-

HPV-HPV-013 = HPV-16/18 from study HPV-HPV-013; HPV-001 =HPV-16/18 from study HPV-001.
Pos = Seropositive; Neg = Seronegative.
MISSING = Status not available.
N = number of subjects included in the ATP cohort for immunogenicity (HPV-HPV-013 study) and in t he HPV-001 group.
n/% = number/percentage of subjects with the corresponding seropositivity status.
Source: STN 125259/0, CSR HPV-013, Supplement 71, p. 220

The anti-HPV-16 and anti-HPV-18 results in HPV vaccine recipients in study HPV-013 and study HPV-001 are presented in Table 227 and Table 228.

Table 227-Study HPV-HPV-013 and Study HPV-001:Seropositivity rates and GMTs for HPV-16 IGG ELISA antibodies by pre-vaccination status (ATP cohort for immunogenicity)

				≥ 8 EU/ML				GMT				
						95% CI			95% CI			
Group	Pre-vaccination status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-013	S-	PRE	630	0	0.0	0.0	0.6	4.0	4.0	4.0	<8.0	<8.0
		PII(M2)	625	622	99.5	98.6	99.9	4696.9	4388.6	5026.8	<8.0	49477.0
		PIII(M7)	619	619	100	99.4	100	19882.0	18626.7	21221.9	706.0	244471.0
	S+	PRE	40	40	100	91.2	100	15.1	11.8	19.3	8.0	141.0
		PII(M2)	37	37	100	90.5	100	5402.9	4162.4	7013.1	1028.0	26626.0
		PIII(M7)	37	37	100	90.5	100	22437.5	17807.6	28271.1	3631.0	67566.0
	Total	PRE	670	40	6.0	4.3	8.0	4.3	4.2	4.5	<8.0	141.0
		PII(M2)	662	659	99.5	98.7	99.9	4733.8	4433.1	5054.9	<8.0	49477.0
		PIII(M7)	656	656	100	99.4	100	20018.1	18799.3	21315.9	706.0	244471.0
HPV-001	S-	PRE	347	0	0.0	0.0	1.1	4.0	4.0	4.0	<8.0	<8.0
		PIII(M7)	339	339	100	98.9	100	4415.9	3976.7	4903.6	65.0	110768.0
	S+	PRE	24	24	100	85.8	100	13.0	11.3	15.0	9.0	30.0
		PIII(M7)	23	23	100	85.2	100	3862.0	2504.0	5956.5	375.0	34561.0
	Total	PRE	371	24	6.5	4.2	9.5	4.3	4.2	4.5	<8.0	30.0
		PIII(M7)	362	362	100	99.0	100	4378.4	3956.2	4845.7	65.0	110768.0

HPV-HPV-013 = HPV-16/18 from study HPV-HPV-013; HPV-001 = HPV-16/18 from study HPV-001
S- = seronegative subjects (antibody titer < 8 EU/ML) prior to vaccination
S+ = seropositive subjects (antibody titer≥8 EU/ML) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; MIN/MAX = Minimum/Maximum
PRE=prevaccination; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR HPV-013, Table 34, p. 86

Table 228-Study HPV-013 and Study HPV-001: Seropositivity rates and GMTs for HPV-18 IGG ELISA antibodies by pre-vaccination status (ATP cohort for immunogenicity)

				≥ 7 EU/ML				GMT				
						95% CI			95% CI			
Group	Pre-vaccination status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-013	S-	PRE	639	0	0.0	0.0	0.6	3.5	3.5	3.5	<7.0	<7.0
		PII(M2)	633	631	99.7	98.9	100	3741.7	3499.3	4000.9	<7.0	47111.0
		PIII(M7)	628	628	100	99.4	100	8262.0	7725.0	8836.2	567.0	187560.0
	S+	PRE	29	29	100	88.1	100	19.7	15.0	25.8	7.0	89.0
		PII(M2)	28	28	100	87.7	100	3825.9	2840.4	5153.3	1124.0	14514.0
		PIII(M7)	27	27	100	87.2	100	10981.1	7202.5	16742.0	2244.0	200687.0
	Total	PRE	668	29	4.3	2.9	6.2	3.8	3.7	3.9	<7.0	89.0
		PII(M2)	661	659	99.7	98.9	100	3745.2	3508.8	3997.7	<7.0	47111.0
		PIII(M7)	655	655	100	99.4	100	8359.4	7820.8	8935.1	567.0	200687.0
HPV-001	S-	PRE	334	0	0.0	0.0	1.1	3.5	3.5	3.5	<7.0	<7.0
		PIII(M7)	325	325	100	98.9	100	3471.8	3161.9	3811.9	107.0	51346.0
	S+	PRE	37	37	100	90.5	100	11.3	10.0	12.9	7.0	33.0
		PIII(M7)	37	37	100	90.5	100	3356.8	2421.3	4653.6	227.0	18774.0
	Total	PRE	371	37	10.0	7.1	13.5	3.9	3.8	4.1	<7.0	33.0
		PIII(M7)	362	362	100	99.0	100	3459.8	3162.8	3784.8	107.0	51346.0

HPV-HPV-013 = HPV-16/18 from study HPV-HPV-013.
HPV-001 = HPV-16/18 L1 from study HPV-001
S- = seronegative subjects (antibody titer < 7 EU/ML) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 7 EU/ML) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence intervalMIN/MAX = Minimum/Maximum
PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR HPV-013, Table 35, p. 87

The reverse cumulative curves for both anti-HPV-16 and anti-HPV-18 at Month 7 (1 month after dose 3) show that antibody titers are higher in the 10-14 year old females in study HPV-013 as compared to 15-25 year old females in study HPV-001 who received HPV 16/18 vaccine. (Source: STN 125259/0, CSR HPV-013, Supplement, 72 and 73, p. 221 and 222).

Seropositivity rates and GMTs for anti-MPL antibodies and anti-HAV antibodies: Analysis of additional immunogenicity data were performed on blood samples for anti-MPL antibodies and Anti-HAV antibodies. A second analysis based on the Total Vaccinated cohort was performed to supplement the primary analysis. A total of 1412 subjects were evaluated in the immunogenicity analysis and 1341 subjects were included in the according-to-protocol (ATP) cohort for immunogenicity.

At study entry, most of the subjects in the HPV group and in the HAV group had anti-MPL antibody titers above or equal to the limit of quantification of the ELISA assay -b(4)- EU/mL). In subjects with detectable anti-MPL antibody titers before vaccination (ATP cohort), there was a 4.25-fold increase in GMT values following the third dose of HPV-16/18 vaccine compared to pre-vaccination levels (Month 7). In the HAV group, there was no noticeable difference in anti-MPL antibody titers after Dose 2 and Dose 3 compared to the titer at study entry. (Source: STN 125259.0, CSR 013, Annex 2, Table 3, p.16, not shown here)

Results were also presented for seropositivity rates for anti-HAV antibodies through Month 7. **Reviewer's Comment:** 99.7% of subjects who received HAV vaccine seroconverted by Month 7, and GMTs were well above the ≥ 15 mIU/mL level of cut-off for seropositivity. (Source: STN 125259.0, CSR 013, Annex 2, Table 4, p.19, not shown here)

Total Vaccinated Cohort Analysis: The immunogenicity data obtained from the analysis of the Total Vaccinated Cohort were consistent with those obtained from the analysis of immunogenicity in the ATP cohort for both anti-MPL and anti-HPV. (Source: STN 125259.0, CSR 013, Annex 2, Supplements 4 and 8, p.27 and 29, not shown here)

ANNEX REPORT TO STUDY HPV-013: The safety analyses performed on subjects enrolled from Korea and Taiwan and the immunogenicity analyses performed per country (Colombia, Germany, Honduras, Korea, Panama and Taiwan) were presented. The adverse events reporting in Korea and Taiwan follow a similar pattern seen in the primary safety analysis performed on all countries together. In both countries, the reporting of adverse events tended to be higher in the HPV group than in the HAV group for any symptoms, general symptoms and local symptoms, regardless of the follow-up period (7-day or 30-day). The incidence of solicited local symptoms was higher in the HPV group with pain being the most frequently reported solicited local symptom. The incidence of solicited general symptoms and unsolicited symptoms was similar in both groups. The reactogenicity profile of both vaccines observed in Korea and Taiwan were consistent with the reactogenicity profile in the whole study.

The immunogenicity data obtained from analysis of the ATP cohort in each country shows that all initially seronegative subjects in the HPV group had seroconverted for both HPV-16 and HPV-18 antigens one month after the third dose of HPV-16/18 vaccine. GMTs were comparable to the main analysis considering all countries except in Honduras (where GMTs were slightly lower) and Taiwan (where GMTs were higher). The seroconversion rates and GMTs values obtained from the analysis of the Total vaccinated cohort in each country were consistent with those obtained for the ATP cohort for immunogenicity.

SAFETY FOLLOW-UP THROUGH MONTH 12
In another annex report to Study 013, additional safety reports are presented at Month 12 and Month 24 for subjects (Extended Safety Follow-Up or ESFU).

Extended Safety Follow-up Objective (ESFU): To compare the occurrence of SAEs, new onset of chronic diseases (NOCDs) and other medically significant conditions between the HPV-16/18 vaccine group and the HAV control group through the Month 12 follow-up telephone call.

ESFU endpoint: Occurrence of SAEs, NOCDs and other medically significant conditions up to Month 12 (extended safety follow-up).

Study cohorts/data sets analyzed
All safety analyses were performed on the ESFU vaccinated cohort and on the Total vaccinated cohort. The ATP safety cohort was not evaluated.

- **Total vaccinated cohort (Month 0 to Month 12):** The Total vaccinated cohort included all vaccinated subjects for whom data were available (Month 0 to Month 12).

- **ESFU vaccinated cohort (Month 7 to Month 12):** The ESFU vaccinated cohort included all vaccinated subjects for whom data were available (Month 7 to Month 12), i.e., subjects that could be contacted at the safety follow-up telephone contact.

Analysis of safety: The primary analysis of safety was based on the ESFU vaccinated cohort (Month 7 to Month 12). A secondary analysis of safety was performed on the Total vaccinated cohort (Month 0 to Month 12).

Serious adverse events: Serious adverse events and withdrawal due to adverse event(s) were described in detail. The two-sided standardized asymptotic 95% CI for the difference of SAE rates (SAE rate in HPV vaccine group minus SAE rate in HAV control group).

A list of potential new onset chronic diseases is shown in Appendix B-Overview of Safety, Table 1B.

Results

Study dates: The first subject was enrolled in the study on the 6/30/04 and the last visit (Month 7) of the study active phase was on the 8/22/05. The last subject completed the extended safety follow-up Month 12 telephone contact on the 1/25/06.

Number and distribution of subjects: A total of 2067 subjects were enrolled and vaccinated in the study. The Total vaccinated cohort therefore included 2067 subjects (1035 subjects received the HPV-16/18 vaccine and 1032 received the HAV control vaccine). The ESFU vaccinated cohort included 2023 subjects (1014 in the HPV group and 1009 in the HAV group)

Table 229-Study 013, Annex 3: Number of subjects enrolled into the study as well as the number of subjects excluded from ESFU Vaccinated Cohort analyses with reasons for exclusion (Month 7-12)

Title	Total			HPV		HAV	
	n	s	%	n	s	n	s
Total enrolled cohort	2067						
Total vaccinated cohort	2067		100	1035		1032	
Subject could not be contacted during the extended safety follow-up period (elimination code 3000)	44*	44		21	21	23	23
ESFU vaccinated cohort (Month 7- 12)	2023		97.9	1014		1009	

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
Note: Subjects may have more than one elimination code assigned.
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
* These 44 subjects include three subjects (Subjects 1559, 1577 and 1662) who were contacted during the ESFU while they had withdrawn their consent during the active phase. These subjects also received a 3000 elimination code.
Source: STN 125259/0, CSR HPV-013, Annex 3, Table 3, p. 26

Study completion and withdrawal from study: Overall, 2023 subjects completed the ESFU: 1014 subjects in the HPV group and 1009 in the HAV group. A total of 44 subjects withdrew from the study: 19 subjects in the HPV group and 22 in the HAV group.

- 22 subjects withdrew their consent (10 subjects in the HPV group and 12 subjects in the HAV group)
- 9 subjects were lost to follow-up (5 subjects in the HPV group and 4 subjects in the HAV group)
- 10 subjects either could not be contacted or had migrated from the study area (4 subjects in the HPV group and 6 subjects in the HAV group).
- Among these 44 withdrawals, 9 occurred between the last visit of the active phase of the study and the end of the extended safety follow-up: 6 subjects were lost to follow-up and 3 subjects could not be contacted.

Table 230-Study HPV-013, Annex 3: Number of subjects vaccinated, completed and withdrawn and reason for withdrawal from the study (Total Vaccinated Cohort)

	Group		
	HPV	HAV	Total
Number of subjects in Total vaccinated cohort (Active phase [Month 0 - Month 7)	1035	1032	2067
Number of subjects in ESFU vaccinated cohort	1014	1009	2023
Number of subjects withdrawn from the study	19	22	41*
Reasons for withdrawal:			
Consent withdrawal, not due to an AE	10	12	22
Lost to follow-up	5	4	9
Other	4	6	10

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
ESFU = Extended Safety Follow-Up
Withdrawn = number of subjects who could not be contacted at the concluding contact
* All these subjects received a 3000 elimination code. In addition, these 41 subjects do not include the three subjects (1559, 1577 and 1662) who were contacted during the ESFU while they had withdrawn their consent during the active phase. These subjects also received a 3000 elimination code.
Source: STN 125259/0, CSR HPV-013, Table 4, p. 27

Data sets analyzed: The primary analysis of safety was performed on the ESFU vaccinated cohort [Month 7 to Month 12]. Additional analyses based on the Total vaccinated cohort were performed (data collected between Month 0 and Month 12).

Protocol deviations leading to exclusion of subjects from an analysis: Among the 2067 subjects included in the Total vaccinated cohort, 41 subjects could not be contacted during the extended safety follow-up period and therefore were not included in the extended safety follow-up analyses. In addition, subjects no. 1559, 1577 and 1662 who were contacted during the extended safety follow-up had actually withdrawn their consent during the active phase (Month 0 to Month 12).

Protocol deviations not leading to exclusion of subjects from an analysis: The interval recommended in the protocol between study visit 4 and the Month 12 telephone contact was of 180 to 210 days. These intervals were not considered for the analysis.

Extended safety follow-up cohort analysis (Month 7 to Month 12)
Serious adverse events: Overall, 23 subjects reported at least one SAE: 13 subjects in the HPV group and 10 subjects in the HAV group (10 subjects reported 11 events, so total events for HAV group = 11).

The SAE rates in the two groups were similar: the difference in SAE rates for subjects reporting at least one SAE between the HAV group and the HPV group was equal to -0.29% (95% CI [-1.3; 0.68]). There were no SAEs considered by the investigator as possibly related to study vaccination.

Reviewer's Comment: The SAEs in the Month 7-12 time period occurred days to months after receipt of dose 3. None were assessed as related to receipt of vaccine. Tables have been constructed to present the events with the time to event, duration, and outcome for the HPV recipients (Table 231) and for the HAV recipients (Table 232).

Table 231-Study HPV-013, Annex 3: Subjects with SAE (Month 7-12) [HPV group, N=1014] (CBER generated)

Case number, age (years)	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome
B0348369B, 14 years old	Migraine with aura (right hemiparesis)	5 months after dose 3	2 days	Recovered
B0383087A, 12 years old	Abdominal pain	59 days after dose 3	3 days	Recovered
B0383354A, 13 years old	Abdominal pain-dysmenorrhea (tylenol)	85 days after dose 3	4 days	Recovered
B0390431A, 13 year old	Acute phlegmon hand (surgical drainage)	4 months after dose 3	34 days	Recovered
B0391499A, 11 year old	Acute bronchitis (antibiotics)	115 days after dose 3	3 days	Recovered
B0391503A, 13 year old	Abdominal pain	4 months after dose 3	1 day	Recovered
B0391515A, 15 year old	Convulsion (CSF negative) (?intercurrent illness)	92 days after dose 3	1 day	Recovered
B0396086A, 15 year old	Drug and alcohol overdose	5 months after dose 3	1 day	Recovered
B0500505A, 13 year old	Tympanic membrane perforation (tympanoplasty)	6 month after dose 3	6 days	Recovered
B0400510A, 12 year old	Concussion after fall (hit head)	83 days after dose 3	2 days	Recovered
B0402053A, 15 year old	Ruptured ovarian cyst	6 months after dose 3	1 day	Recovered
B0415789A, 14 year old	Mastoiditis (surgery and antibiotics)	118 days after dose 3	9 days	Recovered
B0371230B, 14 year old	Ovarian cyst (surgical removal of cyst)	4 months after dose 3	14 days	Recovered

Table 232-Study HPV-013, Annex 3: Subjects with SAE (Month 7-12) [HAV group, N=1009] (CBER generated)

Case number, age (years)	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome
B0381788A, 11 year old	Right ovarian cyst (surgical removal of cyst, right ovary, appendectomy)	41 days after dose 3	18 days	Recovered
B0383225A, 14 year old	Dysmenorrhea	74 days after dose 3	4 days	Recovered
B0387866A, 11 year old	Viral gastroenteritis (IV hydration)	87 days after dose 3	3 days	Recovered
B0392931A, 12 year old	Hashimoto's thyroiditis (Thyroxine, psychiatry rx)	57 days after dose 3	~2 months	Recovered
B0393854A, 12 year old	Fever then UTI	106 days after dose 3	~1 month	Recovered
B0399642A, 21 year old	Wrist ganglion (surgical removal)	2 months after dose 3	~4.5 months	Recovered
B0399764A, 14 year old	Anorexia nervosa	2 months after dose 2	-	Unresolved
B0400423A, 13 year old	Dyspnea (possible psychosomatic etiology)	110 days after dose 3	14 days	Recovered
B0401142A, 15 year old	Atypical pneumonia (oxygen, antibiotics)	6 months after dose 3	9 days	Recovered
B0403339A, 15 year old	Suicide attempt (pills)	90 days after dose 3	5 days	Recovered

Adverse events leading to premature discontinuation of study vaccine and/or study: In both groups, no subjects were withdrawn from the extended safety follow-up due to AEs.

Fatal events: There were no fatalities during the extended safety follow-up period [Month 7 to Month 12.]

New onset of chronic diseases: Three subjects reported 3 events in the in the HPV group and six subjects reported 6 events in the HAV group during the extended safety follow-up [Month 7 to Month 12] based on GSK assessment. The specific events are presented in Table 233.

Table 233-Study HPV-013, Annex 3: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the extended safety follow-up [Month 7 - 12] (ESFU Vaccinated Cohort)

		HPV N = 1014				HAV N = 1009			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one NOCD		3	0.3	0.1	0.9	6	0.6	0.2	1.3
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	0	0.0	0.0	0.4	1	0.1	0.0	0.6
Immune system disorders (10021428)	House dust allergy (10057631)	0	0.0	0.0	0.4	1	0.1	0.0	0.6
	Seasonal allergy (10048908)	0	0.0	0.0	0.4	1	0.1	0.0	0.6
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	2	0.2	0.0	0.7	1	0.1	0.0	0.6
	Asthmatic crisis (10064823)	0	0.0	0.0	0.4	1	0.1	0.0	0.6
Skin and subcutaneous tissue disorders (10040785)	Dermatitis contact (10012442)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
	Urticaria (10046735)	0	0.0	0.0	0.4	1	0.1	0.0	0.6

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
NOCD(s) = New Onset of Chronic Disease(s)
At least one NOCD = at least one NOCD experienced
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOCD
Source: STN 125259/0, CSR HPV-013, Annex 3, Table 9, p. 34

Medically significant adverse events: A total of 80 medically significant AEs were reported by 71 subjects during the extended safety follow-up (Months 7-12). The number of subjects reporting at least one medically significant AE was similar in both groups: 36 subjects reported 41 medically significant events in the HPV group and 35 subjects in the HAV group reported 39 medically significant AEs. The percentages of subject reporting at least one medically significant AE are similar in both groups: 3.6% of subjects in the HPV group and 3.5% subjects in the HAV group.

The most frequently reported medically significant AEs in each group are presented in Table 234 below.

Table 234-Study 013: Percentage of subjects reporting the occurrence of medically significant AEs classified by MedDRA Primary System Organ Class and Preferred Term, during the extended safety follow-up [Month 7 -12] (ESFU Vaccinated)

Primary System Organ Class	Preferred Term	HPV N=1014	HAV N=1019
		n (%)	n (%)
At least one symptom		**36 (3.6%)**	**35 (3.5%)**
Gastrointestinal disorders	Abdominal pain	4 (0.4%)	0 (0.0%)
Infections and Infestations	Bronchitis	4 (0.4%)	1 (0.1%)
	Bronchopneumonia	0 (0.0%)	2 (0.2%)
Reproductive system and breast disorders	Ovarian cyst	3 (0.3%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	Asthma	3 (0.3%)	2 (0.2%)

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
At least one medically significant AE = at least one medically significant AE experienced
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the medically significant AE
95% CI= exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Annex 3, Table 11, p. 36-37

Pregnancy: During the extended safety follow-up period, three subjects in the HPV group were reported to be pregnant and none in the HAV group. None of these pregnancies were reported as SAEs or AEs.

Table 235-Study 013, Annex 3: Outcome of reported pregnancies [Month 7 - 12] (ESFU Vaccinated Cohort)

Outcome	HPV	HAV
Healthy baby	2	0
Miscarriage/spontaneous abortion/foetal death	0	0
Elective abortion	0	0
Neonatal death	0	0
Unknown	1	0
Total	**3**	**0**

HPV = HPV-16/18 ; HAV = Hepatitis A vaccine group
Source: STN 125259/0, CSR HPV-013, Annex 3, Table 11, p. 36-37

Two subjects were reported to be pregnant 7 months after the second dose of HPV vaccine and gave birth, respectively, to a healthy female infant and a healthy male infant, both by normal vaginal delivery. Another subject was reported to be pregnant 13 months after the third dose. At the time of reporting, the outcome was unknown as this pregnancy was ongoing.

Month 0-12 Summary safety data: Because the entire Month 0-12 time period is of interest, in that it provides adverse events through 6 months after dose 3, a summary of the adverse events is reviewed for the entire time period.

Serious adverse events: Among the 2067 subjects included in the Total vaccinated cohort, 45 subjects reported 53 SAEs during the Month 0 to Month 12 follow-up period: 27 SAEs reported by 22 subjects (2.1%) in the HPV group and 26 SAEs reported by 23 subjects (2.2%) in the HAV group. Overall, the SAE rates in the two groups were similar: the difference in SAE rates for subjects reporting at least one SAE between the HAV group and the HPV group was equal to 0.10% (95% CI [-1.20; 1.41]).
Reviewer's Comment: There were no additional cases of appendicitis in the Month 7-12 time period, so the difference between HAV and HPV groups (0.48% [95% CI: 0.11, 1.13]) is also noted in this analysis.

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study: During the Month 0 to Month 12 follow-up period there were no withdrawals due to AEs in the HPV group. The two subjects who withdrew from the HAV group for non-serious adverse events (injection site pain and joint swelling) were previously noted.

New onset of chronic diseases: Overall, based on GSK assessment, 60 subjects reported 65 NOCDs. In the HPV group, 32 subjects reported 36 events (3.1% of subjects), and in the HAV group 28 subjects reported 29 events (2.7% of subjects). The specific events are presented in Table 236.

Table 236-Study HPV-013, Annex 3: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, reported during the Month 0 to Month 12 follow-up period (Total Vaccinated Cohort)

		HPV N = 1035				HAV N = 1032			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one NOCD		32	3.1	2.1	4.3	28	2.7	1.8	3.9
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Goitre (10018498)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
	Hyperthyroidism (10020850)	0	0.0	0.0	0.4	2	0.2	0.0	0.7
	Hypothyroidism (10021114)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
Eye disorders (10015919)	Conjunctivitis allergic (10010744)	1	0.1	0.0	0.5	2	0.2	0.0	0.7
Immune system disorders (10021428)	Food allergy (10016946)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
	House dust allergy (10057631)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Hypersensitivity (10020751)	4	0.4	0.1	1.0	3	0.3	0.1	0.8
	Seasonal allergy (10048908)	0	0.0	0.0	0.4	3	0.3	0.1	0.8
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	7	0.7	0.3	1.4	4	0.4	0.1	1.0
	Asthmatic crisis (10064823)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Rhinitis allergic (10039085)	10	1.0	0.5	1.8	5	0.5	0.2	1.1
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	2	0.2	0.0	0.7	2	0.2	0.0	0.7
	Dermatitis atopic (10012438)	1	0.1	0.0	0.5	1	0.1	0.0	0.5
	Dermatitis contact (10012442)	2	0.2	0.0	0.7	0	0.0	0.0	0.4
	Urticaria (10046735)	4	0.4	0.1	1.0	2	0.2	0.0	0.7

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
At least one NOCD = at least one NOCD experienced
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOCD
95% CI= exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Annex 3, Table 16, p. 43

Medically significant adverse events: During the Month 0 to Month 12 follow-up period, a total of 654 medically significant AEs were reported by 458 subjects: 312 medically significant AEs were reported by 214 subjects (20.7%) in the HPV group and 342 medically significant AEs were reported by 244 subjects (23.6%) in the HAV group.

Table 237-Study HPV-013, Annex 3: Percentage of Subjects Reporting Most Frequently Reported Medically Significant AEs Classified by MedDRA Primary System Organ Class and Preferred Term, Month 0 to Month 12 follow-up period (Total Vaccinated Cohort)

Primary System Organ Class	Preferred Term	HPV N=1014	HAV N=1019
		n (%)	n (%)
At least one symptom		**214 (20.7%)**	**244 (23.6%)**
Gastrointestinal disorders	Abdominal pain	10 (1.0%)	3 (0.3%)
General and administration site disorders	Influenza like illness	5 (0.5%)	5 (0.5%)
Infections and Infestations	Bronchitis	13 (1.3%)	11 (1.1%)
	Ear infection	5 (0.5%)	2 (0.2%)
	Impetigo	2 (0.2%)	6 (0.6%)
	Influemza	7 (0.7%)	17 (1.6%)
	Lice infestation	3 (0.3%)	7 (0.7%)
	Otitis media	5 (0.5%)	8 (0.8%)
	Viral infection	7 (0.7%)	9 (0.9%)
Injury, poisoning and procedural complications	Joint sprain	1 (0.1%)	5 (0.5%)
Nervous system disorders	Headache	6 (0.6%)	9 (0.9%)
	Migraine	6 (0.6%)	2 (0.2%)
Respiratory, thoracic and mediastinal disorders	Asthma	8 (0.8%)	6 (0.6%)
	Cough	7 (0.7%)	8 (0.8%)
	Pharyngolaryngeal pain	9 (0.9%)	5 (0.5%)
	Rhinitis allergic	10 (1.0%)	7 (0.7%)
Skin and subcutaneous tissue disorders	Acne	4 (0.4%)	8 (0.8%)
	Dermatitis	5 (0.5%)	1 (0.1%)
	Rash	3 (0.3%)	5 (0.5%)

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
At least one medically significant AE = at least one medically significant AE experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose.
n/% = number/percentage of subjects reporting at least once the medically significant AE
95% CI= exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Annex 13, Table 18, p. 46-51

Pregnancy: A total of 7 pregnancies were reported during the Month 0 to Month 12 follow-up period: 5 subjects in the HPV group and 2 subjects in the HAV group. Four subjects (3 subjects in the HPV group and 1 subject in the HAV group) gave birth to healthy infants, 2 subjects (one subject in each vaccine group) underwent elective abortion and one pregnancy (HPV group) outcome was at the time of reporting unknown.

Table 238-Study HPV-013, Annex 3: Outcome of reported pregnancies (Month 0 to Month 12) (Total Vaccinated Cohort)

Outcome	HPV	HAV
Healthy baby	3	1
Miscarriage/spontaneous abortion/foetal death	0	0
Elective abortion	1	1
Neonatal death	0	0
Unknown	1	0
Total	**5**	**2**

HPV = HPV-16/18 ; HAV = Hepatitis A vaccine group
Source: STN 125259/0, CSR HPV-013, Annex 3, Table 19, p. 51

HPV-013: MONTH 18 REPORT

Long-term follow-up in study HPV-013: Once the HPV-013 study (Month 12 telephone contact) had concluded for all subjects and the treatment allocation had been unblinded (4/27/06), only subjects who received the HPV vaccine were invited to continue with study visits until Month 48. Subjects who received HAV vaccine were invited to attend one further visit as their study conclusion visit.

Antibody responses against MPL were assessed in all study subjects enrolled in the follow-up study such that the subjects who received HAV vaccine in the primary study provided a control for the subjects who received HPV vaccine, which is formulated with MPL.

Primary objective: Evaluate the long-term HPV-16/18 L1 AS04 vaccine immunogenicity (for all subjects in the HPV vaccine group) by enzyme-linked immunosorbent assay (ELISA).

Secondary objectives

- To evaluate antibody responses against MPL by ELISA.
- To evaluate the safety of the candidate vaccine during the long-term follow-up study (approximately 48 months after administration of the first dose).
- To compare the immune responses to the candidate HPV vaccine (as determined by anti-HPV-16/18 ELISA) in healthy female subjects aged 10 - 14 years in this study with responses measured in sera from adults of the efficacy study HPV-001 at Month 18.

Study Design of long-term follow-up extension study, Ext HPV-013 study

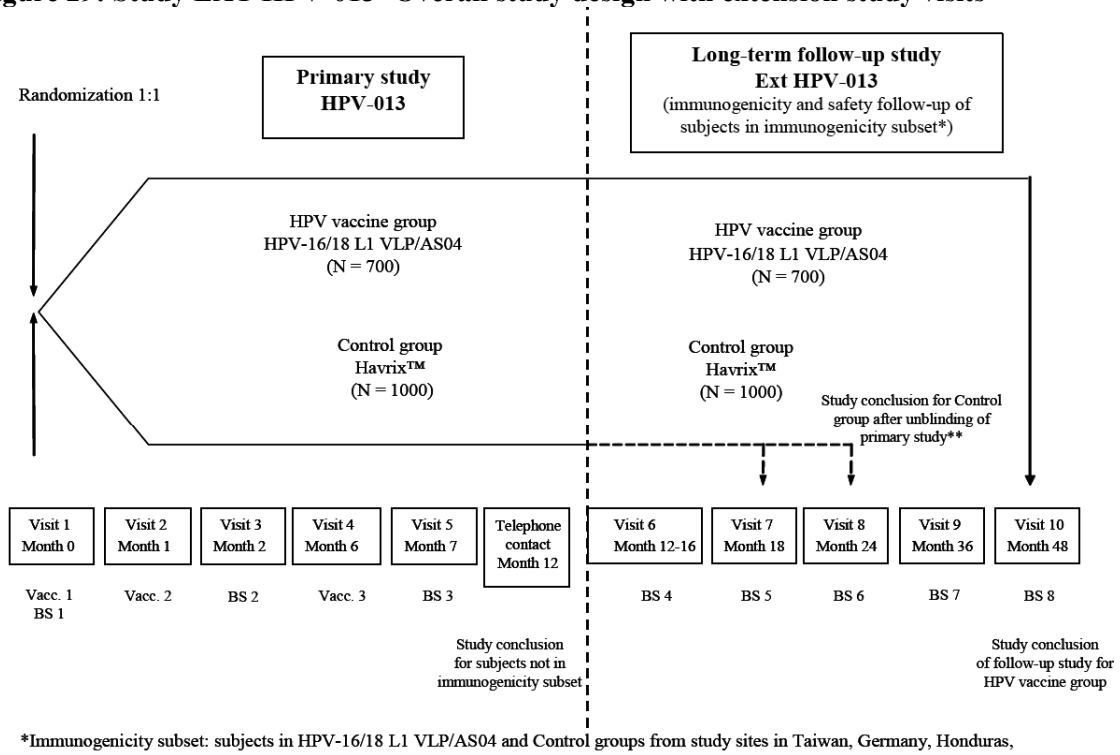
- Experimental design and blinding: A phase III, multi-country trial. All subjects from the immunogenicity subset at study sites in Taiwan, Germany, Honduras, Panama and Colombia were invited to continue in the study. Korea was also invited to participate, but declined participation.
- The long-term follow-up study was blinded until the primary study was unblinded, and thereafter was conducted in an open fashion. After unblinding, subjects who received the HPV-16/18 L1 AS04 vaccine during the HPV-HPV-013 study were to continue their participation in the follow-up study until Month 48. Subjects who had received the HAV control vaccine attended one further visit as their last study visit (depending on time of their enrollment, either Visit 7 at Month 18 or Visit 8 at Month 24.

Until the unblinding of the HPV-013 study, there were two parallel groups: HPV vaccine group and HAV control vaccine group. After the unblinding of the HPV-013 study, one single open group [HPV vaccine group] is to continue the study until Month 48.

- Blood sample collection was planned at Month 12-16, Months 18, 24, 36 and 48.
- Safety assessments during the entire study period (up to Month 48) in all subjects who participated in the study:
  - Reporting of Serious adverse events (SAEs).
  - Recording of new onset of chronic diseases (NOCDs) and other medically significant conditions were reported.
  - Reporting of pregnancies and their outcome.
- Duration of the long-term follow-up study: Up to 36 additional months for subjects who received the HPV vaccine and up to 12 additional months for subjects who received HAV vaccine in the primary study.
- Total study duration (HPV-013 primary study and long-term follow-up study): approximately 48 months after the administration of the first vaccine/control dose in HPV-013 study.
- Subjects were enrolled in the extension study within 120 days following the telephone contact at Month 12.

- Interim analyses are to be conducted to assess all endpoints from data obtained after visit 7 (Month 18), 8 (Month 24) and 9 (Month 36). Final analyses are to be conducted to assess all endpoints from data after study conclusion at visit 10 (Month 48).
- Data collection: Remote Data Entry (RDE).
- Subjects in the HPV vaccine group may also be invited later to participate in a booster vaccination study (time yet to be determined) and/or parallel research studies to evaluate the HPV vaccine response (i.e. evaluation of mucosal antibodies, etc). If needed, such studies will be described in separate study protocols.

Figure 29: Study EXT HPV-013- Overall study design with extension study visits



*Immunogenicity subset: subjects in HPV-16/18 L1 VLP/AS04 and Control groups from study sites in Taiwan, Germany, Honduras, Panama and Colombia
**Once HPV-013 (primary study) has been completed and unblinded, subjects from Control group enrolled in follow-up study will attend one further visit as their last study visit, i.e. depending on time of their enrolment, either Visit 7 (at Month 18) or Visit 8 (at Month 24).
BS: Blood sample Vacc.: vaccination

Source: STN 125259/30, CSR HPV-013, Month 24, p. 25

Unblinding of the primary study HPV-013: The primary study HPV-013 was unblinded following the last study contact, (when the telephone contact at Month 12 had been completed for all subjects (4/27/06). At this point in time, the study investigators were provided with the treatment allocation of all subjects and were instructed to contact all subjects eligible for participation in the long-term follow-up study, so that the subjects could either continue in the study until study conclusion at Month 48 if they are in the HPV vaccine group, or attend one further study visit as their concluding visit, if they were in the control group.

Table 239- Study EXT HPV-013 - List of study procedures for subjects in control group

Visit	EXT HPV-013		
	VISIT 6	VISIT 7	VISIT 8
Timing	Month 12-16	Month 18	Month 24
Informed consent for Ext HPV-013	●		
Check inclusion criteria for Ext HPV-013	●		
Check exclusion criteria for Ext HPV-013	●		
Check elimination criteria for Ext HPV-013		●	●
Blood sampling for anti-MPL serology	●	●	●
Telephone or contact by mail to remind subjects to return to the site for the visit	○	○	○
Reporting of SAEs, new onset of chronic diseases and other medically significant conditions	●	●	●
Reporting of all pregnancies and pregnancy outcome	●	●	●
Record any concomitant medication	●	●	●‡
Study Conclusion for subjects in control group*		●	●

‡ : Administration of any HPV vaccine other than that used in the primary study, HPV-HPV-013, is also recorded.
* Once HPV-HPV-013 (primary study) had been completed and unblinded, subjects from control group participating in the follow-up study were to attend one further visit as their last study visit, i.e. depending on time of their enrolment, either Visit 7 (at Month 18) or Visit 8 (at Month 24).
Note: The double-line border following Month 18 (eTrack study number 104896 Ext HPV-HPV-013 Mth 18) and Month 24
(eTrack study number 104902 Ext HPV-HPV-013 Mth 24) indicates the interim analyses that are to be performed on all data obtained up to that point in time.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF
STN 125259/30, CSR HPV-013, Month 24, Table 1, p. 28

Table 240-Study HPV-013- List of study procedures for subjects in HPV vaccine group

Visit	EXT HPV-013				
	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10
Timing	Month 12-16	Month 18	Month 24	Month 36	Month 48
Informed consent for Ext HPV-013	●				
Check inclusion criteria for Ext HPV-013	●				
Check exclusion criteria for Ext HPV-013	●				
Check elimination criteria for Ext HPV-013		●	●	●	●
Blood sampling for anti-HPV-16, anti-HPV-18 and anti-MPL serology testing	●	●	●	●	●
Telephone or contact by mail to remind subjects to return to the site for the visit	○	○	○	○	○
Reporting of SAEs, new onset of chronic diseases and other medically significant conditions	●	●	●	●	●
Reporting of all pregnancies and pregnancy outcome	●	●	●	●	●
Record any concomitant medication	●	●	●*	●*	●*
Study Conclusion for subjects in HPV vaccine group		●	●	●	●

* : Administration of any HPV vaccine other than that used in the primary study, HPV-HPV-013, is also recorded.
Note: The double-line border following Month 18 (eTrack study number 104896 Ext HPV-HPV-013 Mth 18), Month 24
(eTrack study number 104902 Ext HPV-HPV-013 Mth 24), and Month 36 (eTrack study number 104918 Ext HPV-HPV-013 Mth
36) indicates the interim analyses which is performed on all data obtained up to that point in time.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
STN 125259/30, CSR HPV-013, Month 24, Table 2, p. 29

Primary endpoint: Anti-HPV-16/18 antibody titers in all study subjects in the HPV vaccine group (ELISA).

Secondary endpoints

- Anti-MPL antibody titers (ELISA).
- Comparison of anti-HPV-16/18 antibody titers (by ELISA) assessed in sera from 10 - 14 year olds (Ext HPV-013) subjects and in sera from adults in study HPV-001 at Month 18.
- Occurrence of pregnancies, serious adverse events, new onset of chronic diseases, and conditions prompting emergency room visits or physician visits that are not related to common diseases throughout the entire study period (including the period from the Month 12 telephone contact of the primary HPV-013 study until visit 6 [Month 12-16] of the Ext HPV-013 study).

Study cohorts/data sets analyzed

Total Vaccinated cohort: The Total Vaccinated cohort included all vaccinated subjects (i.e. subjects from the immunological subset of HPV-HPV-013 who received three doses of vaccine in the primary HPV-013 study) for whom data were available.

- **Total analysis of safety:** included all subjects
- **Total analysis of immunogenicity** included subjects who returned for blood sampling at the particular long-term blood sampling timepoints (Months 12-16, 18) and for whom serology results were available.

ATP immunogenicity cohort: The ATP cohort for analysis of immunogenicity included all evaluable subjects (i.e., subjects who were included in the ATP immunogenicity analysis in the primary HPV-013 study meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom serology results were available for a particular blood sampling time point (Months 12-16, 18) of the Ext HPV-013 study.

Analysis of immunogenicity: The primary analysis of immunogenicity was based on the ATP cohort. A second analysis based on the Total Vaccinated cohort was performed to supplement the primary analysis. The following antibodies were analyzed: anti-HPV-16, anti-HPV-18 and anti-MPL.

Analysis of safety: The safety analysis in the long-term follow-up was based on the Total Vaccinated cohort. Withdrawal due to adverse event(s) was described in detail. No formal comparisons were made between groups. Pregnancies and their outcome were described in detail. New onset of chronic diseases (NOCD) and medically significant conditions were reported throughout the study period regardless of causal relationship to vaccination and intensity.

Protocol amendments/modifications: The protocol was further amended following study completion, on September 08, 2006 as follows:

- Subsequent to the licensure of Gardasil (Merck & Co.'s HPV-6/11/16/18 vaccine) in several countries, from Visit 8 (Month 24) onwards, vaccination with an HPV vaccine other than the study vaccine has to be recorded.
- In case an autoimmune disease is suspected, autoantibody testing may be performed on blood samples collected, provided that the legal representative and the subject consent to this procedure.

Other Changes
This study was conducted according to the protocol. Analyses were performed as planned in the protocol and in the RAP with the following exceptions:

- Demographic characteristics were not tabulated or calculated.
- Immunogenicity analyses have not been performed for the kinetic cohort.
- Anti-MPL results were evaluated using Assay Version 2 in a subset of subjects. Results up to Month 24 are included in the Month 24 Clinical Study Report.
- The comparison of the immune response of the vaccine in the Ext HPV-013 study population was compared to the HPV-007 plateau immunogenicity. In addition, the observed immunogenicity in the Ext HPV-013 study participants was compared to natural infection titers measured in the HPV-008 trial (HPV-008 interim report dated February 2007)

Study dates: Study visits took place between 10/19/05 and 7/13/06 for all subjects. The data-lock point was 10/25/06 for all data except for anti-MPL results (data lock point 1/12/07).

Number and distribution of subjects: In the primary HPV-013 study, 2067 subjects were enrolled and were vaccinated: 1035 subjects received the HPV-16/18 vaccine and 1032 subjects received the HAV control vaccine. All subjects who had received 3 doses of vaccine in the primary HPV-013 study and who were included in the immunogenicity subset were invited to participate in the Ext HPV-013 study. Once the primary HPV-013 study was unblinded, subjects in the HPV vaccine group (N = 626) continued in this long-term follow-up study, whereas subjects from the HAV control group (N = 619) continued for one further visit as their last study visit (Visit 7 [Month 18] or Visit 8 [Month 24]). These subjects comprised the Total Vaccinated cohort and were recruited in 34 centers located in 5 countries: Taiwan, Germany, Honduras, Panama and Colombia.

The number of subjects excluded from the ATP analyses and the reasons for exclusion are shown in Table 241. Of the 2067 subjects included in the Total Vaccinated cohort of the primary HPV-HPV-013 study, 822 did not attend visit 7 (Month 18) of the Ext HPV-013 study. Of these, 655 subjects were not part of the immunogenicity subset and therefore were not eligible; 54 subjects were from the study site of Korea, which although in the immunogenicity subset, declined to participate in the Ext HPV-013 study. 113 subjects could not be contacted or refused to participate in the Ext HPV-013 study. A total of 1245 subjects attended visit 7 (Month 18) and comprised the Total Vaccinated cohort.

Sixty-six subjects were excluded from the ATP cohort for analysis of immunogenicity. The reasons for exclusion and the numbers of excluded subjects were as follows:

- 18 subjects with non-compliance with the blood-sampling schedule in the primary HPV-013 study
- 6 subjects with non-compliance with blood-sampling schedule in Ext HPV-013 study
- 17 missing essential serological data in the primary HPV-013 study
- 10 with noncompliance with the vaccination schedule in the primary HPV-013 study
- 7 with administration of any medication forbidden by the protocol in the primary HPV-013 study
- 3 with study vaccine dose not administered according to the protocol in the primary HPV-013 study
- 2 with administration of vaccine(s) in the primary HPV-013 study forbidden in the protocol
- 2 with obvious incoherence in the data in the primary HPV-013 study
- 1 with protocol violation (inclusion/exclusion criteria) in the Ext HPV-013 study

The ATP immunogenicity cohort included 1179 subjects (595 subjects in the HPV group and 584 subjects in the HAV group).

Table 241-Study Ext HPV-13: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

	Total			HPV		HAV	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled cohort (Primary HPV-013 study)	2067						
Total vaccinated cohort (Primary HPV-013 study)	2067		100	1035		1032	
Subjects not enrolled in extension study (code 4000)*	822	822		409	409	413	413
Total Vaccinated Cohort (Ext HPV-013 study)	1245		60.2	626		619	
Administration of vaccine(s) forbidden in the protocol (code 1040)†	2	25		2	13	0	12
Study vaccine dose not administered according to protocol (code 1070)†	3	10		1	3	2	7
Protocol violation (inclusion/exclusion criteria) (code 2010)†	0	1		0	1	0	0
Administration of any medication forbidden by the protocol (code 2040)†	7	9		3	3	4	6
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)†	10	21		3	7	7	14
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)†	18	21		10	12	8	9
Essential serological data missing (code 2100)†	17	22		6	9	11	13
Obvious incoherence or abnormality or error in data (code 2120)†	2	3		2	3	0	0
Protocol violation (inclusion/exclusion criteria) (code 4010)	1	2		1	1	0	1
Non compliance with blood sampling schedule for extension Month 18 (code 4090)	6	6		3	3	3	3
Essential serological data missing for extension Month 18 (code 4100)	0	2		0	2	0	0
ATP Cohort for immunogenicity	1179		57.0	595		584	

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated cohort
* Subjects who were not in the immunogenicity subset received the code 4000 (N = 655).
Subjects in Korea received the code 4000: this study site was in the immunogenicity subset but decided not to participate in the extension (N = 54).
Subjects who could not be contacted or who refused to participate to the extension study received the code 4000 (N =113).
† Codes assigned for criteria in primary HPV-HPV-013 study.
Source: STN 125259/0, CSR HPV-013, Month 18 report, Table 5, p. 42

Study completion and withdrawal from study: A total of 622 subjects in the HPV group and 619 subjects in the HAV group completed visit 7 (Month 18). A total of 4 subjects withdrew from the study. All withdrawals were in the HPV group: 1 subject withdrew consent, 2 subjects were lost to follow-up, and one subject was withdrawn because no blood sampling was possible.

Table 242-EXT Study HPV-013: Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total Vaccinated Cohort)

	Group		
	HPV	HAV	Total
Number of subjects vaccinated	626	619	1245
Number of subjects completed	622	619	1241
Number of subjects withdrawn	4	0	4
Reasons for withdrawal:			
Serious Adverse Event	0	0	0
Non-serious adverse event	0	0	0
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	1	0	1
Migrated/moved from study area	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	2	0	2
Others	1	0	1

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit (i.e., Month 18)
Withdrawn = number of subjects who did not come for the last visit (i.e., Month 18)
Source: STN 125259/0, CSR HPV-013, Month 18 report, Table 6, p. 43

Protocol deviations leading to exclusion of subjects from an analysis: The protocol deviations leading to the exclusion of subjects from the ATP cohort for immunogenicity comprised those deviations applicable to the primary HPV-013 study (59 subjects) and those applicable to the Ext HPV-013 study. Ext HPV-013 study deviations (excluding subjects assigned a lower elimination code) were a protocol violation (1 subject) and non-compliance with blood sampling schedule (6 subjects).

Protocol deviations not leading to exclusion of subjects from an analysis: Visit intervals were adapted so as to avoid eliminating subjects for irrelevant clinical reasons. Subjects outside the protocol intervals but within the adapted intervals were not eliminated from any of the analyses. Visit intervals fell outside the predefined protocol interval for 142 subjects (75 subjects in the HPV group and 67 subjects in the HAV group) and visit intervals fell outside the adapted intervals for 4 subjects (2 subjects in the HPV group and 2 subjects in the HAV group)

SAFETY RESULTS TO MONTH 18

This portion of the review is limited to Month 12-Month 18 because Month 0-Month 24 reports are included in the Clinical Study report for study HPV-013 below which includes the adverse events through the longest possible follow-up time.

Serious adverse events Month 0 through Month 18: There were no fatalities during the study. Overall, 9 subjects (7 subjects in the HPV group and 2 subjects in the HAV group) reported at least one SAE during Months 12-18 of follow-up and 51 subjects (26 subjects in the HPV group and 25 subjects in the HAV group) reported at least one SAE during the entire follow-up period (Months 0-18). None of the SAEs reported during the extension follow-up period (Months 12-18) were considered by the investigator to be causally related to vaccination.

Tables 243 and 244 presents the SAEs for the HPV and HAV group by time to event and outcome. None of these events were assessed as related to vaccination by the investigator.

Table 243-Study HPV-013, Annex 4: Subjects with SAE (Month 12-18) [HPV group, N=626] (CBER generated)

Case number, age (years)	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome
B0414568A, 15 year old	Acute pyelonephritis	10 months after dose 3	19 days	Resolved
B0416224A, 14 year old	EBV infection	12 months after dose 3	17 days	Resolved
B0419389A & B, 14 year old	Abdominal pain with ovarian cyst Headache (x several years) and dizziness, dx schizophreniform disorder	7 months after dose 3 9 months after dose 3	~1 month 5 weeks	Resolved Resolved
B0421544A, 14 year old	Dengue fever	12 months after dose 3	8 days	Resolved
B0427320A, 14 year old	Arthralgia, myalgia, splenomegaly (CRP, CBC, C3, C4 reported as normal –no etiology noted)	6 months after dose 3	4 days	Resolved
B0429006A, 15 year old	Appendicitis and ruptured ovarian cyst (appendectomy)	11 months after dose 3	5 days	Resolved
B0431930A, 14 year old	Rupture cruciate ligament (surgical repair)	11 months after dose 3	~3 months	Resolved

Table 244-Study HPV-013, Annex 4: Subjects with SAE (Month 12-18) [HAV group, N=619] (CBER generated)

Case number, age (years)	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome
B0411442A, 15 year old	Orthostatic dysregulation	8 months after dose 3	7 days	Resolved
B0420035A, 14 year old	Suicide attempt	10 months after dose 3	8 days	Resolved

Reviewer's Comment: All events in Tables 243 and 244 occurred at ≥ 6 months after dose 3, all resolved, and do not appear to be related to vaccine administered.

Adverse events leading to premature discontinuation of study vaccine and/or study control: There were no withdrawals due to AEs in either the HPV group or the HAV group during Months 12-18.

New onset of chronic diseases: Based on GSK assessment, 10 subjects (7 subjects in the HPV group (1.1%) and 3 subjects (0.5%) in the HAV group) with NOCDs were identified during Months 12-18 of follow-up. In the Month 0-18 follow-up period, 70 subjects (39 subjects in the HPV group and 31 subjects in the HAV group) reported at least one NOCD. Similar rates were observed for the HPV group (3.8%) and the HAV group (3.0%) when considered for the entire study period (Months 0-18). The specific NOCDs reported Month 12-18 are presented in Table 245 below.

Table 245-EXT Study HPV-013: Percentage of subjects reporting the occurrence of New Onset of Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the extension follow-up (Month 12 to Month 18) (Total Vaccinated Cohort)

		HPV N = 626				HAV N = 619			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one NOCD		7	1.1	0.5	2.3	3	0.5	0.1	1.4
Endocrine disorders (10014698)	Goitre (10018498)	2	0.3	0.0	1.1	1	0.2	0.0	0.9
Immune system disorders (10021428)	Hypersensitivity (10020751)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	2	0.3	0.0	1.1	1	0.2	0.0	0.9
Skin and subcutaneous tissue disorders (10040785)	Dermatitis atopic (10012438)	2	0.3	0.0	1.1	0	0.0	0.0	0.6
	Psoriasis (10037153)	0	0.0	0.0	0.6	1	0.2	0.0	0.9
	Vitiligo (10047642)	1	0.2	0.0	0.9	0	0.0	0.0	0.6

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOCD
95% CI= exact 95% confidence interval
Source: STN 125259/0, CSR HPV-013, Month 18 report, Table 18, p. 58

The most frequently identified NOCDs during the entire follow-up period (Months 0-18) were allergic rhinitis (reported by 10 subjects in the HPV group and by 5 subjects in the HAV group), asthma (reported by 9 subjects in the HPV group and by 5 subjects in the HAV group), hypersensitivity (reported by 5 subjects in the HPV group and by 3 subjects in the HAV group) and urticaria (reported by 4 subjects in the HPV group and by 2 subjects in the HAV group).

Medically significant adverse events: Eighty subjects (53 subjects in the HPV group and 27 subjects in the HAV group) were reported with medically significant AEs during Months 12-18 of follow-up and 497 subjects (241 subjects in the HPV group and 256 subjects in the HAV group) were reported with medically significant AEs during the entire follow-up period (Months 0-18). There appeared to be an imbalance in the rate of medically significant AEs reported in the HPV group (8.5%) compared with the HAV group (4.4%) from Months 12-18, however similar rates were observed for the HPV group (23.3%) and the HAV group (24.8%) when considered for the entire study period (Months 0 -18). None of the events reported as medically significant during Months 12-18 were considered by the investigator as related to vaccination.
Reviewer's Comment: Review of the categories of medically significant AEs reported for the two groups during Months 12-18 showed that group differences could not be accounted for by any one specific preferred term category. Given the times to events, there is no apparent temporal relationship between the event and vaccination. (Source: STN 125259/0, CSR HPV-013, Month 18 report, Table 22, p. 61-62, not shown here)

Pregnancy: A total of 11 pregnancies (4 in the HPV group and 7 in the HAV group) were reported during the Months 12-18 follow-up. Three subjects gave birth to healthy infants, whereas 8 pregnancies were ongoing at the time of this report. A total of 18 pregnancies (9 in each vaccine group) were reported during the entire follow-up period (Months 0-18). Six subjects (4 in the HPV group, 2 in the HAV group) gave birth to healthy babies, 1 subject in the HAV group had a premature baby, 2 subjects (1 subject in each vaccine group) underwent elective abortion; 8 pregnancies are ongoing (3 subjects in the HPV group, 5 subjects in the HAV group); and 1 pregnancy (HPV group) outcome was unknown at the time of reporting.

STUDY HPV-013: MONTH 24 REPORT

The dates for this study are as follows:

- Primary Study HPV-HPV-013 Initiation Date: 30 June 2004
- Date of First Visit (Visit 8, Month 24): 26 May 2006
- Date of Last Visit (Visit 8, Month 24): 15 February 2007
- Data Lock Point for Month 24 interim analysis: 19 September 2007

Number of subjects:

Completed Visit 8 (Month 24; EXT HPV-013 study): 1188 subjects (617 subjects in the HPV group and 571 subjects in the HAV group).

Safety:

Total vaccinated cohort (EXT HPV-013 study): 1188 subjects (617 subjects in the HPV group and 571 subjects in the HAV group).

Immunogenicity:

According-to-protocol (ATP) Cohort: 893 subjects (554 subjects in the HPV group and 339 subjects in the HAV group).

Criteria for evaluation for the interim analysis:

Primary endpoint: Anti-HPV-16/18 antibody titers in all subjects in the HPV vaccine group (ELISA).

Secondary endpoints:

- Anti-MPL antibody titers (ELISA).
- Occurrence of pregnancies, serious adverse events (SAEs), new onset chronic diseases (NOCDs), and medically significant adverse events (AEs) throughout the entire study period.

Statistical methods: An interim analysis was planned after each phase of the long-term follow-up: Month 18, Month 24, and Month 36. This final part includes results through Month 24.

Immunogenicity: The primary analysis of immunogenicity was based on the ATP cohort and was supplemented by a second analysis based on the Total Vaccinated cohort. The following antibodies were analyzed: anti- HPV-16, anti-HPV-18 and anti-MPL. All analyses were stratified according to serostatus at Day 0 in the primary HPV-HPV-013 study. A descriptive comparison with anti-HPV-16 and anti-HPV-18 serology antibody titers from study HPV-001 and from study HPV-007 was performed. In addition, a descriptive comparison with anti-HPV-16 and anti-HPV-18 antibody titers resulting from natural infection was performed.

Safety: The safety analysis was based on the Total Vaccinated Cohort, which included all vaccinated subjects (subjects from the immunological subset of HPV-HPV-013 who received three doses of vaccine in the primary HPV-HPV-013 study) for whom data were available. No formal comparisons were made between groups. SAEs, pregnancies, NOCD, and medically significant medical illnesses are presented. All analyses were performed for the extension period (Months 18 - 24) and for the complete study period (Months 0-24).

Results:

Subjects: A total of 1188 subjects (617 subjects in the HPV group and 571 subjects in the HAV group) comprised the Ext HPV-HPV-013 study Total Vaccinated cohort and were analyzed for safety. The ATP immunogenicity cohort included 893 subjects (554 subjects in the HPV group and 339 subjects in the HAV group).

Table 246-Study EXT HPV-013: Number of subjects enrolled into the study as well as the number excluded from the ATP analyses with reasons for exclusion (Month 0-Month 24)

	Total			HPV		HAV	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled cohort	2067						
Total vaccinated cohort active phase	2067			1035		1032	
Subject not enrolled in the extension study* (code 5000)	879	879		418	418	461	461
Total Vaccinated cohort (Ext HPV-013 study)	1188		100	617		571	
Administration of vaccine(s) forbidden in the protocol (code 1040)†	2	25		2	13	0	12
Randomization code broken at the investigator site (code 1060) †	0	1		0	0	0	1
Study vaccine dose not administered according to protocol (code 1070)	3	10		1	3	2	7
Protocol violation (inclusion/exclusion criteria) (code 2010)	0	1		0	1	0	0
Administration of any medication forbidden by the protocol (code 2040) †	6	9		3	3	3	6
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080) †	9	21		3	7	6	14
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090) †	17	21		10	12	7	9
Essential serological data missing (code 2100) †	16	22		5	9	11	13
Obvious incoherence or abnormality or error in data (code 2120) †	2	3		2	3	0	0
Subject not planned to be bled for their all blood sampling visits (code 2130) †	0	655		0	327	0	328
Protocol violation (inclusion/exclusion criteria) for extension Month 24 (code 5010)	129	136		33	34	96	102
Administration of any medication forbidden by the protocol for extension Month 24 (code 5040)	1	1		1	1	0	0
Non compliance with blood sampling schedule for extension Month 24 (code 5090)	3	3		2	2	1	1
Essential serological data missing for extension Month 24 (code 5100)	107	121		1	1	106	120
ATP Cohort for immunogenicity	893		75.2	554		339	

HPV = HPV-16/18; AS04; HAV = Hepatitis A vaccine group
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number in the annex phase
s = number of subjects with the elimination code assigned in the Total vaccinated cohort active phase
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
* Subjects who were not in the immunogenicity subset received the code 5000 (N=655). Subjects in Korea received the code 5000 (N=54): this site decides not to participate in the extension study. Subjects who could not be contacted or who refused to participate received a code 5000 (N=170)
† Codes assigned during the primary HPV-HPV-013 study
Source: STN 125259/30, CSR HPV-013, Month 24, Table 5, p. 42

Immunogenicity Results: Immunogenicity analyses were performed on the ATP cohort for immunogenicity (primary analysis) and on the Total Vaccinated cohort (Ext HPV-013 study) (secondary analysis). The results of the immunogenicity analyses of both cohorts were similar.

At Month 24, 99.8% of the subjects remained seropositive for anti-HPV-16 antibodies and all subjects (100%) remained seropositive for anti-HPV-18 antibodies. GMTs for HPV-16 and HPV-18 antibodies at Month 24 were 3226.3 EL.U/mL [95% CI: 2988.4 - 3483.1] and 1263.4 EL.U/mL [95% CI: 1165.1 - 1370.1], respectively. The antibody kinetics for both HPV-16 and HPV-18 antibodies were similar to data in other HPV studies (peak antibody levels at Month 7 followed by gradual decline of antibodies until Month 18). Similar to other studies, the decrease of the antibody levels between Month 18 and Month 24 is less pronounced than the decrease observed between previous time points.

Table 247-Study EXT HPV-013: Seropositivity rates and GMTs for HPV-16 VLP IgG antibodies by prevaccination status in the HPV group (ATP Cohort for immunogenicity)

			≥ 8 EL.U/mL				GMT				
					95% CI			95%			
Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
S-	PRE	519	0	0.0	0.0	0.7	4.0	4.0	4.0	<8.0	<8.0
	PII(M2)	519	516	99.4	98.3	99.9	4739.5	4384.0	5123.8	<8.0	49477.0
	PIII(M7)	519	519	100	99.3	100	19982.1	18600.3	21466.4	706.0	244471.0
	PIII(M12-M16)	438	436	99.5	98.4	99.9	4626.7	4182.7	5117.8	<8.0	162392.0
	PIII(M18)	518	518	100	99.3	100	3910.1	3612.7	4232.0	156.0	67894.0
	PIII(M24)	518	517	99.8	98.9	100	3198.0	2952.8	3463.6	<8.0	46999.0
S+	PRE	31	31	100	88.8	100	15.0	11.3	19.8	8.0	141.0
	PII(M2)	31	31	100	88.8	100	6355.7	4905.2	8235.2	1781.0	26626.0
	PIII(M7)	31	31	100	88.8	100	24563.7	19411.0	31084.4	6662.0	67566.0
	PIII(M12-M16)	26	26	100	86.8	100	5454.3	3954.2	7523.3	886.0	22603.0
	PIII(M18)	31	31	100	88.8	100	4315.7	3240.2	5748.3	605.0	15320.0
	PIII(M24)	31	31	100	88.8	100	3736.6	2883.8	4841.5	561.0	11861.0
Total	PRE	550	31	5.6	3.9	7.9	4.3	4.2	4.4	<8.0	141.0
	PII(M2)	550	547	99.5	98.4	99.9	4818.5	4470.1	5194.1	<8.0	49477.0
	PIII(M7)	550	550	100	99.3	100	20215.9	18870.3	21657.4	706.0	244471.0
	PIII(M12-M16)	464	462	99.6	98.5	99.9	4669.5	4238.9	5144.0	<8.0	162392.0
	PIII(M18)	549	549	100	99.3	100	3932.0	3643.5	4243.3	156.0	67894.0
	PIII(M24)	549	548	99.8	99.0	100	3226.3	2988.4	3483.1	<8.0	46999.0

HPV = HPV-16/18
S- = seronegative subjects (antibody titer < 8 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 8 EL.U/mL) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
PIII(M12-M16) = Post Dose III (Month 12- Month 16); PIII(M18) = Post Dose III (Month 18); PIII(M24) = Post Dose III (Month 24)
Source: STN 125259.30. CSR HPV-013, Month 24, Table 7, p. 45

Table 248-EXT Study HPV-013: Seropositivity rates and GMTs for HPV-18 VLP IgG antibodies by prevaccination status in the HPV group (ATP Cohort for immunogenicity)

			≥ 7 EL.U/mL				GMT				
					95% CI			95% CI			
Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
S-	PRE	526	0	0.0	0.0	0.7	3.5	3.5	3.5	<7.0	<7.0
	PII(M2)	526	524	99.6	98.6	100	3790.2	3515.0	4086.8	<7.0	47111.0
	PIII(M7)	526	526	100	99.3	100	8248.6	7658.6	8884.1	567.0	187560.0
	PIII(M12-M16)	445	444	99.8	98.8	100	1827.8	1657.5	2015.6	<7.0	53993.0
	PIII(M18)	525	525	100	99.3	100	1539.4	1414.4	1675.4	38.0	57489.0
	PIII(M24)	525	525	100	99.3	100	1251.3	1152.7	1358.3	38.0	34318.0
S+	PRE	23	23	100	85.2	100	19.7	14.2	27.2	7.0	89.0
	PII(M2)	23	23	100	85.2	100	4089.8	2872.8	5822.1	1124.0	14514.0
	PIII(M7)	23	23	100	85.2	100	11478.5	7321.5	17995.9	2244.0	200687.0
	PIII(M12-M16)	18	18	100	81.5	100	3519.9	1720.3	7202.1	362.0	104097.0
	PIII(M18)	23	23	100	85.2	100	2447.7	1387.5	4318.0	333.0	72237.0
	PIII(M24)	23	23	100	85.2	100	1575.1	958.8	2587.7	183.0	10257.0
Total	PRE	549	23	4.2	2.7	6.2	3.8	3.6	3.9	<7.0	89.0
	PII(M2)	549	547	99.6	98.7	100	3802.3	3532.8	4092.2	<7.0	47111.0
	PIII(M7)	549	549	100	99.3	100	8363.6	7771.5	9000.8	567.0	200687.0
	PIII(M12-M16)	463	462	99.8	98.8	100	1875.0	1700.0	2068.0	<7.0	104097.0
	PIII(M18)	548	548	100	99.3	100	1569.6	1442.6	1707.9	38.0	72237.0
	PIII(M24)	548	548	100	99.3	100	1263.4	1165.1	1370.1	38.0	34318.0

HPV = HPV-16/18 L1 VLP AS04
S- = seronegative subjects (antibody titer < 7 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 7 EL.U/mL) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7); PIII(M12-M16) = Post Dose III (Month 12- Month 16); PIII(M18) = Post Dose III (Month 18); PIII(M24) = Post Dose III (Month 24)
STN 125259/30, CSR HPV-013, Month 24, table 8, p. 46

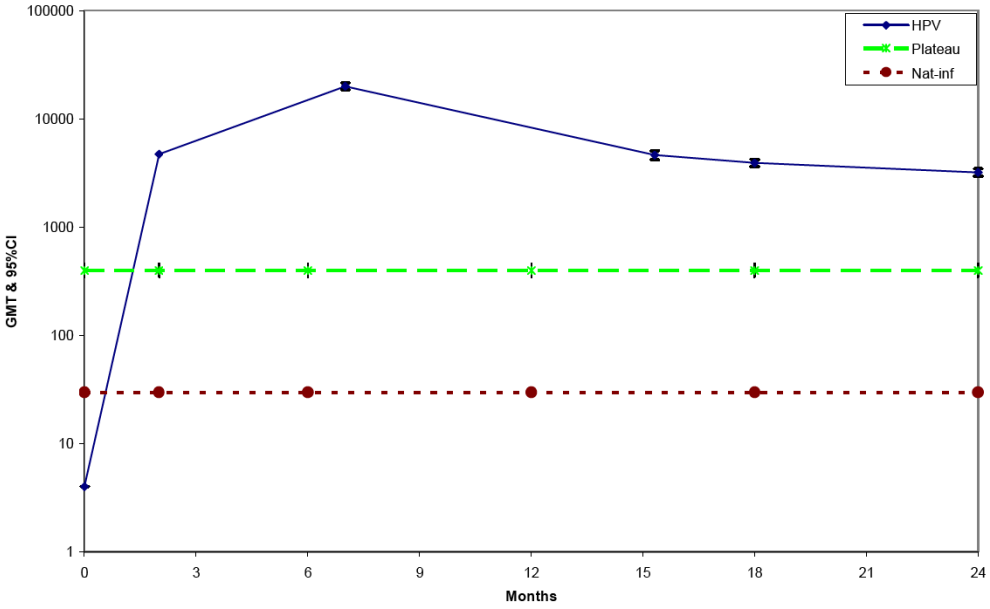
The reverse cumulative curves for HPV 16 and 18 IgG antibodies were presented, and the curves for Months 18 and 24 were approximately overlapping for both HPV 16 and HPV 18, although there was a slight decrease in levels from Month 18 to Month 24, and a more pronounced decrease from month 7 to Month 18. (Source: STN 125259/30, CSR HPV-013, Month 24, Supplements 6 and 7, p/ 92-93, not shown here).

At Month 24, anti-HPV-16 and anti-HPV-18 antibody titers in the HPV group in the HPV-013 EXT study were 107 and 55-fold higher, respectively, than those associated with natural infection in study HPV-008. In addition, HPV-16 and HPV-18 antibody titers were 8-fold and 4-fold higher, respectively, than the plateau level from study HPV-007. No correlate of protection has been identified, although GSK points out that no new cases of persistent infection or CIN2+ in the ATP cohort in study HPV-007 had been detected at the antibody levels measured at the same time (up to 5.5 years.)

Reviewer's Comment: These antibody levels are not immune correlates of protection, although it is possible that the immune correlate of protection may lie between the low point (at which natural infection has occurred) and the high point (the level of antibody at which no evidence of breakthrough cases occurred). GSK has presented reverse cumulative distribution curves which compare antibody levels for anti-HPV-16 and anti-HPV-18 which demonstrate that anti-HPV-16 and anti-HPV-18 antibody levels at Month 24 in EXT Study HPV-013 > Plateau level 5.5 years in HPV-007 > natural infection. (Source: STN 125259/30, CSR HPV-013, Month 24, Figure 1 and 2, p. 48 and 49, not shown here)

GSK also provided the kinetics for anti-HPV 16 and anti-HPV 18 antibodies in subjects 10-14 years of age out to Month 24 (Figures 30 and 31).

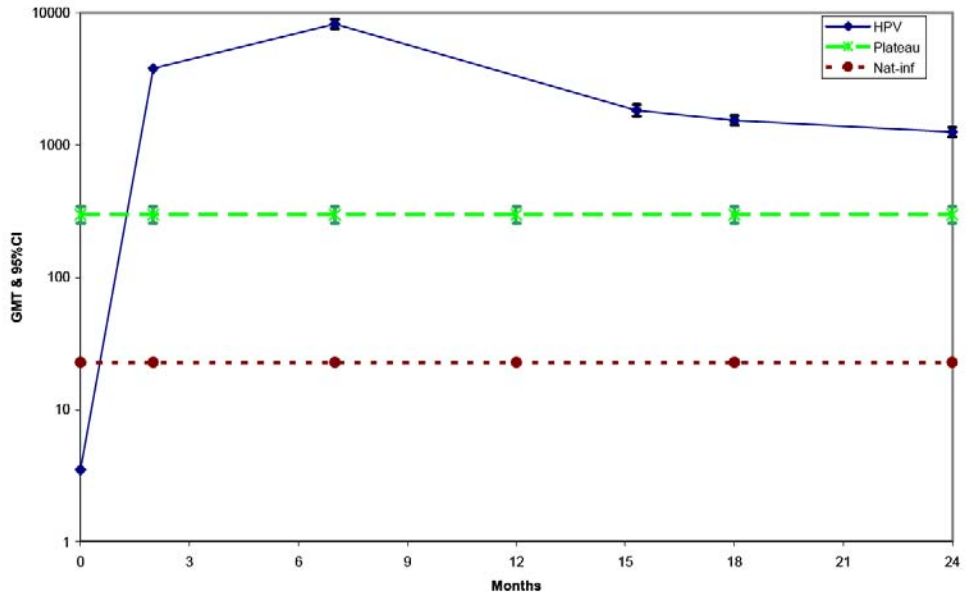
Figure 30-Study HPV-007, HPV-008, EXT HPV-013: Kinetic of anti-HPV-16 antibodies for subjects seronegative for HPV- 16 at pre-vaccination (HPV group; ATP cohort for immunogenicity)



Nat Inf = Subjects in study HPV-008 who were HPV DNA negative and seropositive at enrolment.
Plateau = Subjects in study HPV-007 at the Month 45 - Month 50 timepoint, i.e., during the plateau phase.

Source: STN 125259/30, CSR HPV-013, Month 24, Figure 3, p. 50

Figure 31-Study HPV-007, HPV-008, EXT HPV-013: Kinetic of anti-HPV-18 antibodies for subjects seronegative for HPV- 18 at pre-vaccination (HPV group; ATP cohort for immunogenicity)



Nat Inf = Subjects in study HPV-008 who were HPV DNA negative and seropositive at enrolment.
Plateau = Subjects in study HPV-007 at the Month 45 - Month 50 timepoint, i.e., during the plateau phase.

Source: STN 125259/30, CSR HPV-013, Month 24, Figure 4, p. 50

Anti-MPL antibodies: At study entry, most of the subjects in the HPV group and in the HAV group had detectable anti-MPL antibody titers above or equal to the limit of quantification of the ELISA assay -b(4)- EL.U/mL). Subjects in the HPV group with detectable anti-MPL antibody titers before vaccination, showed a 3.4-fold increase in GMT following the third dose of HPV-16/18 vaccine (Month 7 GMT=554.0 EL.U/mL) compared to pre-vaccination levels (GMT=162.1 EL.U/mL). By Month 18 the GMT had decreased and by Month 24 GMTs had reached 294.3 EL.U/mL, 1.8-fold higher than pre-vaccination levels. In the HAV group, there was no noticeable change in anti-MPL antibody titers at Months 7, 18 and 24 compared to the titers at study entry.

Reviewer's Comment: This study demonstrated that young girls in study HPV-013 had evidence of anti-MPL antibodies at baseline prior to vaccination with either the bivalent HPV vaccine or with Havrix. The anti-MPL levels increased in subjects who received Cervarix, but not in subjects who received Havrix. The implications of this finding are not clear. Reverse distribution curves for comparison of Month 18 and Month 24 results in the Cervarix group demonstrate overlapping curves, and those for the HAV group show lower, but also overlapping curves at the two time points.

Safety Results: The safety analysis was performed on the Total Vaccinated cohort (Ext HPV-013 study) for the follow-up period from Month 18 to 24 and on the Total Vaccinated cohort for the entire study period from Month 0 (Visit 1 of primary study HPV-013) to Month 24 (Visit 8 of Ext HPV-013 study).

Fatal events: There were no fatalities between Month 18 and Month 24 or at any time during the study.

Non-fatal SAEs: Overall, 13 subjects reported each one SAE during the follow-up period from Month 18 to 24. None of the events were considered related to vaccination by the investigator. Please see Tables 249 and 250 for times to event, duration, and outcome.

Table 249-Study HPV-013, Annex 4: Subjects with SAE (Month 18-24) [HPV group, N=617] (CBER generated)

Case number, age (years)	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome
151	Abdominal pain uncertain etiology (possible PID)	14 months after dose 3	7 days	Resolved
2775	Abdominal pain, umbilical hernia, chronic appendicitis	13 months after dose 3	~4 months	Resolved
2742	Constipation (stomach cramps x 6 months)	17 months after dose 3	5 days	Resolved
1754	Cellulitis (left foot)	12 months after dose 3	19 days	Resolved
2063	Skull fracture after bicycle accident (no intracranial bleeding)	17 months after dose 3	Not clear	Resolved
515	Uterine leiomyoma (D&C)	15 months after dose 3	6 days	Resolved
1369	Premature labor (delivered healthy baby at term)	14 months after dose 3	4 days	Resolved
2525	Attempted suicide	15 months after dose 3	1 day	Resolved

Table 250-Study HPV-013, Annex 4: Subjects with SAE (Month 18-24) [HAV group, N=571] (CBER generated)

Case number, age (years)	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome
1273	Ovarian cyst	6 months after dose 3	11 days	Resolved
1710	Dermoid cyst of ovary	16 months after dose 3	5 days	Resolved
713	Loss of consciousness (with epistaxis) Pneumonia	15 months after dose 3 16 months after dose 3	1 days 16 days	Resolved Resolved
3045	Splenic rupture due to horse riding accident	14 months after dose 3	6 days	Resolved

Reviewer's Comment: These events occurred many months after vaccination, and these subjects appeared to have other concurrent conditions which precipitated the event. None of these events were assessed as related to vaccination.

Adverse events leading to premature discontinuation of the study (Month 18 to Month 24): None of the subjects withdrew from the study due to AEs or SAEs during the follow-up period from Month 18 to Month 24.

Medically significant adverse events: In the time period from Month 18-Month 24, 40 (6.5%) subjects reported such an event in the HPV group and 21 (3.7%) reported such an event in the HAV group. No specific preferred term is noted which accounts this difference in this time period. Eczema was reported in 4 (0.6%) of subjects in the HPV group and 0 (0.0%) in the HAV group, but the time to these events are at least 12 months after the last dose of vaccine received, and relationship to vaccination appears less likely due to lack of temporal relationship. Overall (from Month 0- month 24) there were comparable proportions of such events. (Source: STN 125259, CSR 013, Month 24, Table 11, p. 55-56, not shown here) .

NOCD's: In the Month 18-24 time period, 5 (0.8%) NOCDs were reported in the HPV group, and 3(0.5%) in the HAV group.

Table 251: Study EXT HPV-013: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, between Month 18 and Month 24 (Total Vaccinated cohort)

		HPV N = 617				HAV N = 571			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one NOCD		5	0.8	0.3	1.9	3	0.5	0.1	1.5
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Immune system disorders (10021428)	Hypersensitivity (10020751)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Infections and infestations (10021881)	Arthritis bacterial (10053555)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Rhinitis allergic (10039085)	0	0.0	0.0	0.6	1	0.2	0.0	1.0
Skin and subcutaneous tissue disorders (10040785)	Dermatitis atopic (10012438)	0	0.0	0.0	0.6	1	0.2	0.0	1.0
	Henoch-schonlein purpura (10019617)	1	0.2	0.0	0.9	0	0.0	0.0	0.6
	Psoriasis (10037153)	1	0.2	0.0	0.9	1	0.2	0.0	1.0

HPV = HPV-16/18 L1 VLP AS04
HAV = Hepatitis A vaccine group
At least one NOCD = at least one NOCD experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOCD
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/30, CSR HPV-013, Month 24, Table 12, p. 58

Pregnancies: During the follow-up period from Month 18 to Month 24, a total of 9 pregnancies were reported, i.e., for eight subjects in the HPV group and one subject in the HAV group.

Table 252- EXT Study HPV-013: Outcome of pregnancies reported between Month 18 and Month 24 (Total Vaccinated cohort

Outcome	HPV	HAV
Healthy baby	4	1
Ongoing	3	0
Unknown	1	0
Total	**8**	**1**

Source: STN 125259/30, CSR HPV-013, Month 24

Month 0-24:
NOCD's: In the Total Vaccinated Cohort (N=1035 HPV recipients and 1032 HAV recipients), 42 subjects (4.1%) in the HPV group reported 50 NOCDs over the 24 months of the study and 35 subjects (3.4%) in the HAV group reported 36 NOCDs over this same time period. These are presented in Table 253 below.

Table 253- Study EXT HPV-013: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, reported during the entire follow-up period (Month 0 to Month 24) (Total Vaccinated cohort)

		HPV N = 1035				HAV N = 1032			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one NOCD		42	4.1	2.9	5.4	35	3.4	2.4	4.7
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	1	0.1	0.0	0.5	1	0.1	0.0	0.5
	Goiter (10018498)	3	0.3	0.1	0.8	1	0.1	0.0	0.5
	Hyperthyroidism (10020850)	0	0.0	0.0	0.4	2	0.2	0.0	0.7
	Hypothyroidism (10021114)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
Eye disorders (10015919)	Conjunctivitis allergic (10010744)	1	0.1	0.0	0.5	2	0.2	0.0	0.7
Immune system disorders (10021428)	Food allergy (10016946)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
	House dust allergy (10057631)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Hypersensitivity (10020751)	6	0.6	0.2	1.3	3	0.3	0.1	0.8
	Seasonal allergy (10048908)	0	0.0	0.0	0.4	3	0.3	0.1	0.8
Infections and infestations (10021881)	Arthritis bacterial (10053555)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	10	1.0	0.5	1.8	5	0.5	0.2	1.1
	Asthmatic crisis (10064823)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Rhinitis allergic (10039085)	10	1.0	0.5	1.8	6	0.6	0.2	1.3
Skin and subcutaneous tissue disorders (10040785)	Cutaneous lupus erythematosus (10056509)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Dermatitis allergic (10012434)	2	0.2	0.0	0.7	2	0.2	0.0	0.7
	Dermatitis atopic (10012438)	3	0.3	0.1	0.8	2	0.2	0.0	0.7
	Dermatitis contact (10012442)	2	0.2	0.0	0.7	0	0.0	0.0	0.4
	Henoch-schonlein purpura (10019617)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
	Psoriasis (10037153)	1	0.1	0.0	0.5	2	0.2	0.0	0.7
	Urticaria (10046735)	4	0.4	0.1	1.0	2	0.2	0.0	0.7
	Vitiligo (10047642)	1	0.1	0.0	0.5	0	0.0	0.0	0.4

HPV = HPV-16/18; HAV = Hepatitis A vaccine group
At least one NOCD = at least one NOCD experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOCD
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/30, CSR HPV-013, Table 20, p. 73

Deaths Month 0-24: There were no fatalities reported through Month 0-24.

SAEs Month 0-24: Over 24 months, 32 subjects (3.1%) in the HPV group reported 46 SAEs and 29 subjects (2.8%) in the HAV group reported 33 SAEs. These SAEs have been tabulated for all time periods through Month 24. The one event considered possibly related to vaccine was the subject with increased transaminases after HAV (also associated with a UTI). The most common SAEs reported throughout the entire study period were abdominal pain (HPV group: 6 subjects, 0.6%; HAV group: none), appendicitis (HPV group: 1 subject, 0.1%; HAV group: 5 subjects, 0.5%). (Source: STN 125259/30, CSR HPV-013, Month 24, Table 22, p. 77-79, not shown here)

Medically significant adverse events (Month 0 to Month 24): During the entire study period up to Month 24, the number of subjects reporting at least one medically significant event was similar in the HPV group (256 subjects, 24.7% reported 419 events) compared to the HAV group (270 subjects, 26.2% reported 386 such events). (Source: STN 125259/30, CSR HPV-013, Month 24, Table 17, p. 63, not shown here)

The most frequently reported medically significant AEs during the entire follow-up period were bronchitis, abdominal pain, influenza, headache, asthma and acne. Abdominal pain was more frequently reported in the HPV group (1.6%) than in the HAV group (0.6%), while the opposite was observed for influenza (0.8% vs. 1.6%). The incidences of bronchitis (1.8% vs. 1.5%), headache (0.9% vs. 1.1%), asthma (1.1% vs. 0.7%) and acne (0.7% vs. 1.1%) were similar in the HPV and HAV groups, respectively. The events which occurred at $\geq$ 0.5% in either group are presented in Table 254 below.

Table 254-Study HPV-013, Annex 3: Percentage of Subjects Reporting Medically Significant AEs ≥ 0.5% of Subjects in Either Treatment Group Classified by MedDRA Primary System Organ Class and Preferred Term, Month 0 to Month 24 follow-up period (Total Vaccinated Cohort)

Primary System Organ Class	Preferred Term	HPV N=1035	HAV N=1032
		n (%)	n (%)
At least one symptom		**214 (20.7%)**	**244 (23.6%)**
Eye Disorders	Conjunctivitis	**6 (0.6%)**	**3 (0.3%)**
Gastrointestinal disorders	Abdominal pain (includes upper and lower)	19 (1.8%)	10 (1.0%)
	Constipation	5 (0.5%)	2 (0.2%)
General and administration site disorders	Influenza like illness	5 (0.5%)	5 (0.5%)
Infections and Infestations	Bronchitis	21 (2.0%)	16 (1.8%)
	Ear infection	5 (0.5%)	2 (0.2%)
	Influemza	8 (0.8%)	17 (1.6%)
	Viral infection	8 (0.8%)	9 (0.9%)
Immune system disorders	Hypersensitivity	5 (0.5%)	0 (0.0%)
Injury, poisoning and procedural complications	Joint sprain	2 (0.2%)	5 (0.5%)
Musculoskeletal and connective system disorders	Arthralgia	5 (0.5%)	1 (0.1%)
Nervous system disorders	Headache	9 (0.9%)	11 (1.1%)
	Migraine	7 (0.7%)	4 (0.4%)
	Syncope and vasovagal syncope	6 (0.6%)	6 (0.6%)
Reproductive system and breast disorders	Ovarian cyst	5 (0.5%)	4 (0.4%)
Respiratory, thoracic and mediastinal disorders	Asthma	11 (1.1%)	7 (0.7%)
	Cough	8 (0.8%)	8 (0.8%)
	Pharyngolaryngeal pain	9 (0.9%)	5 (0.5%)
	Rhinitis allergic	10 (1.0%)	9 (0.9%)
Skin and subcutaneous tissue disorders	Acne	7 (0.7%)	11 (1.1%)
	Dermatitis	6 (0.6%)	1 (0.1%)
	Eczema	6 (0.6%)	4 (0.4%)
	Rash	3 (0.3%)	5 (0.5%)

HPV = HPV-16/18 L1 VLP AS04
HAV = Hepatitis A vaccine group
At least one medically significant AE = at least one medically significant AE experienced
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the medically significant AE
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/30, CSR HPV-013, Month 24, Table 18, p. 64-71

New onset of chronic diseases (Month 0 to Month 24): During the entire study period up to Month 24, a similar number of subjects reported NOCDs in the HPV (42 subjects, 4.1%, 49 events) and HAV (35 subjects, 3.4%, 36 events).

The most common NOCDs reported throughout the entire study period were asthma (HPV group: 10 subjects, 1.0%; HAV group: 5 subjects, 0.5%), allergic rhinitis (HPV group: 10 subjects, 1.0%; HAV group: 6 subjects, 0.6%), hypersensitivity (HPV group: 6 subjects, 0.6%; HAV group: 3 subjects, 0.3%) and urticaria (HPV group: 4 subjects, 0.4%; HAV group: 2 subjects, 0.2%).

Table 255- Study EXT HPV-013: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, reported during the entire follow-up period (Month 0 to Month 24) (Total Vaccinated cohort)

		HPV N = 1035				HAV N = 1032			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one NOCD		42	4.1	2.9	5.4	35	3.4	2.4	4.7
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	1	0.1	0.0	0.5	1	0.1	0.0	0.5
	Goiter (10018498)	3	0.3	0.1	0.8	1	0.1	0.0	0.5
	Hyperthyroidism (10020850)	0	0.0	0.0	0.4	2	0.2	0.0	0.7
	Hypothyroidism (10021114)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
Eye disorders (10015919)	Conjunctivitis allergic (10010744)	1	0.1	0.0	0.5	2	0.2	0.0	0.7
Immune system disorders (10021428)	Food allergy (10016946)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
	House dust allergy (10057631)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Hypersensitivity (10020751)	6	0.6	0.2	1.3	3	0.3	0.1	0.8
	Seasonal allergy (10048908)	0	0.0	0.0	0.4	3	0.3	0.1	0.8
Infections and infestations (10021881)	Arthritis bacterial (10053555)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	10	1.0	0.5	1.8	5	0.5	0.2	1.1
	Asthmatic crisis (10064823)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Rhinitis allergic (10039085)	10	1.0	0.5	1.8	6	0.6	0.2	1.3
Skin and subcutaneous tissue disorders (10040785)	Cutaneous lupus erythematosus (10056509)	0	0.0	0.0	0.4	1	0.1	0.0	0.5
	Dermatitis allergic (10012434)	2	0.2	0.0	0.7	2	0.2	0.0	0.7
	Dermatitis atopic (10012438)	3	0.3	0.1	0.8	2	0.2	0.0	0.7
	Dermatitis contact (10012442)	2	0.2	0.0	0.7	0	0.0	0.0	0.4
	Henoch-schonlein purpura (10019617)	1	0.1	0.0	0.5	0	0.0	0.0	0.4
	Psoriasis (10037153)	1	0.1	0.0	0.5	2	0.2	0.0	0.7
	Urticaria (10046735)	4	0.4	0.1	1.0	2	0.2	0.0	0.7
	Vitiligo (10047642)	1	0.1	0.0	0.5	0	0.0	0.0	0.4

HPV = HPV-16/18 L1 VLP AS04
HAV = Hepatitis A vaccine group
At least one NOCD = at least one NOCD experienced
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOCD
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/30, CSR HPV-013, Table 20. p. 73

Adverse events leading to premature discontinuation of the study (Month 0 to Month 24): No additional subjects discontinued due to AE except as previously reported.

Pregnancies (Month 0 to Month 24): During the entire study period from Month 0 to Month 24, a total of 16 pregnancies were reported, i.e., for 12 subjects in the HPV group and 4 subjects in the HAV group.

One subject in the HPV group reported premature labor as an SAE. The pregnancy case was considered as a follow-up of the initial pregnancy (as part of study Ext HPV-013 Month 18) but the SAE was reported within this study.

Table 256-Study EXT HPV-013: pregnancies reported between Month 0 and Month 24 (Total Vaccinated cohort)

Outcome	HPV	HAV
Healthy baby	9	4
Ongoing	2	0
Unknown	1	0
Total	**12**	**4**

Soure: STN 125259/30, CSR HPV-013, Month 24, Table 23, p. 80

CONCLUSIONS FOR STUDY HPV-013:

- As noted in females 15-25 years of age in study HPV-008, Cervarix elicited local adverse reactions in a higher proportion of subjects as compared to the comparator Havrix. In addition, there were higher proportions of subjects with solicited general adverse events (myalgia, arthralgia, and fatigue) in the 7 days after vaccination in Cervarix recipients as compared to Havrix recipients. However, the duration of the events was several days for both groups and the increased reactogenicity apparently did not lead to an increase in discontinuations due to these adverse events.
- Regarding unsolicited adverse events in the 30 days after vaccination, a higher proportion of subjects in the Havrix group developed appendicitis as compared to Cervarix recipients. These events were not considered related to vaccine administration by investigators. This finding was not replicated in studies in females 15-25 years of age.
- Regarding serious adverse events and new onset chronic illnesses, there was no apparent imbalance in incidences of these events in the two treatment groups.
- Cervarix was immunogenic in females 10-14 years through Month 24. When immune responses were observationally compared to females 15-25 years of age who participated in study HPV-001, the immune response was more robust in females 10-14 years of age as compared to females 15-25 years of age. See Study HPV-012 for formal comparisons of immune responses between the 10-14 year old subjects and the 15-25 year old subjects.

8.8 HPV-012 (Trial #8): A phase III, double-blind, randomized study to assess the consistency of the immunogenicity of three consecutive production lots of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects aged 10 – 25 years and to demonstrate non-inferiority of the candidate HPV vaccine manufactured using different production processes.

Study Dates: 9/4/04-7/15/05

Study Sites: 17 centers in 6 countries (Denmark, Estonia, Finland, Greece, The Netherlands and Russia).

STUDY OBJECTIVES

Primary Objectives

First primary objective: To demonstrate lot-to-lot consistency in terms of immunogenicity between three different industrial production lots b(4) L scale) of the HPV-16/18 L1/AS04 vaccine (i.e. -b(4)- production process). Consistency 1 month after the third dose was reached if, for all pairs of lots, the two-sided 90 % confidence intervals (CIs) of the geometric mean titer (GMT) ratio were within the [0.5, 2] clinical limit interval.

If consistency was demonstrated, the -b(4)-*lots were to be pooled and non-inferiority of the* -b(4)-*produced vaccine versus the* -b(4)- *-produced vaccine was to be evaluated as a second primary objective. (If consistency was not demonstrated, non-inferiority could not be tested.)*

Second primary objective: To demonstrate that the HPV vaccine produced with the -b(4)cell line process (industrial scale production) was non-inferior in terms of immunogenicity to the HPV vaccine produced with the -b(4)---- cell line process. Two criteria for non-inferiority were assessed sequentially (if the first one was not demonstrated, the second one could not be tested): (1) 1 month after the third dose, the difference between the percentage of subjects who seroconverted after administration of the -b(4)- -produced vaccine versus the pooled -b(4)-produced vaccine lots was below 10%; (2) 1 month after the third dose, GMT ratio between the -b(4)- -produced vaccine and pooled -b(4)- -produced vaccine lots was below 2.

Secondary Objectives

- To evaluate the safety and reactogenicity of all study vaccines after each dose.
- To demonstrate that the 10-14 years age group was non-inferior to the 15-25 years age group in terms of immunogenicity when receiving the same industrial production lot.

Two criteria for non-inferiority were assessed sequentially (if the first one was not demonstrated, the second one could not be tested): (1) 1 month after the third dose, the difference between the percentage of subjects who seroconverted in the older age group versus the younger age group was below 10%; (2) 1 month after the third dose of HPV vaccine, the GMT ratio between the older age group and younger age group was below 2.

- To demonstrate that the -b(4)- -produced HPV vaccine was non-inferior in terms of immunogenicity to the HPV vaccine used in study HPV-001 (i.e. previous -b(4)-manufacturing process).

Two criteria for non-inferiority were assessed sequentially (if the first one was not demonstrated, the second one could not be tested): (1) 1 month after the third dose, the difference between the percentage of subjects who seroconverted after administration of the vaccine lot used in study HPV-001 versus the pooled -b(4)- -produced vaccine lots was below 10%; (2) 1 month after the third dose, the GMT ratio between the -b(4)- -produced vaccine lot used in study HPV-001 and the pooled -b(4)- -produced vaccine lots was below 2.

Study design
This was a phase III, randomized, multi-country and multi-centre study with five parallel groups as follows:

- Three groups (150 subjects per group) of women aged 15-25 years received one of three consecutive production lots of the industrial scale HPV-16/18 L1/AS04 vaccine -b(4)-produced vaccine) [Groups Lot -----b(4)----------
- The fourth group (150 subjects) of women aged 15-25 years received the -b(4)- -produced HPV vaccine (Group -b(4)-).
- The fifth group (150 subjects) of pre-teen and adolescent women (aged 10-14 years) received the -b(4)- -produced HPV vaccine (Group [10-14]).

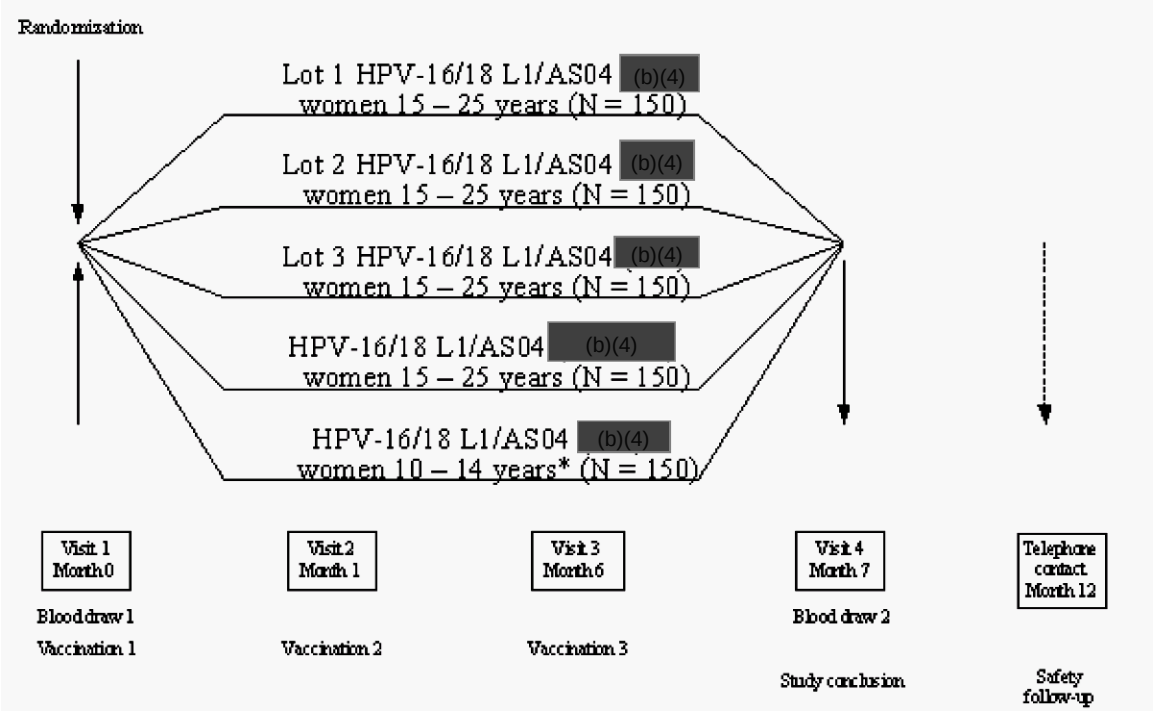
Overview of Visits

- Four visits were scheduled per subject at Months 0, 1, 6 and 7, as well as a telephone contact at Month 12.
- Three doses of vaccine were administered intramuscularly according to a 0, 1, 6-month schedule.
- Blood samples were collected at visits 1 and 4 (i.e. at Months 0 and 7) from all subjects to evaluate immunogenicity.
- Safety and reactogenicity monitoring was as follows:
  - Solicited signs and symptoms were self-reported in all subjects, using a diary card, on the day of vaccination and six follow-up days.
  - Unsolicited signs and symptoms were reported in all subjects within 30 days after each vaccination.
  - Serious adverse event (SAEs) were reported in all subjects throughout the study period (and up to the month 12 telephone contact).
  - New onset chronic diseases and other medically significant conditions were reported in all subjects throughout the study (and up to the Month 12 telephone contact) regardless of causal relationship to vaccination and intensity.

Randomization: Subjects (N = 750) were assigned to groups using an internet based randomization system.

Blinding: The study was double-blind for subjects of 15-25 years of age and single-blind for subjects of 10- 14 years of age. Neither subjects of 15-25 years of age nor study personnel were aware which production process was used for the preparation of the HPV-16/18 vaccine the subjects received. For subjects of 10- 14 years of age, the subjects were unaware of the production process used while the study personnel were aware of this information (i.e. -b(4)-produced vaccine) but were not aware of the lot used for this group.

Figure 32-Study HPV-012: Overview of Study HPV-012



Source: STN 125259/0, CSR 012, p.39

Duration: Including safety follow-up, the duration for each subject was 12 months with a telephone contact at Month 12.

Study Procedures: See Table 257 below.

Table 257-Study HPV-012: Outline of Study Procedures

Visit Timing Sampling time point	VISIT 1 MONTH 0 Pre-vacc	VISIT 2 MONTH 1 Post vacc I	VISIT 3 MONTH 6 Post vacc II	VISIT 4 MONTH 7 Post vacc III	TELEPHONE CONTACT† MONTH 12
Informed consent/assent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check elimination criteria		●	●	●	
Check contraindications		●	●		
Record any concomitant medication/vaccination	●	●	●	●	
Medical history	●				
History-directed physical examination	●				
Collect demographic data	●				
Urine sample for pre-vaccination pregnancy test	●	●	●		
Pre-vaccination body temperature	●	●	●		
Blood sampling: 5 ml for HPV-16/18 antibody titres	●			●	
Internet randomization	●				
Vaccination	●	●	●		
Distribution of diary cards for post-vaccination recording of solicited symptoms (Days 0 – 6) and unsolicited symptoms (Days 0 – 29)*	○	○	○		
Counselling	●	●	●	●	
Return of diary cards*		○	○	○	
Diary card transcription*		●	●	●	
Reporting of all pregnancies and pregnancy outcomes		●	●	●	●
Reporting of SAEs, new onset chronic diseases and other medically significant conditions	●	●	●	●	●
Safety follow-up contact					●
Study Conclusion				●	
Safety follow-up conclusion					●

● was used to indicate a study procedure that required documentation in the individual eCRF.
○ was used to indicate a study procedure that did not require documentation in the individual eCRF.
* All subjects / subjects parents/legally acceptable representatives received diary cards to record solicited adverse events within 7 days (Day 0 – 6) following vaccination and any unsolicited adverse events within 30 days (Day 0 – 29) following vaccination. Subjects were instructed to return the diary cards at the next study visit for transcription.
† The study was concluded, and final report written, after all subjects completed visit 4 (month 7) and all results are available. However, a safety follow-up telephone contact is planned for all subjects at month 12. The results of the safety follow-up will be reported in an annex report.
Source: STN 125259/0, CSR 012, Table 1, p.42

Study Population: This study was conducted in healthy females aged 10-25 years (Denmark, Estonia, Finland, Greece, the Netherlands and Russia).

Inclusion criteria:

- Healthy females 10 - 25 years of age written informed consent
- Written informed consent from subject or parent/guardian (and assent for minors)
- Have a negative urine pregnancy test and use appropriate contraception for 30 days prior to vaccination and for two months after completion of the vaccination series

- No more than six lifetime sexual partners prior to enrolment. (This criterion may not have been applicable in subjects less than 18 years of age, according to local regulatory requirements.

Exclusion criteria:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period
- Pregnant (or planning to become pregnant before Month 8) or breastfeeding
- Chronic administration (>than 14 days) of immune-modifying drugs within six months prior to the first vaccine dose, or planned administration during the study period
- Planned administration/administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after (i.e. days 0 – 29) the first dose of vaccine (specific instructions given for routinely administered vaccines)
- Previous administration of MPL or AS04 adjuvant
- Previous vaccination against HPV
- Medically diagnosed or suspected immunodeficient condition
- History of allergic disease, suspected allergy or reactions likely to be exacerbated by any component of the study vaccine
- Clinically significant neurologic, hepatic or renal functional abnormality (acute or chronic)
- Administration of immunoglobulins and/or any blood product within three months preceding the first dose of study vaccine or planned administration during the study period
- Acute disease at the time of enrolment until condition was resolved. All vaccines could have been administered to persons with a minor illness such as diarrhoea or mild upper respiratory infection with or without low-grade febrile illness, oral/axillary temperature <37.5°C (99.5°F).

Vaccine components are noted in Table 258 below. In this study, two different production processes of the HPV vaccine were evaluated, referred to as ----b(4)----------. This reflected the use of different cell culture systems during production. The --b(4)-- vaccine formulation used in study HPV-001 was identical to the --b(4)-- formulation used in the present study.

Table 258-Study HPV-012: Vaccine components

Vaccine	Formulation Each dose (0.5 ml) contains:	Lot no.	Group
Candidate HPV-16/18 vaccine (b)(4) production process)	20 μg HPV-16 L1 VLP 20 μg HPV-18 L1 VLP 50 μg MPL® 500 μg aluminium as $Al(OH)_3$	DHPVA004A	Lot 1
		DHPVA005A	Lot 2
		DHPVA006A	Lot 3
		DHPVA004A	[10-14]
HPV-16/18 vaccine (b)(4) production process)	20 μg HPV-16 L1 VLP 20 μg HPV-18 L1 VLP 50 μg MPL® 500 μg aluminium as $Al(OH)_3$	DHPV007A9	(b)(4)

Source: STN 125259/0, CSR 012, Table 3, p.48

Dosage and administration: The HPV-16/18 L1/AS04 vaccine was supplied as liquid in individual pre-filled syringes to be administered (0.5 ml) intramuscularly into the deltoid of the non-dominant arm according to a 0, 1, 6-month schedule.

Laboratory Assays: Blood was collected from all subjects at Visits 1 and 4.

Table 259-Study HPV-012: Laboratory Assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
Quantitative	anti-HPV-16	ELISA	In-house assay	EU/ml	8 EU/ml for anti-HPV-16	GSK Biologicals
	anti-HPV-18				7 EU/ml for anti-HPV-18	

Source: STN 125259/0, CSR 012, Table 5, p.51

Assessment of Safety Variables
Solicited Local Adverse Events: pain, redness and swelling at the injection site.
Solicited General Adverse Events: fever, headache, fatigue, gastrointestinal symptoms (including nausea, vomiting, diarrhea, and/or abdominal pain), arthralgia, myalgia, rash, and urticaria. Temperature was recorded in the evening.

Intensity of AEs were as described in study HPV-001.

SAEs and AEs related to new onset chronic diseases (NOCDs)and other medically significant conditions prompting emergency room visits or physician visits that were not related to common diseases were to be reported throughout the study period (through Month 7). Common medical conditions (as noted in Study HPV-013) did not require reporting after 30 days unless considered SAEs. Causality was to be assessed and outcomes reported.

Pregnancy: Subjects who became pregnant during the study were not to receive additional doses of study vaccine but could continue other study procedures at the discretion of the investigator. The investigator collected pregnancy information on any subject who became pregnant while participating in this study, and outcomes were to be reported.

Significant adverse events and new onset chronic diseases:
- **New onset chronic diseases (NOCD)** and other medically significant conditions prompting emergency room visits or physician visits that are not related to common diseases were reported throughout the study period regardless of causal relationship to vaccination and intensity.
- **Medically significant AEs** are defined as conditions prompting either emergency room (ER) visits that are not related to common diseases or physician visits (MD) that are not related to common diseases.

STATISTICAL CONSIDERATIONS
Primary endpoints
- Anti-HPV-16/18 seroconversion rates and antibody titers for the three consecutive lots of the industrial scale HPV-16/18 L1/AS04 vaccine (i.e. -b(4)-produced vaccine) assessed by ELISA at month 7.
- Anti-HPV-16/18 seroconversion rates and antibody titers for the -b(4)----produced HPV vaccine assessed by ELISA at month 7.

Secondary endpoints

- Anti-HPV-16/18 seroconversion rates and antibody titers in adult women aged 15-25 years and in pre-teen and adolescent women aged 10-14 years who received the same lot of the -b(4)-produced vaccine assessed by ELISA at month 7.
- Anti-HPV-16/18 seroconversion rates and antibody titers in adult women aged 15-25 years who received the -b(4)--produced vaccine in this study and in all subjects from the ATP immunogenicity cohort of the efficacy study 580299/001 (HPV-001) assessed by ELISA at month 7.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms, and occurrence and intensity of solicited local symptoms within 7 days (days 0 – 6) after each and any vaccination.
- Occurrence, intensity and causal relationship to vaccination of unsolicited symptoms within 30 days (days 0 – 29) after any vaccination.
- Occurrence and relationship to vaccination of SAEs throughout the study period (up to month 7).
- Occurrence of new onset chronic diseases and other medically significant conditions prompting emergency room visits or physician visits that were not related to common diseases throughout the study period (up to month 7) regardless of causal relationship to vaccination and intensity.
- Occurrence of SAEs, new onset chronic diseases and other medically significant conditions up to Month 12 (extended safety follow-up).

Determination of sample size

Primary objectives

A sample size of 480 evaluable subjects was needed (120 subjects aged 15-25 years for each consistency lot of the b(4)-produced vaccine and 120 subjects aged 15-25 years for the --b(4)--produced vaccine) to demonstrate both primary objectives of this study. Assuming 20% non-evaluable subjects (10% drop-out rate and 10% seropositive for both HPV-16 and -18), 600 subjects aged 15-25 years needed to be enrolled.

- 150 subjects per group were needed to conclude consistency between the three -b(4)-produced vaccine lots with at least 92% power,
- 150 subjects were needed for the -b(4)---produced vaccine group to rule out the null hypothesis that the -b(4)-produced vaccine was inferior to the --b(4)---produced vaccine with at least 98% power.

Secondary objectives: One hundred and fifty subjects aged 10 – 14 years were needed for the secondary objectives.

Study cohorts/data sets analyzed

Total Vaccinated cohort: The Total Vaccinated cohort included all vaccinated subjects for whom data were available.

- **Total analysis of safety** included all subjects with at least one vaccine administration documented.
- **Total analysis of immunogenicity** include vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

The Total Vaccinated cohort analysis was performed per treatment actually administered.

According-To-Protocol (ATP) cohort for analysis of safety

- **ATP cohort for analysis of safety** included all subjects: who had received at least one dose of study vaccine according to their random assignment; with sufficient data to perform an

analysis of safety (at least one dose with safety follow-up); for whom administration site of study vaccine was known; who had not received a vaccine not specified or forbidden in the protocol; for whom the randomization code had not been broken.

According-To-Protocol (ATP) cohort for analysis of immunogenicity

- **ATP cohort for analysis of immunogenicity** included all evaluable subjects (those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study and who were not seropositive for both HPV antigens) for whom data concerning immunogenicity endpoint measures were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

For the endpoints linked to study HPV-001, sera from HPV-001 subjects in the ATP cohort for analysis of immunogenicity was used. The ATP immunogenicity cohort (N = 362) included subjects who: received all vaccine doses in HPV-001, had at least the month 0 and month 7 post-vaccination blood samples analyzed, were seronegative for HPV-016 and HPV-018 at month 0, did not develop an HPV-16 or HPV-18 infection endpoint prior to month 7, and met the required eligibility criteria.

Analysis of immunogenicity: The primary analysis was based on the ATP cohort for analysis of immunogenicity. A second analysis based on the Total Vaccinated cohort was performed to complement the ATP analysis. The analysis of immunogenicity was performed on initially seronegative subjects only (subjects seropositive for one antigen were eliminated for the analysis of that antigen but were still evaluable for the analysis of the other antigen).

Analysis of safety: The analysis of safety was performed on the total vaccinated cohort (primary analysis) and on the ATP cohort (secondary analysis) in all groups. All analyses on solicited local and general symptoms were also presented by baseline serostatus. No formal comparisons were made between groups. Unsolicited AEs, SAEs, NOCDs, medically significant AEs, and pregnancy outcomes were reported.

Interim analysis: No interim analysis was conducted.

Changes in the conduct of the study or planned analyses

Protocol amendments/modifications: There was one amendment to the study protocol (1/19/05). The changes were as follows:

- Reference to a recent article on data from HPV-001 study (published at that time), was added.
- Clarification on the period for collection of information on concomitant medication, which started 30 days before and ended 30 days after each dose of study vaccine, was provided.
- Indication that information on administration of oral contraceptives was to be recorded.
- The purpose of the safety follow-up by telephone contact after visit 4 was specified, i.e. reporting of SAEs, new onset chronic diseases and other medically significant conditions and pregnancies.

Other Changes

Changes to planned analysis

- The analyses of the solicited symptoms were performed using documented doses (doses for which information on the solicited local/general symptom sheet is available).
- The duration of solicited symptoms is presented.

- All analyses on solicited local and general symptoms were done on subjects by baseline serostatus
- The analysis to demonstrate the non-inferiority of the -b(4)- produced HPV-16/18 compared with the HPV vaccine used in the HPV-001 study was performed on all subjects in the ATP immunogenicity cohort from the HPV-001 study rather than a pre-specified subset of subjects randomly selected from the HPV-001 study.

Description of an error in the attribution of treatment to subjects during the trial:
An error in the attribution of treatment to subjects was discovered during the trial due to a programming problem in -b(4)- (web-based application used for treatment allocation to study subjects) resulting in an error with respect to randomization of some subjects (231/767 or 30.1%). In this study, the primary endpoint focused on the immunological response. To evaluate the impact of these randomization deviations on the validity of the results, additional immunological analyses were performed and assessed the global effect of a variable randomized (1=appropriate; 2= non-appropriate). The analyses demonstrated that there was no statistically significant effect on the validity of the immunogenicity results.

RESULTS
Study dates: 9/5/00 to 7/15/05.

STUDY POPULATION RESULTS
Number of subjects: A total of 773 healthy subjects were enrolled in the study to receive three doses of HPV vaccine. All except three subjects received at least one vaccine dose. For the three subjects who were enrolled but not vaccinated reasons for not vaccinating were: inability to obtain a month-0 blood; renal failure; and latex allergy.

Of the 770 subjects who were vaccinated, 200 were from Denmark, 101 were from Estonia, 100 were from Finland, 99 were from Greece, 150 were from The Netherlands, and 120 were from Russia.

Study completion and withdrawal from study: Of the 770 subjects vaccinated in this study, 742 completed the month 7 study visit. Twenty-eight subjects dropped out of the study. The reasons are presented in Table 260 below.

Table 260-Study HPV-012: Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Vaccinated Cohort)

	Group					
	Lot 1	Lot 2	Lot 3	(b)(4)	[10-14]	Total
Number of subjects vaccinated	156	156	146	154	158	770
Number of subjects completed	148	149	145	147	153	742
Number of subjects withdrawn	8	7	1	7	5	28
Reasons for withdrawal :						
Serious Adverse Event	0	0	0	0	0	0
Non-serious adverse event	1	2	0	1	1	5
Protocol violation	0	0	0	0	0	0
Consent withdrawal (not due to an adverse event)	4	1	1	4	3	13
Migrated/moved from study area	1	2	0	0	0	3
Lost to follow-up (subjects with incomplete vaccination course)	0	1	0	1	1	3
Lost to follow-up (subjects with complete vaccination course)	0	0	0	0	0	0
Others	2	1	0	1	0	4

Lot 1 = DHPVA004A (-b(4)-) (15≤Age≤25); Lot 2 = DHPVA005A (-b(4)-) (15≤Age≤25);
Lot 3 = DHPVA006A (-b(4)-) (15≤Age≤25); Hi5/SF9 = DHPV007A9 (--b(4)--) (15≤Age≤25)
[10-14] = DHPVA004A (-b(4)-) (10≤Age≤14)
Vaccinated = number of subjects who were vaccinated in the study; Completed = number of subjects who completed last study visit; Withdrawn = number of subjects who did not come for the last visit
Source: STN 125259/0, CSR 012, Table 18, p.70

Five subjects were withdrawn after experiencing non-serious AEs. These are provided in review in safety results section. Additionally, the four subjects in which the reason for withdrawal is categorized as "other" in Table 260 and were withdrawn because of pregnancies that were not reported as AEs or SAEs.

An additional 19 subjects did not complete the study due to non-clinical reasons.

- 13 were reported as consent withdrawal (not due to an adverse event) (distribution similar among the groups)
- 3 subjects moved from the study area
- 3 subjects were lost to follow-up.

Protocol deviations leading to exclusion of subjects from an analysis: The number of subjects enrolled and eligible for the analyses and the reasons for elimination are presented in Table 261 below.

Table 261-Study HPV-012: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

	Total			Lot 1		Lot 2		Lot 3		Pooled		(b)(4)		[10-14]	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**	**n**	**s**	**n**	**s**	**n**	**s**
Total enrolled cohort	773														
Study vaccine dose not administrated but subject number allocated (code 1030)	3	3*													
Total vaccinated cohort	**770**		**100**	**156**		**156**		**146**		**458**		**154**		**158**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	11	11		3	3	3	3	0	0	6	6	3	3	2	2
Study vaccine dose not administered according to protocol (code 1070)	2	2		1	1	0	0	1	1	2	2	0	0	0	0
ATP safety cohort	**757**		**98.3**	**152**		**153**		**145**		**450**		**151**		**156**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	0	2†		0	0	0	0	0	0	0	0	0	0	0	0
Initially seropositive or initially unknown antibody status (code 2020)	42	47$		14	15	8	9	6	6	28	30	12	12	2	2
Administration of any medication forbidden by the protocol (code 2040)	1	1		0	0	0	0	0	0	0	0	1	1	0	0
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	5	5		2	2	0	0	1	1	3	3	2	2	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	2	3		0	1	0	0	2	2	2	3	0	0	0	0
Essential serological data missing (code 2100)	25	31$		6	8	7	7	1	1	14	16	7	7	4	5
ATP cohort for immunogenicity	**682**		**88.6**	**130**		**138**		**135**		**403**		**129**		**150**	

Lot 1 = DHPVA004A (-b(4)-) (15≤Age≤25) Lot 2 = DHPVA005A (-b(4)-) (15≤Age≤25)
Lot 3 = DHPVA006A (-b(4)-) (15≤Age≤25) Pooled = Pooled lots (-b(4)-) (15≤Age≤25)
(b)(4) = DHPV007A9 (--b(4)--) (15≤Age≤25) [10-14] = DHPVA004A (-b(4)-) (10≤Age≤14)
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
* Subject nos. 01511, 01576 and 01580 (code 1030): these subjects were not vaccinated
† Subject nos. 01576 and 01580 (code 2010): these subjects had protocol violations
$ Includes subject nos. 01511, 01576 and 01580 (codes 2020 and 2100): no blood sample was taken from these subjects;
Source: STN 125259/0, CSR 012, Table 19, p.72

From the 773 subjects enrolled, 770 subjects were vaccinated, and comprised the total vaccinated cohort. 682 subjects were included in the ATP cohort for immunogenicity.

Demographic characteristics

ATP immunogenicity cohort: Demographic characteristics for the ATP cohort for immunogenicity are summarized in Table 262. The demographic profile of the four groups aged 15-25 years was comparable with respect to mean age and racial distribution. The fifth group of subjects aged 10-14 years had a similar racial distribution but a mean age of 12.4 years. The study population was predominantly white (96.5%).

Table 262-Study HPV-012: Summary of demographic characteristics (ATP cohort for immunogenicity)

		Lot 1 N=130	Lot 2 N=138	Lot 3 N=135	Pooled N=403	(b)(4)	10-14 N=150	Total N=682
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	20.2	20.3	19.9	20.1	20.1	12.4	18.4
	SD	2.9	3.0	3.1	3.0	3.0	1.4	4.2
	Median	21.0	21.0	20.0	20.0	21.0	13.0	19.0
	Min-Max	15-25	15-25	15-25	15-25	15-25	10-14	10-25
Race	Black	1 (0.8%)	0 (0.0%)	3 (2.2%)	4 (1.0%)	1 (0.8%)	2 (1.3%)	7 (1.0%)
	White/Caucasian	127 (97.7%)	135 (97.8%)	129 (95.6%)	391 (97.0%)	125 (96.9%)	142 (94.7%)	658 (96.5%)
	Arabic/North African	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	5 (3.3%)	6 (0.9%)
	East/South East Asia	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.2%)	1 (0.8%)	0 (0.0%)	2 (0.3%)
	Other	2 (1.5%)	1 (0.7%)	3 (2.2%)	6 (1.5%)	2 (1.6%)	1 (0.7%)	9 (1.3%)

Lot 1 = DHPVA004A (-b(4)-) (15≤Age≤25); Lot 2 = DHPVA005A (-b(4)-) (15≤Age≤25); Lot 3 = DHPVA006A (-b(4)-) 15≤Age≤25)
Pooled = Pooled lots (-b(4)-) (15≤Age≤25); -b(4) = DHPV007A9 (-b(4)-) (15≤Age≤25); [10-14] = DHPVA004A (-b(4)-) (10≤Age≤14)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = standard deviation
Source: STN 125259/0, CSR 012, Table 20, p.75

Reviewer's Note: The demographics are presented for the Total Vaccinated Cohort and they are similar to those in the ATP cohort for immunogenicity. (Source: STN 125259/0, CSR 012, Supplement 3, p. 116, not shown here)

IMMUNOGENICITY RESULTS: Analysis of immunogenicity was performed on the ATP cohort (primary analysis) and on the total vaccinated cohort for seronegative subjects only (subjects seropositive for one antigen were eliminated for the analysis of that antigen but were still evaluable for the analysis of the other antigen).

An error in the attribution of treatment to subjects did not result in a statistically significant effect on the validity of the immunogenicity results.

According-To-Protocol analysis: The ATP cohort for immunogenicity analysis consisted of 682 subjects (130 subjects in the Lot 1 (-b(4)-) group, 138 subjects in the Lot 2 (b(4)) group, 135 subjects in the Lot 3 (b(4)) group, 129 subjects in the -b(4)- group, and 150 subjects in the [10-14] group).

First primary objective: lot-to-lot consistency of b(4)-produced lots: The ratios of post-vaccination anti-HPV 16/18 GMTs at Month 7 between the b(4)- produced vaccine lot groups [Lots 1 -----b(4)----------] are presented in Table 263 below.

Table 263-Study HPV-012: Ratios of post-vaccination anti-HPV16 and anti-HPV18 GMT at Month 7 between the three b(4)-produced vaccine lots with their 90% CIs (ATP cohort for immunogenicity). Calculation performed on subjects seronegative prior to Dose 1 to the respective antigen

							GMT ratio			
									90% CI	
Antibody	Group description	N	GMT	Group description	N	GMT	Ratio order	Value	LL	UL
HPV 16 IgG	Lot 1	118	7438.9	Lot 2	122	7150.3	Lot 1 /Lot 2	1.04	0.85	1.27
	Lot 1	118	7438.9	Lot 3	119	7297.2	Lot 1 /Lot 3	1.02	0.84	1.24
	Lot 2	122	7150.3	Lot 3	119	7297.2	Lot 2 /Lot 3	0.98	0.80	1.19
HPV 18 IgG	Lot 1	116	3070.1	Lot 2	126	3173.4	Lot 1 /Lot 2	0.97	0.80	1.17
	Lot 1	116	3070.1	Lot 3	122	3743.3	Lot 1 /Lot 3	0.82	0.68	1.00
	Lot 2	126	3173.4	Lot 3	122	3743.3	Lot 2 /Lot 3	0.85	0.70	1.02

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25); Lot 2 = DHPVA005A (b(4)) (15≤Age≤25); Lot 3 = DHPVA006A (b(4)) (15≤Age≤25)
GMT = geometric mean antibody titer, expressed in EU/ml
N = Number of subjects with available results
90% CI = 90% asymptotic confidence interval for the GMT ratio (ANOVA model - pooled variance with more than 2 groups)
Source: STN 125259/0, CSR 012, Table 21, p.77

The 2-sided 90% CIs of the GMT ratio of anti-HPV 16 and anti-HPV 18 antibodies between each pair among the -b(4)- produced vaccine at month 7 were within the pre-defined clinical limits of [0.5, 2.0]. The conclusion was that the 3 lots were consistent for the antigens. Results were similar for the Total Vaccinated Cohort.

Second primary objective: non-inferiority assessment between groups -b(4)- and pooled vaccine lots: The differences in seroconversion rates at Month 7 between subjects who received the -b(4)--produced vaccine versus subjects who received the -b(4)--produced vaccine are presented in Table 264.

Table 264-Study HPV-012: Non-inferiority assessment between groups -b(4)- and the -b(4)- vaccine lots for anti- HPV 16 IgG and anti-HPV 18 IgG at Month 7 (ATP cohort for immunogenicity). Calculation performed on subjects seronegative prior to Dose 1 to the respective antigen

Antibody	Group				Difference in seroconversion rate (b(4) Pooled)		
	(b(4)		Pooled		%	95 % CI	
	N	%	N	%		LL	UL
HPV-16 IgG	111	100	359	100	0.00	-3.35	1.06
HPV-18 IgG	117	100	364	100	0.00	-3.18	1.04

Pooled = Pooled lots (-b(4)-) (15≤Age≤25); --b(4)-- = DHPV007A9 (-b(4)--) (15≤Age≤25)
N = number of subjects with available results
% = percentage of subjects with HPV 16 IgG titer ≥8 EU/ML / HPV 18 IgG titer ≥7 EU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 012, Table 22, p.77

For both HPV-16 and HPV-18, the upper limits of the CIs were less than the pre-specified limit of 10%, and the pooled b(4)-produced vaccine lots were concluded to be non-inferior compared to the --b(4)---produced vaccine in terms of seroconversion rates. The results were similar for the Total Vaccinated Cohort

The ratios of the anti-HPV-16/18 GMTs at Month 7 between the -b(4)-----produced vaccine versus the pooled b(4)-produced vaccine lots are presented in Table 265.

Table 265-Study HPV-012: Ratios of post-vaccination anti-HPV16 and anti-HPV18 GMT at Month7 between the pooled vaccine lots and -b(4)- with their 95% CIs ATP cohort for immunogenicity). Calculation performed on subjects seronegative prior to Dose 1 to the respective antigen

Antibody	Group				GMT ratio (b)(4) / Pooled)		
	(b)(4)		Pooled		Value	95% CI	
	N	GMT	N	GMT		LL	UL
HPV 16 IgG	111	9595.5	359	7292.9	1.32	1.08	1.61
HPV 18 IgG	117	4164.7	364	3318.8	1.25	1.04	1.51

Pooled = Pooled lots (b(4)) (15≤Age≤25); b(4) = DHPV007A9 (b(4)) (15≤Age≤25)
GMT = geometric mean antibody titer, expressed in EU/ml
N = Number of subjects with available results
95% CI = 95% asymptotic confidence interval for the GMT ratio (ANOVA model); LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 012, Table 23, p.78

For both HPV-16 and HPV-18, the upper limits of the 95% CIs were less than the pre-specified limit of 2 and the pooled -b(4)-produced vaccine lots were concluded to be non-inferior compared to the -b(4)--produced vaccine in terms of GMT ratios. These results are similar to the Total Vaccinated Cohort.

Secondary objective: non-inferiority assessment between the 10-14 years age group and the 15-25 years age group: The differences in seroconversion rates between the percentages of subjects who seroconverted at Month 7 in the older age group (15-25 years; Lot 1, b(4) versus the younger age group (10-14 years; -b(4)-) are presented in Table 266.

Table 266-Study HPV-012: Non-inferiority assessment between 10-14 year olds (group [10-14]) and 15-25 year olds (Lot-b(4)-) for anti-HPV 16 IgG and anti-HPV 18 IgG seroconversion rates at Month 7 (ATP cohort for immunogenicity). Calculation performed on subjects seronegative prior to Dose 1 to the respective antigen

Antibody	Group				Difference in seroconversion rate Lot 1 - [10-14]		
	Lot 1		[10-14]		%	95 % CI	
	N	%	N	%		LL	UL
HPV-16 IgG	118	100	143	100	0.00	-3.15	2.62
HPV-18 IgG	116	100	141	100	0.00	-3.21	2.65

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25); [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
N = number of subjects with available results
% = percentage of subjects with HPV 16 IgG titer ≥8 EU/ML / HPV 18 IgG ≥7 EU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 012, Table 24, p.79

For both HPV-16 and HPV-18, the upper limits of the 95% CIs were shown to be less than the pre-specified limit of 10% and the 10-14 years age group was shown to be non-inferior compared to the 15-25 years age group in terms of seroconversion rates.

The ratios of the anti-HPV-16/18 GMTs at Month 7 between 15-25 year olds and 10-14 year olds for the Lot 1 (b(4)) vaccine lot are presented in Table 267. For both HPV-16 and HPV-18, the upper limits of the 95% CIs were shown to be less than the pre-specified limit of 2. The 10-14 years age group was concluded to be noninferior compared to the 15-25 years age group in terms of GMT ratios.

Table 267-Study HPV-012: Ratios of post-vaccination anti-HPV16 and anti-HPV18 GMT at Month 7 between 10-14 year olds (group [10-14]) and 15-25 year olds [Lot 1 (-b(4)-)] with their 95% CIs (ATP cohort for immunogenicity).
Calculation performed on subjects seronegative prior to Dose 1 to the respective antigen

Anti body	Group				GMT ratio (Lot 1 / [10-14])		
	Lot 1		[10-14]		Value	95% CI	
	N	GMT	N	GMT		LL	UL
HPV 16 IgG	118	7438.9	143	17272.5	0.43	0.35	0.53
HPV 18 IgG	116	3070.1	141	6863.8	0.45	0.36	0.55

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25); [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
GMT = geometric mean antibody titer, expressed in EU/ml
N = Number of subjects with pre-vaccination results available
95% CI = 95% asymptotic confidence interval for the GMT ratio (ANOVA model); LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 012, Table 25, p.79

Secondary objective: non-inferiority assessment between b(4) produced vaccine and HPV vaccine used in study HPV-001 (--b(4)--)
The differences in seroconversion rates between the percentages of subjects who seroconverted at Month 7 in study HPV-001 (----------b(4)-- process) versus the pooled -b(4)-produced vaccine lots in the present study are shown in Table 268.

Table 268-Study HPV-012: Non-inferiority assessment between --b(4)------- lots and HPV-001 groups for anti-HPV 16 IgG and anti-HPV 18 IgG seroconversion rates at Month 7 (ATP cohort for immunogenicity).
Calculation performed on subjects seronegative prior to Dose 1

Antibody	Group				Difference in seroconversion rate (HPV-001 - Pooled)		
	HPV-001		Pooled		%	95 % CI	
	N	%	N	%		LL	UL
HPV-16 IgG	339	100	359	100	0.00	-1.12	1.06
HPV-18 IgG	325	100	364	100	0.00	-1.17	1.04

Pooled = Pooled lots (b(4)) (15≤Age≤25); HPV-001 = HPV-001 study (ATP immunogenicity cohort), DVLP017A (-b(4)-) (15≤Age≤25)
N = number of subjects with available results
% = percentage of subjects with HPV 16 IgG titer ≥8 EU/ML / HPV 18 IgG ≥7 EU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 012, Table 26, p.80

For both HPV-16 and HPV-18, the upper limits of the 95% CIs were less than the pre-specified limit of 10%. The immunogenicity of the pooled -b(4)--produced vaccine was shown to be non-inferior in terms of seroconversion rates compared to the HPV vaccine used in study HPV-001 (----b(4)--- process).

The ratios of the anti-HPV-16/18 GMTs at Month 7 between the HPV vaccine used in study HPV-001 and the pooled -b(4)--produced vaccine lots in the present study are presented in Table 269.

Table 269-Study HPV-012: Ratios of post-vaccination anti-HPV16 and anti-HPV18 GMT at Month 7 between the pooled vaccine lots and HPV-001 with their 95% CIs (ATP cohort for immunogenicity). Calculation performed on subjects seronegative prior to Dose 1

Antibody	Group				GMT ratio (HPV-001 / Pooled)		
	HPV-001		Pooled		Value	95% CI	
	N	GMT	N	GMT		LL	UL
HPV 16 IgG	339	4415.9	359	7292.9	0.61	0.53	0.70
HPV 18 IgG	325	3471.8	364	3318.8	1.05	0.92	1.19

Pooled = Pooled lots (b(4)) (15≤Age≤25); HPV-001 = HPV-001 study (ATP immunogenicity cohort), DVLP017A (-b(4)-) (15≤Age≤25)
GMT = geometric mean antibody titer
N = Number of subjects with pre-vaccination results available
95% CI = 95% asymptotic confidence interval for the GMT ratio (ANOVA model); LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 012, Table 27, p.80

For both HPV-16 and HPV-18, the upper limits of the 95% CIs were less than the predefined clinical limit of 2. The immunogenicity of the pooled b(4)-produced vaccine was concluded to be non-inferior in terms of GMT ratios compared to the HPV vaccine used in study HPV-001 (--b(4)----process).

Reviewer's Comment: Tables which include demographics and immunogenicity from study HPV-001 as the compare to study 012 are also presented. The demographic characteristics for subjects in HPV-001 are somewhat different in that there is a slightly lower proportion of subjects who are White Caucasian and slightly higher proportion of subjects classified as Oriental (although the differences are relatively small, and the majority of subjects in both trials were white/Caucasian).

Table 270-Demographic characteristics for subjects in study HPV-001

		HPV-001 N-362	Subjects in studiesHPV-012 and HPV-001 N=1447
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)
Age (years)	Mean	20.2	19.3
	SD	2.9	3.7
	Median	20.0	20.0
	Min-Max	15-26	10.0-26.0
Race	Black	30 (8.3%)	41 (2.8%)
	White/Caucasian	242 (66.9%)	1291 (89.2%)
	Oriental	9 (2.5%)	9 (0.6%)
	Arabic/North African	0 (0.0%)	7 (0.5%)
	East/South East Asia	0 (0.0%)	3 (0.2%)
	Other	81 (22.4%)	96 (6.6%)

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25); Lot 2 = DHPVA005A (b(4)) (15≤Age≤25)
Lot 3 = DHPVA006A (b(4)) (15≤Age≤25); Pooled = Pooled lots (b(4)) (15≤Age≤25)
--b(4)- = DHPV007A9 (-b(4)-) (15≤Age≤25); [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
HPV-001 = HPV-001 study (ATP immunogenicity cohort), DVLP017A (b(4)--) (15≤Age≤25)
N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
Source: STN 125259/0, CSR 012, Supplement 24, p.134

The sponsor also presented the seroconversion status for subjects in studies HPV-012 and HPV-001. These appear similar, and the majority of subjects in both studies were seronegative for both HPV 16 IgG and HPV 18 IgG. See Table 271 below.

Comparisons of seroconversion rates and GMTs are also presented for subjects in each study for each anti-HPV 16 IgG and anti-HPV 18 IgG. These appear to be comparable in each of the studies.

Table 271-Study HPV-012: Seroconversion rates and GMTs for HPV 16 IgG antibodies (ATP cohort for immunogenicity)

				≥ 8 EU/mL		GMT		Min	Max
Antibody	Group	Timing	N	n(%)	95% CI	Value	95% CI		
HPV 16 IgG	HPV-001	PIII(M7)	339	339 (100%)	98.9,100%	4415.9	3976.7, 4903.6	65.0	110768.0
HPV 16 IgG	Pooled	PIII (M7)	368	368 (100%)	99.0, 100%	7380.8	6712.0, 8116.3	669.0	141583.0

Pooled = Pooled lots (b(4)) (15≤Age≤25); HPV-001 = HPV-001 study (ATP immunogenicity cohort), DVLP017A (-b(4)-) (15<=Age<=25)
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR 012, Supplement 26, p.136

Table 272-Study HPV-012: Seroconversion rates and GMTs for HPV 18 IgG antibodies (ATP cohort for immunogenicity)

				≥ 7 EU/mL		GMT		Min	Max
Antibody	Group	Timing	N	n(%)	95% CI	Value	95% CI		
HPV 18 IgG	HPV-001	PIII(M7)	325	325 (100%)	98.9, 100%	3471.8	3161.9, 3811.9	107.0	51346.0
HPV 18 IgG	Pooled	PIII (M7)	373	373 (100%)	99.0, 100%	3369.8	3071.7, 3696.7	412.0	41950.0

Pooled = Pooled lots (b(4)) (15≤Age≤25)
HPV-001 = HPV-001 study (ATP immunogenicity cohort), DVLP017A (--b(4)--) (15<=Age<=25)
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR 012, Supplement 27, p.137

Reverse cumulative distributions are also presented for anti-HPV 16 and anti-HPV 18 at month 7 for both groups, and these are similar. The results for subjects in study HPV-001 are slightly to the left of those in pooled specimens for anti-HPV 16 but the curves are superimposable for HPV 18. (Source: STN 125259/0, CSR 012, Supplements 28 and 29, p. 138-139, not shown here).

Seronegativity at baseline: For both HPV-16 and HPV-18, the percentages of seronegative subjects in the 10-14 years old group were found to be higher (92.4%) than that for 15-25 year olds in the pooled b(4) lots group (80.8%) or the 15-25 year olds in the -b(4)- group (77.3%).

At Month 7, all initially seronegative subjects had seroconverted for anti-HPV-16 and anti-HPV-18 antibodies regardless of age group or the production process used. (Source: STN 125259/0, CSR 012, Table 28, p.81 and Table 29, p. 82, not shown here).

Analysis of total vaccinated cohort: Immunogenicity results of the total vaccinated cohort were consistent with results for the ATP cohort. These are similar to those for results in the ATP cohort. (Source: STN 125259/0, CSR 012, Supplements 9-23, p. 122-133).

Inhibitory ELISA assay for detection of human neutralizing epitopes of HPV-16 or HPV-18 Anti-V5 HPV-16 and Anti-J4 HPV-18 antibody responses:

- At Month 7, all subjects were seropositive for anti-V5 HPV-16 antibodies in all three groups analyzed. Similar GMTs were observed with both production processes (Lot 1 (-b(4)-) and --b(4)--), whereas at least a two-fold higher GMT was seen in the younger age [10-14] group.
- At Month 7, all subjects in the --b(4)-- and [10-14] groups were seropositive for anti-J4 HPV-18 antibodies, and 92.9% of subjects in the Lot 1 (b(4)) group were seropositive. Slightly higher GMTs were observed for subjects in the --b(4)-- group than the Lot 1 (-b(4)-) group, while an almost two-fold higher mean titeras seen in the younger age [10-14] group. (Source: STN 125259/0, CSR 012, Annex 1, Tables 3 and 4, p. 19-20, not shown here)

Immunogenicity conclusions

- The immunogenicity of three different industrial production lots of the HPV-16/18 vaccine (i.e. b(4) production process) was demonstrated to be consistent 1 month following administration of the last dose of study vaccine (i.e. at month 7).
- The HPV vaccine produced with the b(4) cell line process was non-inferior in terms of immunogenicity to the HPV vaccine produced with the -b(4)- process.
- Immunogenicity in the 10-14 year age group was non-inferior to the 15-25 year age group (with the same b(4) process) in terms of seroconversion rates and GMTs. Anti-HPV-16 and anti-HPV-18 GMTs at month 7 for the 10-14 year age group were more than two fold higher than those in the 15-25 year age group.
- The HPV vaccine produced with the b(4) cell line process was non-inferior in terms of immunogenicity to the HPV vaccine used in study HPV-001 (i.e. previous -b(4)- manufacturing process).

SAFETY RESULTS

Data sets analyzed: Analysis of safety was performed on the total vaccinated cohort (primary analysis). A second analysis based on the ATP cohort was performed to complement the primary analysis.

Total vaccinated cohort analysis: The total vaccinated cohort for safety consisted of 770 subjects (156 subjects in group Lot 1 (-b(4)-), 156 in group Lot 2 (b(4)), 146 in group Lot 3 (b(4), 154 in group -b(4)- and 158 in group [10-14]). The pooled b(4) lots group consisted of 458 subjects. Compliance for reactogenicity reporting was high (above 98% for all groups). (Source: STN 125259/0, CSR 012, Supplement 30 and 31, p. 140-142, not shown here).

Overall incidence of adverse events: The percentages of doses and subjects reporting solicited and unsolicited symptoms during the 30-days post-vaccination period (Days 0-29) for each dose and overall are presented in Table 273.

Reviewer's Comments: In all groups, at all doses, there was a higher proportion of local symptoms as compared to the proportion of subjects with a general symptom. The 95% CIs were reviewed for any symptom, general symptoms, and local symptoms. The 95% CIs overlapped for all lots tested within each heading (any symptom, general symptom, and local symptom) and no statistically significant difference was detected between lots, nor among groups tested. The proportion of subjects with any symptom, general symptom, or local symptom was highest after dose 1, and about the same at doses 2 and 3 for all groups. Similar results were noted among the lots when AEs were assessed per dose and per subject. The results for overall per subject are in Table 273.

Table 273-Study HPV-012: Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period per subject (Vaccinated Cohort)

	Any symptom		General Symptoms		Local Symptoms	
Group	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall/subject						
Lot 1	152/153	98.1%	132/155	85.2%	149/154	96.8%
Lot 2	151/153	98.7%	131/153	85.6%	148/153	96.7%
Lot 3	140/145	96.6%	119/145	82.1%	138/145	95.2%
Pooled	443/453	97.8%	382/453	84.3%	435/452	96.2%
(b)(4)	150/153	98.0%	133/153	86.9%	148/153	96.7%
[10-14]	150/155	96.8%	121/155	78.1%	149/155	96.1%

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25); Lot 2 = DHPVA005A (b(4)) (15≤Age≤25)
Lot 3 = DHPVA006A (b(4)) (15≤Age≤25); Pooled = Pooled lots (b(4)) (15≤Age≤25)
-b(4)- = DHPV007A9 (-b(4)-) (15≤Age≤25); [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: STN 125259/0, CSR 012, Table 31, p.85

Reviewer's Comments: In all groups (overall/subject), there was a higher proportion of local symptoms as compared to the proportion of subjects with a general symptom. The 95% CIs were reviewed for any symptom, general symptoms, and local symptoms. The 95% CIs overlapped for all lots tested within each heading (any symptom, general symptom, and local symptom) and no statistically significant difference was detected between lots, nor among groups tested. When calculated by subject, almost all subjects reported a local symptom when considering any dose administered (app. 95-97%), and there were no differences among groups. A slightly lower proportion of subjects reported a general symptom (app. 79%-87%) as compared to the proportion who reported a local symptom. A slightly lower proportion of 10-14 year old age group experienced a general symptom in the 30 days after any vaccination (78.1%) as compared to the 15-25 year old subjects who received Lot 1, 2, or 3 (84.3%). The proportion of subjects with a local symptom were similar in both age groups (96.2% older, 96.1% younger). There were no apparent statistically significant differences detected among the age groups.

Grade 3 adverse events were also reviewed.

Reviewer's Comment: In considering Grade 3 symptoms in the 30 days after vaccination by dose, there was no decrease in the proportion of subjects with any Grade 3 symptoms from dose 1 to dose 3. In all groups except for the 10-14 year old girls, there appeared to be a slightly lower proportion of subjects with a Grade general symptom after doses 2 and 3 compared to dose 1. In the younger subjects, there was a slight increase in proportion of any general symptom in doses 2 and 3 (each 5.8%) as compared to after dose 1, although the 95% CIs were all overlapping. Although there were slightly higher proportions of subjects in each group with a Grade 3 local symptom at dose 3 in most groups, the 95% CIs were also overlapping. the proportions of any subject experiencing any Grade 3 symptom in the 30 days after vaccination was app. 19%-31% (lowest for the 10-14 year old group and highest for the --b(4)-- group). However, 95% CIs were overlapping for all groups. A somewhat higher proportion of subjects in the --b(4)-- group reported any grade 3 symptom, any local symptom, and any general symptom, again with overlapping 95% CIs noted.

Table 274-Study HPV-012: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period overall/subject (Vaccinated Cohort)

	Any symptom		General Symptoms		Local Symptoms	
Group	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall/subject						
Lot 1	35/155	22.6%	23/155	14.8%	22/154	14.3%
Lot 2	33/153	21.6%	14/153	9.2%	26/153	17.0%
Lot 3	38/145	26.2%	23/145	15.9%	24/145	16.6%
Pooled	106/453	23.4%	60/453	13.2%	72/452	15.9%
(b)(4)	48/153	31.4%	27/153	17.6%	30/153	19.6%
[10-14]	30/155	19.4%	18/155	11.6%	18.155	11.6%

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25); Lot 2 = DHPVA005A (b(4)) (15≤Age≤25)
Lot 3 = DHPVA006A (b(4)) (15≤Age≤25); Pooled = Pooled lots (b(4)) (15≤Age≤25)
--b(4)-- = DHPV007A9 (--b(4)--) (15≤Age≤25); [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
For overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: STN 125259/0, CSR 012, Table 32, p.86

Solicited Local Symptoms:

Reviewer's Comment: In the 7 days after dose 1, 2, or 3, the most common solicited local symptom was pain for all groups (87.7%-90.3%), and was highest after dose 1 in all groups. The proportion of subjects with Grade 3 pain was lowest in subjects 10-14 years of age after each dose, but the 95% CIs were overlapping for all groups. Redness was the next most common solicited local symptom followed by swelling. While pain at the injection site did not show any increase with subsequent doses, redness and swelling tended to increase from dose 1 to dose 2. However, there were limited or no further increases in the incidence of redness and swelling from dose 2 to dose 3. Overall, the rate of solicited local symptoms was similar in 10-14 year olds and 15-25 year olds. Grade 3 local symptoms were reported in a relatively small proportion of subjects in all groups, and there were no apparent differences among the groups. There were no statistically significant differences noted among groups or among doses.

Solicited local symptoms are also presented overall/subject. These results are shown in Table 275.

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Table 275-Study HPV-012: Incidence of solicited local symptoms reported during the solicited 7-day follow-up period overall/dose and overall/subject (Vaccinated Cohort)

	Pooled		--b(4)--		10-14	
Group	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall/dose						
Overall/subject						
Pain-						
All	433/452	95.8%	148/153	96.7%	147/155	94.8%
Grade 3	54/452	11.9%	23/153	15.0%	12/155	7.7%
Redness (mm) -						
All	261/452	57.7%	88/153	57.5%	91/155	58.7%
>50	12/452	2.7%	3/153	2.0%	3/155	1.9%
Swelling (mm)-						
All	224/452	49.6%	72/153	47.1%	83/155	53.5%
>50	156/452	3.5%	5/153	3.3%	4/155	2.6%

Pooled = Pooled lots (b(4)) (15≤Age≤25); --b(4)-- = DHPV007A9 (--b(4)--) (15≤Age≤25)
[10-14] = DHPVA004A (b(4)) (10≤Age≤14)
For overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: STN 125259/0, CSR 012, Table 33, p.89

Similar results are noted for Lots 1, 2, and 3 of the b(4) material. (Source: STN 125259/0, CSR 012, Supplement 34, p.147-148, not shown here).

Solicited General Symptoms: The incidence of each individual solicited general symptom, and the incidence of Grade 3 symptoms, during the 7-day post-vaccination period following vaccination in the pooled lots (b(4)) group, the -b(4)- group and the [10-14] group, per dose and overall are presented per subject.

Table 276-Study HPV-012: Incidence of solicited general symptoms reported, during the solicited 7-day follow-up period overall/subject (Vaccinated Cohort)

	Pooled		--b(4)--		10-14	
Group	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall/subject						
Arthralgia						
All	81/453	17.9%	29/153	19.0%	31/155	20.0%
Grade 3	4/453	0.9%	1/153	0.7%	1/155	0.6%
Fatigue						
All	219/453	48.3%	79/153	51.6%	77/155	49.7%
Grade 3	10/453	2.2%	9/153	5.9%	6/155	3.9%
Fever (° C) Axilla						
All	43/453	9.5%	12/153	7.8%	17/155	11.0%
>39.0	0/453	0.0%	0/153	0.0%	2/155	0.2%
Gastrointestinal						
All	136/453	30.0%	43/153	28.1%	36/155	23.2%
Grade 3	5/453	1.1%	1/153	0.7%	7/155	4.5%
Headache						
All	242/453	53.4%	80/153	52.3%	77/155	49.7%
Grade 3	12/453	2.6%	8/153	5.2%	5/155	3.2%
Myalgia						
All	202/453	44.6%	79/153	51.6%	72/155	46.5%
Grade 3	12/453	2.6%	6/153	3.9%	2/155	1.3%
Rash						
All	44/453	9.7%	16/153	10.5%	16/155	10.3%
Grade 3	1/453	0.2%	1/153	0.7%	2/155	1.3%
Urticaria						
All	18/453	3.1%	4/153	2.6%	4/155	2.6%
Grade 3	0/453	0.0%	0/153	0.0%	0/155	0.0%

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25) Lot 2 = DHPVA005A (-b(4)-) (15≤Age≤25)
Lot 3 = DHPVA006A (b(4)) (15≤Age≤25) Pooled = Pooled lots (b(4)) (15≤Age≤25)
--b(4)-- = DHPV007A9 (--b(4)--) (15≤Age≤25) [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
For overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
Source: STN 125259/0, CSR 012, Table 34, p.91-95

During the 7-day solicited post-vaccination period for each dose, the percentage of subjects with solicited general symptoms appeared similar between groups, and there was no apparent increase in the incidence of general symptoms with subsequent doses in any of the groups.

Fatigue, headache and myalgia were the most frequently reported solicited general symptoms. Fever, rash and urticaria were less frequently reported. Solicited general symptoms reported with intensity of grade 3 were not common, regardless of the symptom. The sponsor notes that urticaria/rash was not reported by the investigator within 30 minutes of vaccine administration for any subject.

Overall, the rate of solicited general symptoms was similar in 10-14 year olds and 15-25 year olds.

Duration of Solicited Local and General Symptoms: For all groups, solicited local symptoms tended to be longer lasting than solicited general symptoms with median durations of 2-3 days for local symptoms and 1-2 days for general symptoms, except for rash and urticaria (2-3 days).

The median duration of solicited symptoms was comparable across all groups and there was no apparent increase in the median duration with subsequent doses. The duration of pain at the injection site of grade 3 intensity was comparable for all groups with a median of 1 day. (Source: STN 125259/0, CSR 012, Supplements 38-39, p. 162-175, not shown here).

Unsolicited symptoms: A summary of unsolicited signs and symptoms during the 30-day postvaccination period is presented in Table 277.

Table 277-Study HPV-012: Summary of unsolicited signs and symptoms reported during the 30-day (Days 0-29) post-vaccination period (Vaccinated Cohort)

	Group						
	Lot 1	Lot 2	Lot 3	Pooled	(b)(4)	[10-14]	ALL
Number of subjects with at least one unsolicited symptom reported	76	64	68	208	70	55	333
Number of doses followed by at least one unsolicited symptom	112	104	95	311	104	77	492
Number of unsolicited symptoms classified by MedDRA Preferred Term*	152	133	135	420	135	96	651
Number of unsolicited symptoms reported	162	143	139	444	138	100	682

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25); Lot 2 = DHPVA005A (b(4)) (15≤Age≤25)
Lot 3 = DHPVA006A (b(4)) (15≤Age≤25); Pooled = Pooled lots (b(4)) (15≤Age≤25)
--b(4)-- = DHPV007A9 (-b(4)-) (15≤Age≤25); [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once
Source: STN 125259/0, CSR 012, Table 35, p.96

Reviewer's Comment: The proportions of subjects with specific unsolicited adverse events were similar across lots.

New onset chronic diseases and other medically significant conditions: The percentages of subjects reporting the occurrence of potential new onset chronic diseases during the entire follow-up period, for the pooled lots (b(4)) group, the -b(4)- group and the [10-14] group are shown in Table 278 below.

Table 278-Study HPV-012: Percentage of subjects with potential new onset chronic diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the entire study (Vaccinated Cohort)

		Pooled N=458		-b(4)- N=154		10-14 N=158	
Primary System Organ Class	**Preferred term**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
At least one symptom		15 (3.3%)	1.8, 5.3%	0 (0.0%)	0.0, 2.4%	0 (0.0%)	0.0, 2.3%
Endocrine disorders	Hypothyroidism	2 (0.4%)	0.1, 1.6%	0 (0.0%)	0.0, 2.4%	0 (0.0%)	0.0, 2.3%
Immune system disorders	Hypersensitivity Seasonal allergy	2 (0.4%) 2 (0.4%)	0.1, 1.6% 0.1, 1.6%	0 (0.0%) 0 (0.0%)	0.0, 2.4% 0.0, 2.4%	0 (0.0%) 0 (0.0%)	0.0, 2.3% 0.0, 2.3%
Metabolism & Nutrition Disorders	Diabetes mellitus, insulin dependent	1 (0.2%)	0.0, 1.2%	0 (0.0%)	0.0, 2.4%	0 (0.0%)	0.0, 2.3%
Respiratory, thoracic & mediastinal disorders	Asthma Rhinitis allergic	2 (0.4%) 2 (0.4%)	0.1, 1.6% 0.1, 1.6%	0 (0.0%) 0 (0.0%)	0.0, 2.4% 0.0, 2.4%	0 (0.0%) 0 (0.0%)	0.0, 2.3% 0.0, 2.3%
Skin & subcutaneous disorders	Urticaria Urticaria chronic Urticaria localized	2 (0.4%) 1 (0.2%) 1 (0.2%)	0.1, 1.6% 0.0, 1.2% 0.0, 1.2%	0 (0.0%) 0 (0.0%) 0 (0.0%)	0.0, 2.4% 0.0, 2.4% 0.0, 2.4%	0 (0.0%) 0 (0.0%) 0 (0.0%)	0.0, 2.4% 0.0, 2.4% 0.0, 2.4%

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25) Lot 2 = DHPVA005A (b(4)) (15≤Age≤25)
Lot 3 = DHPVA006A (b(4)) (15≤Age≤25) Pooled = Pooled lots (b(4)) (15≤Age≤25)
-b(4)- = DHPV007A9 (-b(4)-) (15≤Age≤25) [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 012, Table 39, p.101

Medically significant AEs: Wthin the 30-day post-vaccination period, 8.5%, 10.4% and 7.6% of subjects in the pooled lots --b(4)--------- and [10-14] groups, respectively, had at least one symptom of which, infections and infestations appeared to be the most common. Reports from 30 days post-vaccination were even lower in number. No group differences were apparent.

Table 279-Study HPV-012: Percentage of subjects reporting the occurrence of medically significant AEs within the 30-day post-vaccination period and starting from Day 30 post-vaccination (Vaccinated Cohort)

	Pooled N=458		--b(4)-- N=154		10-14 N=158	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
At least one symptom within the 30 day post-vaccination period	39 (8.5%)	6.1, 11.5%	16 (10.4%)	6.1, 16.3%	12 (7.6%)	4.0, 12.9%
At least one symptom starting from Day 30 post-vaccination	11 (2.4%)	1.2, 4.3%	5 (3.2%)	1.1, 7.4%	2 (1.3%)	0.2, 4.5%

Pooled = Pooled lots (b(4)) (15≤Age≤25); -b(4)- = DHPV007A9 (-b(4)-) (15≤Age≤25)
[10-14] = DHPVA004A (b(4)) (10≤Age≤14)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 012, Table 40, p.102

Overall 10.8% of subjects reported at least one medically significant adverse event during the active phase (Month 0-7) of the study, according to the revised definition. While there was a trend for similar numbers of medically significant AEs reported by subjects in the pooled b(4) and

the --b(4)-- groups, fewer subjects in the [10-14] group reported medically significant AEs during the study

Analysis according to anti-HPV-16/18 serostatus at baseline: The vaccine reactogenicity profile did not appear to be different between subjects who were initially seronegative and those who were initially seropositive for one or both vaccine antigens. (Source: STN 125259/0, CSR 012, Supplements 54-72, p. 259-322, not shown here).

Serious adverse events: The percentage of subjects reporting the occurrence of serious adverse events classified by MedDRA primary system organ class and preferred term during the entire study are presented in Table 280.

Table 280-Study HPV-012: Percentage of subjects reporting the occurrence of Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, during the entire study (Vaccinated Cohort)

		Pooled N=458		--b(4)-- N=154		10-14 N=158	
Primary System Organ Class	**Preferred term**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
At least one symptom		7 (1.5%)	0.6, 3.1%	0 (0.0%)	0.0, 2.4%	1 (0.6%)	0.0, 3.5%
Cardiac disorders	Myocarditis Pericarditis	1 (0.2%) 1 (0.2%)	0.0, 1.2% 0.0, 1.2%	0 (0.0%) 0 (0.0%)	0.0, 2.4% 0.0, 2.4%	0 (0.0%) 0 (0.0%)	0.0, 2.3% 0.0, 2.3%
Gastrointestinal disorders	Gastric ulcer	1 (0.2%)	0.0, 1.2%	0 (0.0%)	0.0, 2.4%	0 (0.0%)	0.0, 2.3%
Infections and Infestations	Acute sinusitis	1 (0.2%)	0.0, 1.2%	0 (0.0%)	0.0, 2.4%	0 (0.0%)	0.0, 2.3%
Injury, poisoning and procedural complications	Heat stroke	1 (0.2%)	0.0, 1.2%	0 (0.0%)	0.0, 2.4%	0 (0.0%)	0.0, 2.3%
Metabolism and nutrition disorders	Diabetes mellitus, insulin dependent	1 (0.2%)	0.0, 1.2%	0 (0.0%)	0.0, 2.4%	0 (0.0%)	0.0, 2.3%
Pregnancy, puerperium and periatal conditions	Abortion threatened	1 (0.2%)	0.0, 1.2%	0 (0.0%)	0.0, 2.4%	0 (0.0%)	0.0, 2.3%
Psychiatric disorders	Depression	0 (0.0%)	0.0, 0.8%	0 (0.0%)	0.0, 2.4%	1 (0.6%)	0.0, 3.5%

Pooled = Pooled lots (b(4)) (15≤Age≤25); -b(4)- = DHPV007A9 (-b(4)-) (15≤Age≤25)
[10-14] = DHPVA004A (b(4)) (10≤Age≤14)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 012, Table 41, p.103-104

A total of eight subjects experienced a total of eight SAEs: two in each of the groups Lot 1 (b(4)) and Lot 2 (b(4)); three in group Lot 3 (b(4)); and one in the group [10-14]. There were no fatal events and all SAEs were considered by the investigator to not be related to study vaccination.

Table 281-Study HPV-012, Subjects with SAE (CBER generated)

Case number	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to vaccination per investigator
0040, -b(4)-	IDDM (symptoms predated vaccination)	1 day after dose 1	Ongoing	Continuing	Unrelated
00247, -b(4)-	Pericarditis (intercurrent viral illness)	24 days after dose 3	Ongoing	Recovering	Unrelated
00259, -b(4)-	Heat stroke, UTI	16 days after dose 3	9 days	Resolved	Unrelated
01505, -b(4)-	Depression (domestic issues)	15 days after dose 1	Ongoing	Improving	Unrelated
01568, -b(4)-	Myocarditis	91 days after dose 2	5 days	Resolved	Unrelated
02104, -b(4)-	Gastric ulcer (on meds for headache after dose 1 and 2)	4 months after dose 2	Ongoing	Imrpoving	Unrelated (although was possibly related to meds for headache after doses 1 and 2)
02310, -b(4)-	Acute sinusitis	40 days after dose 2	4 days	Resolved	Unrelated
03403, -b(4)-	Abortion threatened (delivered healthy baby)	4 months after dose 2 (dx pregnancy 1 month after dose 2)	37 ays	Resolved	Unrelated

Adverse events leading to premature discontinuation of study vaccine and/or study: Five subjects were withdrawn from the study after experiencing non-serious adverse events.

Table 282 -Study HPV-012: Withdrawals from study due to non serious adverse events (Vaccinated Cohort)

Subject no.	Group	Timing of withdrawal	Decision for withdrawal	Adverse event	Causal relationship to vaccination
00262	Lot 1 (b)(4)	After visit 1 (06-11-2004) (last contact 18-12-2004)	Subject or parent/LAR	Fatigue	Unknown
00057	Lot 2 (b)(4)	After visit 1 (27-11-2004) (last contact 05-01-2005)	Subject or parent/LAR	Abortion threatened	No
00206	Lot 2 (b)(4)	After visit 1 (30-10-2004) (last contact 11-12-2004)	Subject or parent/LAR	Perioral rash	No
02027	(b)(4)	After visit 2 (12-01-2005) (last contact 23-05-2005)	Subject or parent/LAR	Injection site pain	Yes
01517	[10-14]	After visit 1 (18-11-2004) (last contact 20-12-2004)	Subject or parent/LAR	Nausea	Yes

LAR: legally acceptable representative
Source: STN 125259/0, CSR 012, Table 42, p.105

For two subjects, the adverse event resulting in withdrawal was causally related to vaccination: subject 02027 reported injection site pain, lasting 10 days, following dose 2 and with a maximum intensity of grade 2; subject 01517 reported nausea on day of vaccination of dose 1 with a maximum intensity of grade 3 and lasting 2 days. Subject 57 withdrew following a threatened abortion threatened. Subject 206 reported a perioral rash 16 days following dose 1 of intensity grade 1 which was assessed as not related to study material. Subject 262 reported fatigue but no further details are available.

Pregnancies: Pregnancies were reported in five subjects. The outcomes of these pregnancies are detailed in Table 283.

Table 283-Study HPV-012: Pregnancy Outcomes

Outcome	Lot 1 (b)(4)	Lot 2 (b)(4)	Lot 3 (b)(4)	(b)(4)	[10-14]	Total
Healthy baby	0	1*	0	0	0	1
Elective abortion	1	1**	0	0	0	2
Pregnancy ongoing	1	0	0	1	0	2
Total	2	2	0	1	0	5

* reported threatened abortion as SAE (subject number 03403)
** reported threatened abortion as AE (subject number 00057)
Source: STN 125259/0, CSR 012, Table 43, p.106

Pregnancy were reported as an AE in one subject ("abortion threatened" in subject number 00057) and as an SAE in another subject ("abortion threatened" in subject number 03403). Subject number 00057, in the Lot 2 (b(4)) group, had an elective abortion for socioeconomic reasons 2 days following onset of the threatened abortion. Neither report of threatened abortion was considered to be causally related to vaccination. For the other three pregnancies, one subject (number 03330) in the Lot 1 (b(4)) group underwent an elective abortion and, for the two remaining subjects, the pregnancies were ongoing at time of reporting (subject number 03013 from the Lot 1 [b(4)] group and subject number 03015 from the -b(4)- group). Subjects 03330, 03013 and 03015 had each received a total of 2 doses of study vaccine. Subject 00057 withdrew from the study following onset of threatened abortion; the four remaining subjects withdrew from the study following onset of pregnancy.

Concomitant medications/vaccinations:
Reviewer's Comment: In the 30 days after vaccination, a higher proportion of subjects in the -b(4)- (54.5%) took any medication or any anti-pyretic (33.8%) > b(4) (47.8% any medication, 29.3% any anti-pyretic) > 10-14 year old group (35.4% any medication, 21.5% any anti-pyretic).

Safety conclusions through Month 7:
- The three consecutive production lots of HPV-16/18 vaccine (b(4) process) were similar in terms of reactogenicity.
- The reactogenicity profile of HPV-16/18 produced using the b(4) process was similar to that of the vaccine produced using the -b(4)- process.
- There was little difference in the reactogenicity and safety profile of the HPV-16/18 vaccine (b(4)-produced) in 15-25 year old subjects and 10-14 year old subjects, except for a tendency observed in the younger subjects to report fewer unsolicited symptoms. Few new onset chronic diseases were identified; according to GSK assessment, 15 subjects reported such events.

STUDY HPV-012: MONTH 12 SAFETY FOLLOW-UP
In an Extended Safety Follow-up (ESFU) through Month 12: Additional safety outcomes were reported, including all pregnancies and pregnancy outcomes, SAEs, NOCDs, and medically significant conditions which may have occurred since the last visit. Subjects who received at least one vaccination and for whom data were available were included in the analysis.

In addition, immunogenicity was reported in all subjects for whom immunogenicity data were available (based on treatment actually received).

Study dates: The first volunteer was enrolled in the study on 9/5/04 and the last active study visit (Month 7) was on 7/15/05. The last subject completed the extended safety follow-up Month 12 telephone contact on 12/23/05.

Number and distribution of subjects: The extended safety follow-up vaccinated cohort included 733 subjects (95.2 % of the total vaccinated cohort (Month 7), as 37 subjects were eliminated from this analysis. The number of subjects enrolled into the study as well as the number excluded from ESFU analyses is presented in Table 284.

Table 284-Study HPV-012: Number of subjects enrolled into the study as well as the number excluded from ESFU analyses with reasons for exclusion (through Month 12)

	Total			Pooled		--b(4)--		[10-14]	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total enrolled cohort	773								
Study vaccine dose not administered but subject # allocated	3	3							
Total Vaccinated Cohort	770		100%	458		154		158	
Subjects eliminated from ESFU	37*	40		18	18	10	10	9	9
ESFU Vaccinated Cohort	733		95.2%	440		144		149	

Pooled = Pooled lots (b(4)) (15-25 years)
--b(4)-- = DHPV007A9 (-b(4)-) (15-25 years)
[10-14] = DHPVA004A (b(4)) (10-14 years)
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ESFU cohort relative to the Total vaccinated cohort
Three subjects (2112, 2113 and 2520) were contacted during the ESFU but withdrew their consent during the active phase. Another three subjects (2211, 3101 and 3116) had no information available during the ESFU. The reason for withdraw (consent withdrawal) is taken from the active phase. These subjects all received a 3000 elimination code. The three subjects (1511, 1576, 1580) not administered with vaccine in the active phase (1030) also received the 3000 elimination code in the ESFU.
STN 125259/0, CSR 012, Annex 2, Table 2, p. 21

The 37 subjects excluded from ESFU analyses included 14 subjects that withdrew consent, 15 subjects that were lost to follow-up, three subjects that were contacted but had been withdrawn from the active phase, three subjects with no information available and two subjects that could not be contacted for other reasons. Subjects were not excluded for variations from intervals between visits.

ESFU Safety Results

ESFU vaccinated cohort analysis (Month 7 to Month 12): The ESFU vaccinated cohort for safety consisted of 733 subjects (147 subjects in group Lot 1 (b(4)), 148 in group Lot 2 (b(4)), 145 in group Lot 3 (b(4)), 144 in group -b(4)- and 149 in group [10-14]). The pooled b(4) group consisted of 440 subjects; the --b(4)-- group included 144 subjects; and the [10-14] group included 149 subjects.

New onset chronic diseases (ESFU: Month 7 to Month 12): A total of eight subjects reported nine NOCDs during the follow-up period.

Table 285 shows the assessment by GSK led to the identification of potential NOCDs in subjects aged 15 to 25 years (1.4%), however, no new onset chronic diseases were identified in the subjects aged 10 to 14 years.

Table 285-Study HPV-012: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the extended safety follow-up (ESFU Vaccinated Cohort, Month 7 to Month 12)

		Pooled N=458	---b(4)------ N=154	[10-14] N=158
Primary System Organ Class	**Preferred term**	**n (%)**	**n (%)**	**n (%)**
At least one NOCD		6 (1.4%)	2 (1.4%)	0 (0.0%)
Endocrine disorders	Thyroiditis	1 (0.2%)	0 (0.0%)	0 (0.0%)
Immune system disorders	Hypersensitivity	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Nickel sensivity	0 (0.0%)	1 (0.7%)	0 (0.0%)
	Seasonal allergy	1 (0.2%)	0 (0.0%)	0 (0.0%)
Nervous system disordxers	Demyelination	1 (0.2%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders	Generalized anxiety	0 (0.0%)	1 (0.7%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Angioneurotic edema	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Dermatitis atopic	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Solar urticaris	1 (0.2%)	0 (0.0%)	0 (0.0%)

Pooled = Pooled lots (b(4)) (15-25 years)
--b(4)-- = DHPV007A9 (-b(4)-) (15-25 years)
[10-14] = DHPVA004A (b(4)) (10-14 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
STN 125259/0, CSR 012, Annex 2, Table 7, p. 27-28

Medically significant adverse events (ESFU: Month 7 to Month 12): A total of 22 subjects reported 25 medically significant AEs during the ESFU period.

Table 286 shows the percentage of subjects reporting the occurrence of medically significant AEs during the follow-up period (Month 7 to Month 12), for each group. At least one medically significant AE was reported by 3.9% of subjects in the pooled b(4) group and 3.5% of the subjects in the --b(4)-- group. No subjects in the [10-14] group had such an event.

Table 286-Study HPV-012: Percentage of subjects reporting the occurrence of medically significant AEs classified by MedDRA Primary System Organ Class and Preferred Term, during the extended safety follow-up (ESFU Vaccinated Cohort, Month 7 to Month 12)

		Pooled N=440	--b(4)-- N=144	[10-14] N=149
Primary System Organ Class	**Preferred term**	**n (%)**	**n (%)**	**n (%)**
At least one MSAE		17 (3.9%)	5 (3.5%)	0 (0.0%)
Blood and Lymphatic system disorders	Lympadenitis	1 (0.2%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	Arrythmia	0 (0.0%)	1 (0.7%)	0 (0.0%)
Endocrine disorders	Thyroiditis	1 (0.2%)	0 (0.0%)	0 (0.0%)
Immune system disorders	Hypersensitivity	2 (0.5%)	0 (0.0%)	0 (0.0%)
	Seasonal Allergy	1 (0.2%)	0 (0.0%)	0 (0.0%)
Infections and Infestations	Herpes simplex	0 (0.0%)	1 (0.7%)	0 (0.0%)
	Infectious mononucleosis	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Pertussis	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Pneumonia	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Pyelonephritis	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Salpingitis	0 (0.0%)	1 (0.7%)	0 (0.0%)
	Viral URI	1 (0.2%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications	Alcohol poisoning	1 (0.2%)	0 90.0%)	0 (0.0%)
Investigations	Red blood cell sedimentation increased	1 (0.2%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Shoulder pain	1 (0.2%)	0 (.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Benign breast neoplasm	1 (0.2%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	Demyelination	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Migraine	1 (0.2%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders	Depression	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Generalized anxiety disorder	0 (0.0%)	1 (0.7%)	0 (0.0%)
Reproductive and breast disorders	Endometriosis	1 (0.2%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Angioneurotic edema	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Dermatitis atopic	1 (0.2%)	0 (0.0%)	0 (0.0%)
Surgical and medical procedures	Skin cosmetic procedure	0 (0.0%)	1 (0.7%)	0 (0.0%)

Pooled = Pooled lots (b(4)) (15-25 years)
-b(4)- = DHPV007A9 (-b(4)-) (15-25 years)
[10-14] = DHPVA004A (b(4)) (10-14 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
STN 125259/0, CSR 012, Annex 2, Table 9, p. 30-32

Serious adverse events (ESFU: Month 7 to Month 12): A total of five subjects experienced six SAEs: two in each -b(4)- group (Lot 1, Lot 2 and Lot 3). There were no fatal events and all SAEs were considered by the investigator to not be related to study vaccination. No subjects were withdrawn as a result of an SAE. One SAE (Demyelinating disease of central nervous system) was still ongoing at the conclusion of the ESFU and continued to be monitored, but the event was reported to have improved.
Reviewer's Comment: The subject with demyelination is included in the analysis of neuroinflammatory events in the overall safety discussion.

At least one SAE was reported by 1.1% of subjects in the pooled b(4) group, and no SAEs were reported by subjects in the -b(4)- group or 10-14 group.

Table 287-Study HPV-012: Percentage of subjects reporting the occurrence of Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, during the extended safety follow-up (ESFU Vaccinated Cohort, Month 7 to Month 12)

		Pooled N=440	--b(4)-- N=144	[10-14] N=149
Primary System Organ Class	**Preferred term**	**n (%)**	**n (%)**	**n (%)**
At least one SAE		5 (1.1%)	0 (0.0%)	0 (0.0%)
Blood and Lymphatic system disorders	Lympadenitis	1 (0.2%)	0 (0.0%)	0 (0.0%)
Immune system disorders	Hypersensitivity	1 (0.2%)	0 (0.0%)	0 (0.0%)
Infections and Infestations	Condyloma acuminata	1 (0.2%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications	Alcohol poisoning	1 (0.2%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	Demyelination	1 (0.2%)	0 (0.0%)	0 (0.0%)

Pooled = Pooled lots (b(4)) (15-25 years)
-b(4)- = DHPV007A9 (-b(4)-) (15-25 years)
[10-14] = DHPVA004A (b(4)) (10-14 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259/0, CSR 012, Annex 2, Table 11, p. 34

Table 288 includes subjects with SAEs in the Month 7-12 time period.

Table 288-Study HPV-012, Subjects with SAE (Month 7-12)
(CBER generated)

Case number	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to vaccination per investigator
01554, -b(4)-	Hypersensivity to insect bite and eating nuts and meat (history of food, animal, dust allergies) [anaphylactic reaction]	70 days after dose 3	2 days	Resolved	Unrelated
03202, -b(4)-	Condyloma acuminate	6 months after dose 3	Lost to follow-up	Lost to follow-up	Unrelated
02602, -b(4)-	Alcohol poisoning	6 months after dose 3	1 day	Lost to follow-up	Unrelated
00037, -b(4)-	Demyelination	5 months after dose 3	Ongoing	Improving, not resolved	Unrelated
00013, -b(4)-	Mesenteruc adenitis	6 months after dose 3	1 day	Resolved	Unrelated

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study (ESFU: Month 7 to Month 12): No subjects were withdrawn from the ESFU due to an AE.

Pregnancy (ESFU: Month 7 to Month 12): Pregnancies were reported in two subjects during the ESFU period. One subject delivered to a normal female infant by caesarean section approximately 11 months after the last dose of vaccine. The other subject gave birth to a healthy male infant by vaginal delivery approximately one year after the last dose of the vaccine.

Safety data for **Month 0-12** were also reported. All events have been reported as above.
Total Vaccinated Cohort (Month 0 to Month 12) included 770 subjects (156 subjects in group Lot 1 (-b(4)-), 156 in group Lot 2 (-b(4)-), 146 in group Lot 3 (-b(4)-), 154 in group -b(4)----- and 158 in group [10-14]). The pooled -b(4)- group consisted of 458 subjects.

New onset chronic diseases (Month 0 to Month 12): A total of 23 subjects reported 24 NOCDs during the study from Month 0 to Month 12.

Table 289 shows that over the complete reporting period of 12 month, NOCDs were reported in subjects aged 15 to 25 years (at least 4.6%), but no new onset chronic diseases were identified in the subjects aged 10 to 14 years.

Table 289-Study HPV-012: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, reported during the entire follow-up period (Month 0 to Month 12) (Total vaccinated cohort)

		Pooled N=458	--b(4)-- N=154	[10-14] N=158
Primary System Organ Class	**Preferred term**	**n (%)**	**n (%)**	**n (%)**
At least one NOCD		21 (4.6%)	2 (1.3%)	0 (0.0%)
Endocrine disorders	Hypothyridism	2 (0.4%)	0 (0.0%)	0 (0.0%)
	Thyroiditis	1 (0.2%)	0 (0.0%)	0 (0.0%)
Immune system disorders	Hypersensitivity	3 (0.7%)	0 (0.0%)	0 (0.0%)
	Nickel sensivity	0 (0.0%)	1 (0.6%)	0 (0.0%)
	Seasonal allergy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	Diabetes mellitus insulin dependent	1(0.2%)	0 (0.0%)	0 (0.0%)
Nervous system disordxers	Demyelination	1 (0.2%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders	Generalized anxiety	0 (0.0%)	1 (0.6%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Asthma	2 (0.4%)	0 (0.0%)	0 (0.0%)
	Rhinitis allergic	2 (0.4%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Angioneurotic edema	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Dermatitis atopic	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Solar urticaria	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Urticaria	2 (0.4%)	0 (0.0%)	0 (0.0%)
	Urticaria chronic	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Urticaria localizad	1 (0.2%)	0 (0.0%)	0 (0.0%)

Pooled = Pooled lots (-b(4)-) (15-25 years)
-b(4)-- = DHPV007A9 (-b(4)-) (15-25 years)
[10-14] = DHPVA004A (-b(4)-) (10-14 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259/0, CSR 012, Annex 2, Table 13, p. 37-38

Medically significant adverse events (Month 0 to Month 12): A total of 103 subjects reported 139 medically significant AEs during the study. At least one medically significant AE was reported by 14.6% of subjects in the pooled -b(4)- group, 14.9% of the subjects in the -b(4)-------- group and 8.2% of subjects in the [10-14] group. The medically significant AEs for months 0-12 include those MSAEs already noted. (Source: STN 125259/0, CSR 012, Annex 2, Table 15, p. 40-46, not shown here).

Serious adverse events (Month 0 to Month 12): A total of 13 subjects experienced 14 SAEs. At least one SAE was reported by 2.6% of subjects in the pooled -b(4)- group, 0.6% of subjects in the [10-14] group and no SAEs were reported by subjects in the -b(4)----- group. (Source: STN 125259/0, CSR 012, Annex 2, Table 17, p. 48-49, not shown here.)

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study (Month 0 to Month 12): A total of five subjects were withdrawn from the active phase of the study after experiencing non-serious adverse events. No subjects withdrew after experiencing an SAE. No subjects were withdrawn from the ESFU due to and AE.

Pregnancy (Month 0 to Month 12): A total of seven pregnancies were reported throughout the study period (Month 0-12). Two subjects withdrew from the study and the pregnancy outcome is unknown, two subjects elected to have an abortion, three subjects delivered healthy babies.

STUDY HPV-012: MONTH 24 (INTERIM ANALYSIS): An open follow-up study was designed to evaluate the long-term immunogenicity and safety of the HPV-16/18 vaccine up to approximately 36 months after the end of Study HPV-012 (48 months after administration of the first vaccine dose in the primary study HPV-012). The study also was designed to evaluate the antibody response elicited by the vaccine in cervicovaginal secretions (CVS) samples collected from subjects who volunteered. All subjects from the HPV-012 study from Denmark, Estonia and Finland, who received the three doses of vaccine and who completed Visit 4 (Month 7), were invited to participate in the current extension.

Primary Objective: To evaluate the long-term immunogenicity of the HPV-16/18 vaccine in all subjects who received the three vaccine doses and completed Visit 4 (Month 7) by enzyme-linked immunosorbent assay (ELISA) at each time point (Months 18 and 24).

Secondary Objectives
Safety: To evaluate the long-term safety of the candidate vaccine for approximately 24 months after administration of the first vaccine dose.

Immunogenicity:
In serum samples collected during the primary study (Months 0 and 7) and in serum samples collected during this follow-up study (Months 18 and 24):

- To compare the immune responses to the HPV-16/18 L1 VLP AS04 vaccine (as determined by anti-HPV-16/18 antibodies assessed by ELISA) in subjects enrolled in this study with responses measured in sera from adults of studies HPV-001 and HPV-007.

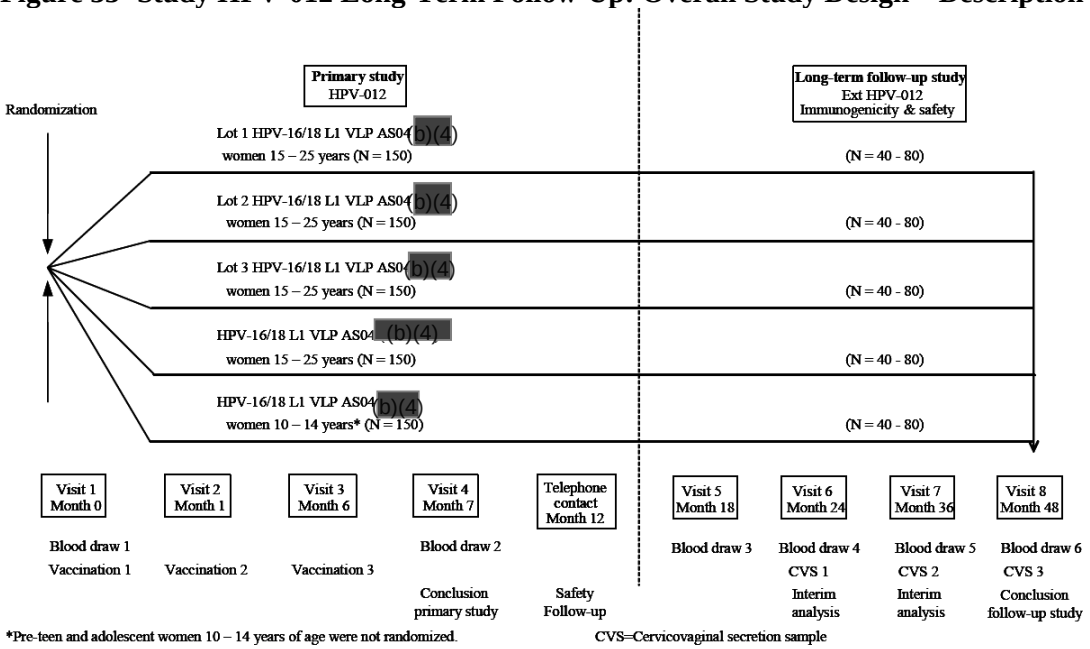
In serum samples collected at Month 24 in subjects who volunteered for cervicovaginal secretion (CVS) sample collection:

- To evaluate total IgG.

In CVS samples collected at Month 24 in post-menarcheal subjects who volunteered for this procedure:

- To evaluate anti-HPV-16 and anti-HPV-18 antibody responses.
- To compare anti-HPV-16 and anti-HPV-18 antibody levels in CVS samples with antibody levels in serum samples in subjects vaccinated pre- and post-menarche.
- To evaluate total IgG.

Figure 33- Study HPV-012 Long-Term Follow-Up: Overall Study Design – Description



Source: STN 125259/30, CSR 012, Month 24, p. 26

Primary endpoint: Anti-HPV-16 and anti-HPV-18 antibody titers assessed by ELISA in all subjects at each time point (Months 18 and 24).

Secondary endpoints

- Occurrence of pregnancies, SAEs, new onset chronic diseases and other medically significant conditions.
- Anti-HPV-16 and anti-HPV-18 antibody titers assessed by ELISA at each time points (Months 0, 7, 1 and 24).
- Anti-HPV-16 and anti-HPV-18 antibody titers from subjects enrolled in studies HPV-001/HPV-007 subjects assessed by ELISA at each time point.
- Anti-HPV-16 and anti-HPV-18 antibody titers in CVS samples at Months 24, 36 and 48 in post-menarcheal subjects who volunteered for the procedure.
- Total IgG evaluation in blood samples at Month 24.
- Total IgG evaluation in CVS samples at Month 24 in the subset of subjects who had CVS samples collected.

Total Vaccinated cohort of the extension follow-up phase (Month 12 - Month 24): The Total Vaccinated cohort Extension Month 24 included all vaccinated subjects enrolled in the Extension of the HPV-012 study (subjects who received three doses of HPV-16/18 L1 VLP AS04 vaccine in the primary HPV-012 study) for whom data were available for Month 24.

- The **analysis of safety** included all enrolled subjects (primary data set for analysis of safety)
- The **analysis of immunogenicity** included subjects who returned for blood sampling at Month 24 and for whom serology results were available.

Total Vaccinated cohort of the active phase of the study (Month 0 - Month 24): The Total Vaccinated cohort of the active phase of the study will be referred to as the **Total Vaccinated cohort** throughout this clinical study report. The Total Vaccinated cohort included all vaccinated

subjects (subjects who received three doses of HPV-16/18 vaccine in the primary HPV-012 study) for whom data were available for Month 24.

ATP immunogenicity cohort: The ATP cohort for analysis of immunogenicity included all evaluable subjects, subjects who were included in the ATP immunogenicity analysis in the primary study (HPV-012).

Interim analysis: An interim analysis was planned after each phase of the long-term follow-up (Ext HPV-012 Month 24 and Ext HPV-012 Month 36).

Study dates: The first volunteer was enrolled in the extension follow-up study on 6/27/06 (Visit 5, Month 18 visit) and on 9/1/06 (Visit 6, Month 24 visit). The last Month 24 visit occurred on 12/21/06. The data lock point date was 9/21/07.

Number and distribution of subjects: In the primary study HPV-012, 770 subjects were enrolled and received at least one dose of the HPV-16/18 L1 VLP AS04 vaccine. A total of 307 subjects, out of 401 subjects initially enrolled in Denmark, Finland and Estonia in the primary study, attended Visit 6 (Month 24): 186 subjects in the pooled b(4)-produced HPV vaccine lots group; 64 subjects in the --b(4)---produced HPV vaccine group and 57 subjects in the b(4)-produced HPV vaccine group (subjects aged 10 - 14 years). Only 8 subjects attended Visit 5 (Month 18). The numbers of subjects enrolled into the study as well as the numbers excluded from the ATP analyses with reasons for exclusion are presented in Table 290.

Table 290-Study EXT HPV-012: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

	Total			Pooled		(b)(4)		[10-14]	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total enrolled cohort	**770**								
Total Vaccinated Cohort (active phase)	**770**			**458**		**154**		**158**	
Subject missed extension Month 24 visit (code 5000)	463	463		272	272	90	90	101	101
Total Vaccinated Cohort Extension M24	**307**		**100**	**186**		**64**		**57**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	5	10		2	5	3	3	0	2
Study vaccine dose not administered according to protocol (code 1070)	0	2		0	2	0	0	0	0
Initially seropositive or initially unknown antibody status (code 2020)	26	44		17	30	8	12	1	2
Administration of any medication forbidden by the protocol (code 2040)	1	1		0	0	1	1	0	0
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	4	5		3	3	1	2	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	1	3		1	3	0	0	0	0
Essential serological data missing (code 2100)	0	28		0	16	0	7	0	5
Protocol violation (inclusion/exclusion criteria) for extension Month 24 (code 5010)	0	1		0	1	0	0	0	0
Concomitant infection not related to vaccine (code 5070)	1	1		1	1	0	0	0	0
Essential serological data missing for extension Month 24 (code 5100)	0	2		0	1	0	0	0	1
ATP Cohort for immunogenicity	**269**		**87.6**	**162**		**51**		**56**	

Pooled = pooled lots (b(4)) (15 - 25 years old); -b(4)- = DHPV007A9 (-b(4)-) (15 - 25 years old)
[10-14] = DHPVA004A (b(4)) (10 - 14 years old)
Note: Subjects may have more than one elimination code assigned
Note: code 1040, 1070, 2020, 2040, 2080, 2090 and 2100 were attributed at the Month 7 database freeze and kept through the study; code 5000, 5010, 5070 and 5100 were attributed at the Month 24 database freeze.
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated cohort
Source: STN 125259/30, CSR 012, Month 24 Report, Table 4, p. 44

subjects (subjects who received three doses of HPV-16/18 vaccine in the primary HPV-012 study) for whom data were available for Month 24.

ATP immunogenicity cohort: The ATP cohort for analysis of immunogenicity included all evaluable subjects, subjects who were included in the ATP immunogenicity analysis in the primary study (HPV-012).

Interim analysis: An interim analysis was planned after each phase of the long-term follow-up (Ext HPV-012 Month 24 and Ext HPV-012 Month 36).

Study dates: The first volunteer was enrolled in the extension follow-up study on 6/27/06 (Visit 5, Month 18 visit) and on 9/1/06 (Visit 6, Month 24 visit). The last Month 24 visit occurred on 12/21/06. The data lock point date was 9/21/07.

Number and distribution of subjects: In the primary study HPV-012, 770 subjects were enrolled and received at least one dose of the HPV-16/18 L1 VLP AS04 vaccine. A total of 307 subjects, out of 401 subjects initially enrolled in Denmark, Finland and Estonia in the primary study, attended Visit 6 (Month 24): 186 subjects in the pooled b(4)-produced HPV vaccine lots group; 64 subjects in the --b(4)---produced HPV vaccine group and 57 subjects in the b(4)-produced HPV vaccine group (subjects aged 10 - 14 years). Only 8 subjects attended Visit 5 (Month 18). The numbers of subjects enrolled into the study as well as the numbers excluded from the ATP analyses with reasons for exclusion are presented in Table 290.

Table 290-Study EXT HPV-012: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

	Total			Pooled		(b)(4)		[10-14]	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total enrolled cohort	**770**								
Total Vaccinated Cohort (active phase)	**770**			**458**		**154**		**158**	
Subject missed extension Month 24 visit (code 5000)	463	463		272	272	90	90	101	101
Total Vaccinated Cohort Extension M24	**307**		**100**	**186**		**64**		**57**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	5	10		2	5	3	3	0	2
Study vaccine dose not administered according to protocol (code 1070)	0	2		0	2	0	0	0	0
Initially seropositive or initially unknown antibody status (code 2020)	26	44		17	30	8	12	1	2
Administration of any medication forbidden by the protocol (code 2040)	1	1		0	0	1	1	0	0
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	4	5		3	3	1	2	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	1	3		1	3	0	0	0	0
Essential serological data missing (code 2100)	0	28		0	16	0	7	0	5
Protocol violation (inclusion/exclusion criteria) for extension Month 24 (code 5010)	0	1		0	1	0	0	0	0
Concomitant infection not related to vaccine (code 5070)	1	1		1	1	0	0	0	0
Essential serological data missing for extension Month 24 (code 5100)	0	2		0	1	0	0	0	1
ATP Cohort for immunogenicity	**269**		**87.6**	**162**		**51**		**56**	

Pooled = pooled lots (b(4)) (15 - 25 years old); -b(4)- = DHPV007A9 (-b(4)-) (15 - 25 years old)
[10-14] = DHPVA004A (b(4)) (10 - 14 years old)
Note: Subjects may have more than one elimination code assigned
Note: code 1040, 1070, 2020, 2040, 2080, 2090 and 2100 were attributed at the Month 7 database freeze and kept through the study; code 5000, 5010, 5070 and 5100 were attributed at the Month 24 database freeze.
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated cohort
Source: STN 125259/30, CSR 012, Month 24 Report, Table 4, p. 44

Fatal events: There were no fatalities during the extension follow-up period from Month 12 to Month 24.

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study: No subjects were withdrawn from the extension follow-up period from Month 12 to Month 24 dues to AEs or SAEs.

Medically significant adverse events: During the Month 12 to Month 24 period, 18 subjects reported 19 medically significant AEs. The percentages of subjects reporting at least one medically significant AE were as follows: 6.5% in the pooled b(4) lots group, 6.3% in the --b(4)-- group and 3.5% in the b(4) group (subjects aged 10 - 14 years). (See Table 292)

Table 292-Study EXT HPV-012: Percentage of subjects reporting the occurrence of medically significant AEs classified by MedDRA Primary System Organ Class and Preferred Term, during the extension follow-up period (Month 12 to Month 24) [Total Vaccinated cohort Extension Month 24]

		Pooled N = 186				(b)(4) N = 64				[10-14] N = 57			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one medically significant AE		12	6.5	3.4	11.0	4	6.3	1.7	15.2	2	3.5	0.4	12.1
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	0	0.0	0.0	2.0	1	1.6	0.0	8.4	0	0.0	0.0	6.3
Infections and infestations (10021881)	Gynaecological chlamydia infection (10053028)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
	Herpes simplex (10019948)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
	Infectious mononucleosis (10021914)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
	Pyelonephritis (10037596)	0	0.0	0.0	2.0	2	3.1	0.4	10.8	0	0.0	0.0	6.3
Injury, poisoning and procedural complications (10022117)	Concussion (10010254)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
Investigations (10022891)	Smear cervix abnormal (10041206)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
Nervous system disorders (10029205)	Epilepsy (10015037)	0	0.0	0.0	2.0	0	0.0	0.0	5.6	1	1.8	0.0	9.4
Pregnancy, puerperium and perinatal conditions (10036585)	Premature separation of placenta (10036608)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
Psychiatric disorders (10037175)	Bulimia nervosa (10006550)	0	0.0	0.0	2.0	1	1.6	0.0	8.4	0	0.0	0.0	6.3
	Depression (10012378)	2	1.1	0.1	3.8	0	0.0	0.0	5.6	0	0.0	0.0	6.3
Reproductive system and breast disorders (10038604)	Cervical dysplasia (10008263)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
	Endometriosis (10014778)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
	Ovarian cyst (10033132)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	1	1.8	0.0	9.4
Skin and subcutaneous tissue disorders (10040785)	Dermatitis (10012431)	1	0.5	0.0	3.0	0	0.0	0.0	5.6	0	0.0	0.0	6.3

Pooled = pooled lots (b(4)) (15 - 25 years old)
--b(4)-- = DHPV007A9 (--b(4)--) (15 - 25 years old)
[10-14] = DHPVA004A (b(4)) (10 - 14 years old)
At least one medically significant AE = at least one medically significant AE experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the medically significant AE
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/30, CSR 012, Month 24 Report, Table 14, p. 60

New Onset of Chronic Diseases: During the Month 12 to Month 24 period, 2 NOCDs reported by 2 subjects were identified (asthma). (See Table 293).

Immunogenicity Results

HPV-16/18 antibody response in serum samples at Month 24: At Month 24 (and at Month 18 for the 7 subjects for whom data have been collected), all subjects in all groups were still seropositive for anti-HPV-16 and anti-HPV-18 antibodies. Similar to what was observed during the primary study (Month 7), the subjects aged 10 -14 years had higher GMTs as compared to the subjects aged 15 - 25 years at Month 24. Similar GMTs and seropositivity rates were noted for subjects who received either the --b(4)-- or b(4) formulation. (Source: STN 125259/30, CSR 012, Month 24 Report, Table 6 and 7, p. 47-48, not shown here).

CVS antibody levels: Twenty-four months after the first vaccine dose, anti-HPV-16 antibodies in CVS were detected in 85.5% and 69.2% in the pooled b(4) lots group and the -b(4)- group, respectively. Similarly, anti-HPV-18 antibodies in CVS were detected in 72.7% and 69.2% in the --b(4)-- lots group and the -b(4)- group, respectively. One subject aged 10 - 14 years was analyzed for the presence of anti-HPV-16/18 antibodies. For this subject, anti-HPV-16 and anti-HPV-18 antibodies were detected. (Source: STN 125259/30, CSR 012, Month 24 Report, Table 8, p. 52, not shown here). Subjects with no detectable anti-HPV-16 and anti-HPV-18 antibodies in their CVS samples had lower GMT values post-vaccination than subjects with demonstrated antibody transudation. (Source: STN 125259/30, CSR 012, Month 24 Report, Table 9 and 10, p. 53-54, not shown here).

- **Correlation between anti-HPV-16 and anti-HPV-18 antibody titers in serum and in CVS samples:** The correlations between anti-HPV-16 and anti-HPV-18 antibody titers in serum and CVS samples with Hemastix lower than 80 erythrocytes per µL were as follows: correlation coefficients were equal to 0.9324 for HPV-16 and 0.9088 for HPV-18 (Month 24). (Source: STN 125259/30, CSR 012, Month 24 Report, Figure 3 and 4, p. 55-56, not shown here).

Safety Results

Total Vaccinated cohort Extension Month 24 analysis [Month 12 - Month 24]

Serious adverse events: Three subjects reported four SAEs during the Month 12 to Month 24 period. 1.6% of subjects in the pooled b(4) group and -b(4)- group had an SAE. No SAEs occurred in the 10-14 year old age group.

Table 291-Study EXT HPV-012, Subjects with SAE (Month 12-24)
(CBER generated)

Case number	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to vaccination per investigator
B0419578A, -b(4)-	Prolonged QT interval (Cardiac arrest, pacemaker)	12 months after dose 3	7 days	Resolved	Unrelated
B0478569A, --b(4)--	Pyelonephritis	7 months after dose 3	1 week	Resolved	Unrelated
B0478574A, -b(4)-	Partial placental abruption (baby born by C-section prematurely at 30 weeks, discharged after respiratory assistance and appaopriate NICU care)	23 months after dose 3 (became pregnant 18 months after dose 3)	1 day	Resolved	Unrelated
B0478578A, -b(4)-	Endometriosis Abdominal pain due to dehisce ovarian cyst	10 months after dose 3 13 months after dose 3	1 day 1 day	SAEs resolved but chronic conidtoin	Unrelated

Reviewer's Comment: None of these events are temporally related to vaccination, and other etiologies are likely causes. It has been reported that there are 450,000 sudden cardiac deaths in the United States, and the leading cause is an inherited disorder of QT interval prolongation. The length of time after vaccination makes a relationship of this event to vaccination unlikely. Stressful situations and caffeine have been known to trigger the events.

Table 295-Study EXT HPV-012: Percentage of subjects reporting the occurrence of Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (Month 0 to Month 24) [Tota (b)(4) inated cohort]

		Pooled N = 457				(b)(4) N = 154				[10-14] N = 158			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one SAE		9	2.0	0.9	3.7	1	0.6	0.0	3.6	1	0.6	0.0	3.5
Cardiac disorders (10007541)	Myocarditis (10028606)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
	Pericarditis (10034484)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Gastrointestinal disorders (10017947)	Gastric ulcer (10017822)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Infections and infestations (10021881)	Acute sinusitis (10001076)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
	Pyelonephritis (10037596)	0	0.0	0.0	0.8	1	0.6	0.0	3.6	0	0.0	0.0	2.3
Injury, poisoning and procedural complications (10022117)	Heat stroke (10019345)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Metabolism and nutrition disorders (10027433)	Diabetes mellitus insulin-dependent (10012608)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Pregnancy, puerperium and perinatal conditions (10036585)	Abortion threatened (10000242)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
	Premature separation of placenta (10036608)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Psychiatric disorders (10037175)	Depression (10012378)	0	0.0	0.0	0.8	0	0.0	0.0	2.4	1	0.6	0.0	3.5
Reproductive system and breast disorders (10038604)	Endometriosis (10014778)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
	Ovarian cyst (10033132)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3

Pooled = pooled lots (b(4)) (15 - 25 years old)
--b(4)-- = DHPV007A9 (--b(4)--) (15 - 25 years old)
[10-14] = DHPVA004A (b(4)) (10 - 14 years old)
At least one SAE = at least one SAE experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the SAE
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/30, CSR 012, Month 24 Report, Table 19, p. 64

Medically significant adverse events: During the entire study period (Month 0 to Month 24), a total of 90 subjects reported 126 medically significant AEs. The percentages of subjects reporting at least one medically significant AE were similar in all groups: 12% in the pooled b(4) lots group, 13% in the --b(4)-- group and 9.5% in the b(4) group (subjects aged 10 - 14 years). The most frequent medically significant AEs reported were cystitis, depression, asthma, pharyngolaryngeal pain and acne. (Source: STN 125259/30, CSR 012, Month 24 report, Table 21, p. 66-69, not shown here).

New Onset of Chronic Diseases: During the entire study period (Month 0 to Month 24), 17 events were identified as NOCDs. The most frequent reported NOCDs were hypothyroidism, immune system disorders (hypersensitivity, seasonal allergy), asthma, rhinitis allergic and urticaria.

Table 296-Study EXT HPV-012: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (Month 0 to Month 24) [Total Vaccinated cohort]

		Pooled N = 457				(b)(4) N = 154				[10-14] N = 158			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one NOCD		16	3.5	2.0	5.6	0	0.0	0.0	2.4	1	0.6	0.0	3.5
Endocrine disorders (10014698)	Hypothyroidism (10021114)	2	0.4	0.1	1.6	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Immune system disorders (10021428)	Hypersensitivity (10020751)	2	0.4	0.1	1.6	0	0.0	0.0	2.4	0	0.0	0.0	2.3
	Seasonal allergy (10048908)	2	0.4	0.1	1.6	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Metabolism and nutrition disorders (10027433)	Diabetes mellitus insulin-dependent (10012608)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	3	0.7	0.1	1.9	0	0.0	0.0	2.4	1	0.6	0.0	3.5
	Rhinitis allergic (10039085)	2	0.4	0.1	1.6	0	0.0	0.0	2.4	0	0.0	0.0	2.3
Skin and subcutaneous tissue disorders (10040785)	Urticaria (10046735)	2	0.4	0.1	1.6	0	0.0	0.0	2.4	0	0.0	0.0	2.3
	Urticaria chronic (10052568)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3
	Urticaria localised (10060771)	1	0.2	0.0	1.2	0	0.0	0.0	2.4	0	0.0	0.0	2.3

Pooled = pooled lots (b(4)) (15 - 25 years old)
--b(4)-- = DHPV007A9 (--b(4)--) (15 - 25 years old)
[10-14] = DHPVA004A (b(4)) (10 - 14 years old)
At least one NOCD = at least one NOCD experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOCD
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/30, CSR 012, Month 24 report, table 23, p. 71

STUDY HPV-012 CONCLUSIONS (MONTH 24):

- Immune responses (anti-HPV-16 and anti-HPV-18 IgG by ELISA) were found to be non-inferior in females 10-14 years of age as compared to females 15-25 years of age (by seropositvity rates and GMT ratios).
- Immune responses (anti-HPV-16 and anti-HPV-18 IgG measured by ELISA) elicited by HPV 16/18 vaccine when manufactured by different methods (--b(4)-- and b(4) and when b(4) lots were similar (seropositivity rates and GMT ratios).
- Immune response (anti-HPV-16 and anti-HPV-18 IgG by ELISA) persisted out to Month 24 in all groups. The 10-14 year old subjects had higher IgG levels at Month 24 as compared to subjects 15-25 years of age in either formulation group.
- Anti-HPV-16 and anti-HPV-18 anitbodies were detected in the CVS and correlated with serum IgG levels.
- SAEs, NOCDs and MsAEs were similar across groups (although a very small number of such events occurred through Month 24).

8.9 HPV-014 (Trial #9): A phase III, open, age-stratified study to assess the immunogenicity and safety of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a three-dose schedule (0, 1, 6 month) in healthy female subjects aged 15 – 55 years.

Study Dates: 10/7/04-7/12/05

Study Sites: 6 centers in 2 countries (3 in Germany and 3 in Poland).

STUDY OBJECTIVES

Primary Objective: To demonstrate non-inferiority of the immune response to the HPV-16/18 vaccine components at Month 7 between young women 15 – 25 years of age and women 26 – 45 years of age, with respect to seroconversion rates.

Criteria for non-inferiority: for both serotypes, the upper limit of the two-sided 95% confidence interval (CI) of the difference between the percentage of subjects who seroconverted in the 15 – 25 years age group versus the 26 – 45 years age group is below 10%.

Reviewer's Comment: As the immunogenicity assessments and comparisons in this protocol did not not contribute to the ultimate decision-making process concerning licensure of the vaccine in females 10-25 years of age, the review of this protocol will focus on the safety data.

Secondary Objectives

- To demonstrate non-inferiority of the immune response to the HPV-16/18 vaccine components at Month 7 between young women 15 – 25 years of age and women 46 –55 years of age, with respect to seroconversion rates.*

Criteria for non-inferiority: for both serotypes, the upper limit of the two-sided 95% CI of the difference between the percentage of subjects who seroconverted in the 15 – 25 years age group versus the 46 – 55 years age group is below 10%.

* In all comparisons, the 15-25 years age group was considered as the reference group.

- To assess geometric mean titers (GMTs) to the HPV-16/18 vaccine components in all age groups at each time point.
- To assess the seroconversion rates in all age groups at Month 2 and Month 7.

Reviewer's Comment: As the immunogenicity assessments and comparisons in this protocol did not not contribute to the ultimate decision-making process concerning licensure of the vaccine in females 10-25 years of age, the review of this protocol will focus on the safety data.

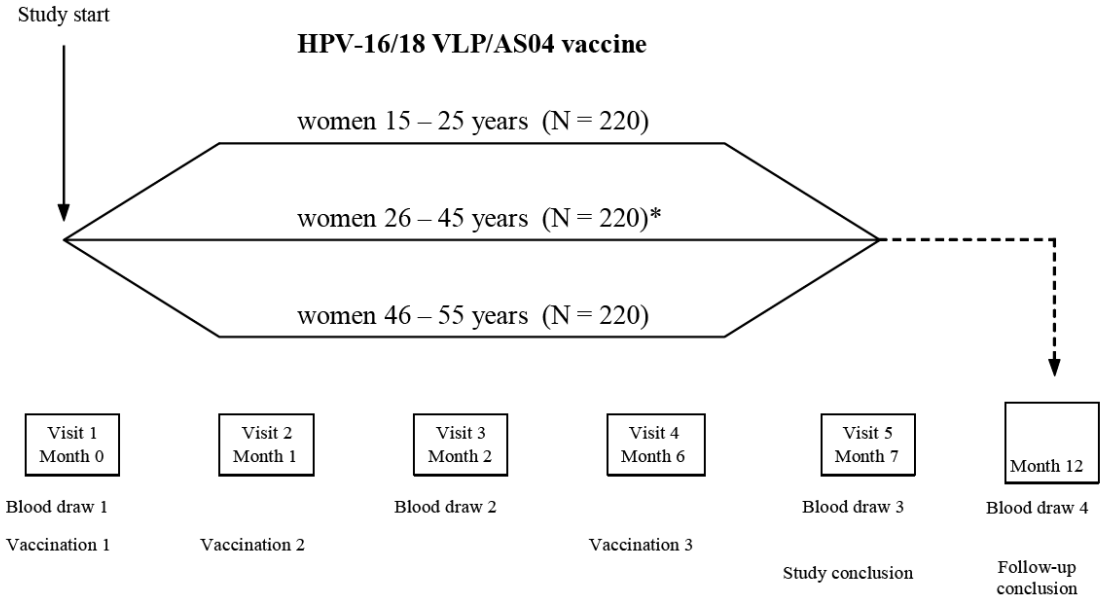
- To assess the safety and reactogenicity of the HPV vaccine in all age groups after each

Study Design

Experimental design: Phase III, open, multicentre study with three parallel groups:

- women 15 – 25 years of age (N=220)
- women 26 – 45 years of age (N=220) (stratified into 26-35 years of age [N=110] and 36-45 years of age [N=110]
- women 46 – 55 years of age (N=220)

Figure 34-Study HPV-014: Overview of Study Design



*This group was stratified into two equally-sized age strata: 26 – 35 years of age (N=110) and 36 – 45 years of age (N=110).

Procedures:

- All women received HPV-16/18 vaccine, three doses of vaccine administered intramuscularly according to a 0, 1, 6-month schedule.
- Duration of the study for each subject: 12 months.
- Five scheduled visits per subject: at Month 0, 1, 2, 6 and 7 + long-term follow-up visit at Month 12.
- Blood samples were collected from all subjects at visits 1, 3 and 5 (i.e. at Month 0, 2 and 7) and are going to be collected at the follow-up visit (i.e. at Month 12) to evaluate immunogenicity.
- Safety and reactogenicity monitoring:
  - Solicited signs and symptoms were self-reported in all subjects, using diary cards, on the day of vaccination and six follow-up days.
  - Unsolicited signs and symptoms were reported in all subjects within 30 days after each vaccination.
  - SAEs were reported in all subjects throughout the study period (to be reported up to the Month 12 follow-up visit).
  - New onset chronic diseases and other medically significant conditions were reported in all subjects throughout the study period (to be reported up to the Month 12 follow up visit), regardless of causal relationship to vaccination and intensity.

The sponsor presented all safety and immunogenicity data collected up to Visit 5 (Month 7), and follow-up safety and immunogenicity in additional reported.

Table 297-Study HPV-014: List of study procedures

Visit Timing Sampling time point	VISIT 1 Month 0 Pre-vacc	VISIT 2 Month 1 Post vacc I	VISIT 3 Month 2 Post vacc II	VISIT 4 Month 6 Post vacc II	VISIT 5 Month 7 Post vacc III	FOLLOW-UP VISIT* Month 12 Post vacc III
Informed consent/assent	●					
Check inclusion criteria	●					
Check exclusion criteria	●					
Check elimination criteria		●	●	●	●	●
Check contraindications		●		●		
Record any concomitant medication/vaccination	●	●	●	●	●	
Medical history	●					
History-directed physical examination	●					
Collect demographic data	●					
Urine sample for pre-vaccination pregnancy test	●	●		●		
Pre-vaccination body temperature	●	●		●		
Blood sampling: for antibody determination (5ml)	●		●		●	●
Treatment number allocation	●					
Vaccination	●	●		●		
Distribution of diary cards for post-vaccination recording of solicited symptoms (Days 0 – 6) and unsolicited symptoms (Days 0 – 29)	○	○		○		
Return of diary cards		○	○		○	
Diary card transcription		●	●		●	
Reporting of all pregnancies and pregnancy outcomes		●	●	●	●	●
Reporting of SAEs, new onset chronic diseases and other medically significant conditions	●	●	●	●	●	●
Study conclusion					●	
Follow-up conclusion						●

● is used to indicate a study procedure that required documentation in the individual eCRF.
○ is used to indicate a study procedure that did not require documentation in the individual eCRF.
* The results of the follow-up visit at Month 12 will be presented in an annex report.
Source: STN 125259/0, CSR 014, Table 1, p. 31

Selection of study population: This study was conducted in 6 centers in Germany and Poland. The target was to enrol 660 women, aged between 15 and 55 years.

Inclusion criteria:

- Healthy females 15 and 55 years of age
- Written informed consent from subject and/or parent/guardian (assent from minor subjects)
- Subject must have a negative urine pregnancy test.
- Subject had to be of non-childbearing potential or agree to use appropriate contraception from 30 days before to 2 months after vaccination.

Exclusion criteria

- Pregnant or breastfeeding
- Woman planning to become pregnant, likely to become pregnant within 8 months (< 2 months after dose 3)
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period (up to Month 12).
- Chronic administration (>14 days) immune-modifying drugs within six months prior to the first vaccine dose, or planned administration during the study period.

- Planned administration/administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after (i.e. days 0 – 29) the first dose of study vaccine. (Allowable intervals for routinely administered vaccines provided).
- Previous administration of MPL or AS04 adjuvant
- Previous vaccination against HPV
- Any medically diagnosed or suspected immunodeficient condition
- History of allergic disease, suspected allergy or reactions likely to be exacerbated by any component of the study vaccine, e.g. aluminium, MPL.
- Hypersensitivity to latex (found in syringe-tip cap and plunger).
- Known acute or chronic, clinically significant neurologic, hepatic or renal functional abnormality
- History of chronic condition(s) requiring treatment such as cancer, chronic hepatic or kidney disease(s), diabetes or autoimmune disease.
- Administration of immunoglobulins and/or any blood product within three months preceding the first dose of study vaccine or planned administration during the study period.
- Acute disease at the time of enrolment. Acute disease was defined as the presence of a moderate or severe illness with or without fever. Enrolment had to be deferred until condition was resolved. All vaccines could be administered to persons with a minor illness such as diarrhoea or mild upper respiratory infection with or without low-grade febrile illness, i.e. oral/axillary temperature <37.5°C (99.5°F).

Table 298-Study HPV-014: Vaccine Components

Vaccine	Formulation Each dose (0.5 ml) contains:	Lot number	Presentation	Injectable volume	Number of doses
Candidate HPV vaccine: HPV-16/18 L1/AS04	20 μg HPV-16 L1 VLP 20 μg HPV-18 L1 VLP 50 μg MPL 500 μg aluminium as $Al(OH)_3$	DHPVA004A (expiry date: 31 May 2007)	Liquid in pre-filled syringes	0.5 ml	3

Source: STN 125259/0, CSR 014, Table 3, p. 37

Treatment allocation and randomization: Approximately 660 healthy female subjects were to be enrolled: 220 women aged 15 – 25 years, 220 women aged 26 – 45 years and 220 women aged 46 – 55 years. The second group was stratified into two equally-sized age strata: 26 – 35 years of age (N=110) and 36 – 45 years of age (N=110). All subjects received the candidate HPV-16/18 vaccine administered according to a three-dose schedule (0, 1, 6 months). Treatment number allocation at the investigator site was performed using a central call-in system on internet (-b(4)-). There was no randomization.

Blinding: Blinding was not applicable since this was an open study. Subjects were allocated to each of the three study groups according to their age.

Assessment of immunogenicity variables
Laboratory assays and time points: The quantitative anti-HPV-16 and anti-HPV-18 assays were to be run by GSK and assay cut-offs were as previously noted (see HPV-008). Priority was given to running anti-HPV-16 IgG.

Assessment of safety variables: The procedures were similar to those described in study HPV-008.

STATISTICAL CONSIDERATIONS

Primary endpoints

- Anti-HPV-16 and anti-HPV-18 seroconversion rates assessed by ELISA at Month 7 in women 15 – 25 years of age and women 26 – 45 years of age.

Secondary endpoints

- Anti-HPV-16 and anti-HPV-18 seroconversion rates assessed by ELISA at Month 7 in women aged 46 – 55 years.
- Anti-HPV-16 and anti-HPV-18 antibody titers assessed by ELISA at each timepoint in all subjects.
- Anti-HPV-16 and anti-HPV-18 seroconversion rates assessed by ELISA at Month 2 and Month 12 in all subjects.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms, and occurrence and intensity of solicited local symptoms within 7 days (days 0 – 6) after each vaccination.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days (days 0 – 29) after each vaccination.
- Occurrence and relationship to vaccination of SAEs throughout the study period (up to Month 7).
- Occurrence of new onset chronic diseases and other medically significant conditions prompting emergency room visits or physician visits that are not related to common diseases throughout the study period (up to Month 7), regardless of causal relationship to vaccination and intensity.

Study cohorts/data sets analyzed

Total Vaccinated cohort: The Total Vaccinated cohort included all vaccinated subjects for whom data were available.

- The **Total analysis of safety** included all subjects with at least one vaccine administration documented. This was considered as the primary data set for the analysis of safety.
- The **Total analysis of immunogenicity** included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

According-To-Protocol (ATP) cohort for analysis of immunogenicity: The ATP cohort for analysis of immunogenicity included all evaluable subjects for whom data concerning immunogenicity endpoint measures were available. The ATP cohort was considered as the primary data set for the analysis of immunogenicity.

According-To-Protocol (ATP) cohort for analysis of safety: This cohort included subjects who had received at least one dose of study vaccine; with sufficient data to perform an analysis of safety (at least one dose with safety follow-up); for whom administration site of study vaccine was known; and who had not received a vaccine not specified or forbidden in the protocol.

Analysis of immunogenicity: The primary analysis was based on the ATP cohort for analysis of immunogenicity. A second analysis based on the Total Vaccinated cohort was performed to complement the ATP analysis. The analyses were conducted in all subjects as well as in subjects seronegative for both antigens and in subjects seropositive for at least one of the two antigens.

Primary objective:

- The primary objective was to demonstrate non-inferiority of the immune response to the HPV vaccine at Month 7 between young women 15 –25 years of age and women 26 – 45 years of age, with respect to seroconversion rates.

Secondary objectives:

- To demonstrate that the 46 – 55 years age group was non-inferior to the 15 – 25 years age group in terms of immunogenicity when receiving the same HPV vaccine.

Analysis of safety

The **primary analysis** was based on the Total Vaccinated cohort. A **second analysis based on the ATP safety cohort** was performed to complement the Total analysis. The two cohorts differed by only 0.8% (5 subjects excluded from the ATP safety cohort), so the results are just about the same. The results for the TVC are presented here.

Reviwer's Comment: As safety was followed over time, the definition of medically significant AEs has changed slightly in that it evolved to include serious adverse events (SAEs) that are not related to common diseases and the category 'Vulvitis' was no longer considered a separate category. (Source: STN 125259/0, CSR 014, Annex 2, Supplement 27, p. 56, not shown here)

Interim analysis: As planned in the protocol, an interim analysis was performed on the 6/6/05 by an independent statistician. Its objective was to provide the clinical development team with descriptive statistics of the immune response after the second vaccine dose. No inferential statistics were done.

Protocol amendments/modifications: The protocol was not amended.

RESULTS

Study Population Results

Study dates: The first volunteer was enrolled in the study on 10/7/04 and the last study visit was on 7/12/05.

Number and distribution of subjects

- 667 subjects were enrolled in the study and 666 subjects were vaccinated (229, 226 and 211 subjects in groups 1, 2 and 3 respectively).
- The ATP safety cohort included 661 subjects (228, 223 and 210 subjects in groups 1, 2 and 3, respectively).
- The ATP immunogenicity cohort included 644 subjects (224, 219 and 201 subjects in groups 1, 2 and 3, respectively).
- The vaccinated cohort, being seronegative both for HPV-16 and HPV-18 before vaccination, included 481 subjects (190, 153 and 138 subjects in groups 1, 2 and 3, respectively). The vaccinated cohort, being seropositive either for HPV-16 or HPV-18 before vaccination, included 187 subjects (40, 73 and 74 subjects in groups 1, 2 and 3, respectively).

Table 299-Study HPV-014: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

Group	Total			[15-25]		[26-45]		[46-55]	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total enrolled cohort	667								
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1							
Total vaccinated cohort	**666**		**100**	**229**		**226**		**211**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	2	2		1	1	1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	3	3		0	0	2	2	1	1
ATP safety cohort	**661**		**99.2**	**228**		**223**		**210**	
Administration of any medication forbidden by the protocol (code 2040)	3	4		1	1	1	2	1	1
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	2	2		0	0	1	1	1	1
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	5	5		1	1	1	1	3	3
Essential serological data missing (code 2100)	7	8		2	3	1	1	4	4
ATP immunogenicity cohort	**644**		**96.7**	**224**		**219**		**201**	

[15-25] = HPV-16/18 VLP (15 years≤Age≤25 years); [26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Source: STN 125259/0, CSR 014, Table 10, p. 53

The number of subjects vaccinated, completed, and withdrawn with reasons for withdrawal are noted in Table 300.

Table 300-Study HPV-014: Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total Vaccinated Cohort)

	Group			
	[15-25]	[26-45]	[46-55]	Total
Number of subjects vaccinated	229	226	211	666
Number of subjects completed	220	221	204	645
Number of subjects withdrawn	9	5	7	21
Reasons for withdrawal :				
Serious Adverse Event	1	0	0	1
Non-serious adverse event	1	1	1	3
Protocol violation	0	0	0	0
Consent withdrawal (not due to an adverse event)	0	0	2	2
Migrated/moved from study area	0	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	4	1	3	8
Lost to follow-up (subjects with complete vaccination course)	0	2	0	2
Others	3	1	1	5

[15-25] = HPV-16/18 VLP (15 years≤Age≤25 years); [26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Source: STN 125259/0, CSR 014, Table 14, p. 57

≥96.2% of subjects in any group received all 3 doses of vaccine.

Demographics: The study was conducted in Germany and Poland. In the ATP cohort for immunogenicity, with the exception of one subject who was black, all the other subjects were white, with a mean age of 34.8 years (ranging from 15 to 55 years). Approximately the same proportions of subjects were smokers (28.3 to 32.8%), exsmokers (7.6 to 15.4%) or non-smokers (51.7 to 61.2%) in the 3 age groups.

Table 301-Study HPV-014: Summary of demographic characteristics (ATP cohort for immunogenicity)

	[15-25]	[26-45]	[46-55]	Total
Number of female subjects enrolled	224	219	201	644
Age				
Mean (SD)	20.8 (2.67)	35.5 (5.95)	49.6 (2.82)	34.8 (12.4)
Median	21.0	35.0	49.0	34.0
Min-Max	15-25	26-45	46-55	15-55
Race/Ethnicity				
White/Non-Hispanic	224 (100%)	218 (99.5%)	201 (100%)	643 (99.8%)
Black	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)

[26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Source: STN 125259/0, CSR 014, Table 17, p. 60

Reviewer's Comment: The ethnicity of the subjects is not diverse due to the limitation of subjects from two countries in which this study was conducted.

In the third group, 53.2% of subjects were post-menopausal. In the first group, 2.7% of subjects were pre-menarcheal. The percentage of subjects taking hormonal contraceptives was 77.5%, 59.0% and 41.5% in groups 1, 2 and 3, respectively.

The demographic characteristics of the Total Vaccinated cohort were similar to those of the ATP Cohort for immunogenicity. (Source: STN 125259/0, CSR 014, Supplement 4, p. 96, not shown here).

Safety Results: Compliance in terms of administration of doses according to the protocol and returning local and general symptom sheets was ≥ 98.7 in all three groups. (Source: STN 125259/0, CSR 014, Table 23, p. 68, not shown here).

Data sets analyzed: The primary analysis was based on the Total Vaccinated cohort. There was little difference in the number of subjects analyzed in the ATP cohort, so only the TVC analyses are presented.

SAFETY RESULTS
Total vaccinated cohort analysis
Overall incidence of adverse events in 30 days after vaccination are presented in Table 302.
Reviewer's Comment: There was a decrease in the proportion of subjects with any symptom in this time period with increasing age.

Table 302-Study HPV-014: Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) postvaccination period overall/subject (Total Vaccinated Cohort)

	Any symptom		General Symptoms		Local Symptoms	
Group	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall/subject						
15-25	225/227	99.1%	197/227	86.8%	220/227	96.9%
26-45	216226	95.6%	174/226	77.0%	214/226	94.7%
46-55	182/207	87.9%	140/207	67.6%	178/207	86.0%

[15-25] = HPV-16/18 VLP (15 years≤Age≤25 years); [26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: STN 125259/0, CSR 014, Table 24, p. 70

Reviewer's Comment: In general, the oldest group was found to have the lowest proportion of subjects with any symptom, with a general symptom, and with a local symptom. When considered **overall/subject,** the oldest group had lower proportions of subjects with any symptom, general symptom, and local symptoms when compared to the youngest group. The proportions of symptoms are not different between the youngest group and middle group. A lower proportion of subjects in the oldest group had general symptoms and local symptoms compared to the middle group, but not for any symptom.

Overall, grade 3 solicited symptoms were reported after 4.4 to 6.6% of doses. No major differences were noted between the three doses. The percentage of subjects reporting grade 3 solicited symptoms was approximately the same in the three age groups (12.1 to 15.0%). The results are presented overall/subject.

Table 303-Study HPV-014: Incidence of grade 3 symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

	Any symptom		General Symptoms		Local Symptoms	
Group	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall/subject						
15-25	34/227	15.0%	20/227	8.8%	24/227	10.6%
26-45	30/336	13.3%	16/226	7.1%	20/226	8.8%
46-55	25//207	12.1%	16/207	7.7%	12/207	5.8%

Source: STN 125259/0, CSR 014, Table 25

Reviewer's Note: There were few Grade 3 adverse events after any dose or overall/dose. When considering events overall/subject, a somewhat higher proportion of the youngest subjects had any symptom as compared to the other groups, and this appears due to a higher proportion of local symptoms. However, there were not apparent statistically different proportions when comparing 95% CIs around the proportions.

GSK reports that there were no major differences were reported between subjects who were seronegative for both antigens or seropositive for at least one antigen before receiving the vaccine.

Solicited local adverse events:

- Pain was the most frequently reported solicited local symptom by 82.6 to 96.9% of subjects. Grade 3 pain was reported by 4.3 to 10.1% of subjects.
- Redness was reported by 48.8 to 58.6% of subjects. Grade 3 redness (> 50 mm) was reported by 0.0 to 2.7% of subjects.

- Swelling was reported by 40.1 to 44.2% of subjects. Grade 3 swelling (> 50 mm) was reported by 0.5 to 1.3% of subjects.

There was an age-dependent decrease in the frequency of reporting for pain and redness. No major differences were noted between doses except for swelling and redness for which frequency tended to increase from dose 1 to dose 3. The frequency of pain decreased after dose 1 and remained relatively stable thereafter. The results are presented overall/subject in Table 304 below.

Table 304-Study HPV-014: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Vaccinated Cohort)

	15-25		26-45		46-55	
Group	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall/subject						
Pain-						
All	220/227	96.9%	210226	92.9%	171/207	82.6%
Grade 3	23/227	10.1%	15/226	6.6%	9/207	4.3%
Redness (mm) -						
All	133/227	58.6%	126/226	55.8%	101/207	48.8%
>50	0/227	0.0%	6/226	2.7%	2/207	1.0%
Swelling (mm)-						
All	96/227	42.3%	100/226	44.2%	83/207	40.1%
>50	3/227	1.3%	3/226	1.3%	1/207	0.5%

[15-25] = HPV-16/18 VLP (15 years≤Age≤25 years); [26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
Source: STN 125259/0, CSR 014, Table 25, p. 72-73

Reviewer'e Comment: The youngest age group had the highest proportion of subjects with pain in the 7 days after any dose, overall/dose and overall/subject when compared to the oldest group. There was no statistical difference in the redness and pain among the three groups. There were no apparent statistical differences for Grade 3 solicite local adverse events.

The mean number of days with redness or swelling, during the solicited post-vaccination period, tended to increase slightly with age. Redness lasted a mean of 2.9, 3.0 and 3.3 days in groups 1, 2 and 3, respectively. Swelling lasted a mean of 3.0, 3.3 and 3.6 days in groups 1, 2 and 3, respectively. Pain lasted a mean of 2.9, 3.0 and 2.8 days in groups 1, 2 and 3, respectively. (Source: STN 125259/0, CSR 014, Supplement 44, p. 143-145, not shown here).

The mean number of days with grade 3 local solicited symptoms in any group was noted to be within 1-3 days (vast majority 1-2 days except for 3 days grade 3 redness in 2 subjects in the 46-55 year old age group). (Source: STN 125259/0, CSR 014, Supplement 45, p. 146, not shown here).

Solicited general adverse events: Fatigue, headache and myalgia were the most frequently reported solicited general symptoms. The results are presented overall/subject in Table 305.

- There was an age-dependent decrease in the frequency of reporting for fatigue, fever, headache, myalgia, rash and urticaria.
- No major differences were noted as a function of the dose in the three age groups.
- Overall, the mean number of days with general symptoms, during the solicited postvaccination period, varied between 1.5 and 2.6 days. The mean number of days with grade 3 symptoms varied between 1 and 2 days.

Table 305-Study HPV-014: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

	15-25		26-45		46-55	
Group	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Overall/subject						
Arthralgia						\22.7%
All	45/227	19.8%	43/226	19.0%	47/227	1.0%
Grade 3	1/227	0.4%	3/226	1.3%	2/227	
Fatigue						
All	128/227	56.4%	116/226	51.3%	81/207	39.1%
Grade 3	5/227	2.2%	2/226	0.9%	4/207	1.9%
Fever (° C) Axilla						
All	21/227	9.3%	19/226	8.4%	5/207	2.4%
>39.0	0/227	0.0%	1/226	0.4%	0/207	0.0%
Gastrointestinal						
All	51/227	22.5%	33/226	14.6%	31/207	15.0%
Grade 3	1/227	0.4%	3/226	1.3%	3/207	1.4%
Headache						
All	123/227	54.2%	100/226	44.2%	82/207	39.6%
Grade 3	10/227	4.4%	5/226	2.2%	6/207	2.9%
Myalgia						
All	126/227	55.5%	97/226	42.9%	83/207	40.1%
Grade 3	8/227	3.5%	9/226	4.0%	4/207	1.9%
Rash						
All	16/227	7.0%	14/226	6.2%	7/207	3.4%
Grade 3	0/227	0.0%	0/226	0.0%	0/207	0.0%
Urticaria						
All	10/227	4.4%	7/226	3.1%	3/207	1.4%
Grade 3	0/227	0.0%	0/226	0.0%	0207	0.0%

[15-25] = HPV-16/18 VLP (15 years≤Age≤25 years); [26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
Source: STN 125259/0, CSR 014, Table 26, p. 75-77

Reviewer's Comment: The oldest group had the lowest proportions of subjects with fatigue, fever, headache, and myalgia, but the 95% CIs around the proportions overlap for the middle and youngest group. There was no apparent difference in the proportions of subjects with Grade 3 solicited general adverse events when different groups were compared.

Unsolicited adverse events: The percentage of subjects reporting unsolicited symptoms within 30 days post-vaccination tended to be slightly lower in the oldest group (group 3). The most frequent unsolicited symptoms were injection site reactions (hemorrhage, pruritus, rash, edema). See Table 306.

Table 306-Study HPV-014: Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class, within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated Cohort)

	15-25 N=229	26-45 N=226	46-55 N=211
Primary System Organ Class	**n (%)**	**n (%)**	**n (%)**
At least one symptom	**43 (18.8%)**	**46 (20.4%)**	**28 (13.3%)**
Blood and lymphatic system disorders	2 (0.9%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	1 (0.4%)	1 (0.5%)
Ear and labyrinth disorders	2 90.9%)	0 (0.0%)	1 (0.5%)
Endocrine disorders	0 (0.0%)	0 (0.0%)	1 (0.5%)
Gastrointestinal disorders	3 (1.3%)	6 (2.7%)	2 90.9%)
General disorders and administration site conditions	7 (3.1%)	16 (7.1%)	5 (2.4%)
Infections and infestations	24 (10.5%)	16 (7.1%)	15 (7.1%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (0.4%)	0 (0.0%)
Investigations	0 (0.0%)	1 (0.4%)	0 (0.0%)
Metabolism and nutrition disorders	1 (0.4%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	1 (0.4%)	2 (0.9%)	3 (1.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps	1 (0.4%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	3 (1.3%)	4 (1.8%)	1 (0.5%)
Reproductive system and breast disorders	3 (1.3%)	3 (1.3%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	3 (1.3%)	7 (3.1%)	1 (0.5%)
Skin and subcutaneous tissue disorders	4 (1.7%)	3 (1.3%)	1 (0.5%)
Surgical and medical procedures	0 (0.0%)	1 (0.4%)	1 (0.5%)

[15-25] = HPV-16/18 (15 years≤Age≤25 years); [26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259/0, CSR 014, Supplement 46, p. 147-148

Overall, six grade 3 unsolicited symptoms were reported by six subjects (2, 0 and 4 subjects in groups 1, 2 and 3, respectively). In group 1, they consisted of upper respiratory tract infection and urticaria (causally related) and in group 3, they consisted of asthenia (causally related), chills (causally related), pharyngitis and tooth extraction. These are presented in Table 307.

Table 307-Study HPV-014: Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated Cohort)

		15-25 N=229	26-45 N=226	46-55 N=211
Primary System Organ Class	**Preferred term**	**n (%)**	**n (%)**	**n (%)**
At least one symptom		2 (0.9%)	0 (0.0%)	4 (1.9%)
General disorders and administration site conditions	Asthenia	0 (0.0%)	0 (0.0%)	1 (0.5%)
	Chills	0 (0.0%)	0 (0.0%)	1 (0.5%)
Infections and Infestations	Pharyngitis	0 (0.0%)	0 (0.0%)	1 (0.5%)
	URI	1 (0.4%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Urticaria	1 (0.4%)	0 (0.0%)	0 (0.0%)
Surgical and medical procedures	Tooth extraction	0 (0.0%)	0 (0.0%)	1 (0.5%)

[15-25] = HPV-16/18 (15 years≤Age≤25 years); [26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259/0, CSR 014, Supplement 48, p. 151

Reviewer's Comment: There were very few unsolicited adverse events grade 3 reported within the 30 days after any vaccination. Chills and asthenia occurred in an older subject and these events were assessed as related to vaccination.

Deaths: There were no deaths.

SAEs: There were 6 SAEs reported by 6 subjects: 3, 1, and 2 subjects in groups 1, 2, and 3 respectively.

Table 308-Study HPV-014, Subjects with SAE (Month 0-7) (CBER generated)

Case number, age	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to vaccination per investigator
0155, 47 years old	Depression (history of depression prior to vaccination)	43 days after dose 3	~11 weeks	Recovered	Unrelated
0704, 27 years old	Optic neuritis	9 days after dose 1	Ongoing (no further vaccinations)	Recovering	Possibly related
1264, 21 years old	Multiple sclerosis	25 days after dose 2	Ongoing	Unresolved	Unrelated
1300, 56 years old	Irritable bowel syndrome	2 months after dose 2	8 months	Recovered	Unrelated
1336, 20 year old	Thermal burn	51 days after dose 2	21 days	Resolved	Unrelated
1597, 20 year bold	Ovarian cyst	7 days after dose 1	2 days	Resolved	Unrelated

Reviewer's Comment: In this study, one case of optic neuritis at 9 days after dose 1 and one case of multiple sclerosis at 25 days after dose 2 were reported. The case of optic neuritis was considered as possibly related to study vaccine by the investigator, although the case of multiple sclerosis was assessed as not related to study vaccine by the study investigator. At the time of the original BLA submission, 6 cases were reported in the HPV-AS04 group as compared to 3 in the pooled control group. Because of this numerical imbalance, further evaluation was requested by CBER. This evaluation included a meta-analysis of events of potential autoimmune nature, as well as review by a panel of neurology experts assembled by GSK. This panel reviewed the cases and concluded there was no increased risk of such events with use of the vaccine. CBER requested a consultation by an expert neurologist for these cases. Although there was no definitive evidence of relationship to vaccine, there was cause for concern, and review of such events in the post-marketing period including in countries where the vaccine was licensed was advised. Four additional cases were reported in the HPV-AS04 group at the time of the final analysis, but the times to events were 2-6 years. The times to event of these additional cases

exceed the proposed biologically plausible time interval of 12 weeks from the time of exposure. At the time of the final BLA submission and with submission of Post-marketing safety updates through May 2009, there were few of these events which had been submitted to the sponsor as spontaneous safety reports, and the estimated rates of occurrence did not exceed expected background rates. Nonetheless, in a meta-analysis conducted by GSK, the relative risk for these events was 2.33, but did not reach statistical significance. These events included a case of multiple sclerosis, a case of optic neuritis, and a case of transverse myelitis. Such events will be collected in the post-marketing period in a large post-marketing study in a health maintenance organization. The protocol is being finalized at the time of the approval of the vaccine and will be included in a post-marketing commitment. Please see overview of safety for assessment of these events.

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study: Three subjects withdrew due to a non-serious AE.

- **Subject number 1278 (group 3)** discontinued the study before the third vaccination because of an **upper respiratory tract infection and a cystitis** (lasting 30 days) of moderate intensities. These were not considered as causally related to the vaccine.
- **Subject number 1294 (group 2)** discontinued the study after the first vaccination for **injection site pain.** This was a local solicited symptom, and was considered as causally related to the vaccine.
- **Subject number 1318 (group 1)** discontinued the study before the third vaccination because of a **benign tumor breast** of mild severity that developed after the second vaccination but was not considered as causally related to the vaccine.

New onset of chronic diseases: In addition to multiple sclerosis and optic neuritis, already described above in the SAEs, two other events qualified for the definition of New Onset Chronic Disease, as established by GSK Biologicals: one event of severe urticaria after the second dose and lasting 2 days, considered as causally related to the vaccine (Subject number 1024) and mild allergic rhinitis after the third dose, not considered as causally related to the vaccine (Subject number 1321).

Table 309-Study HPV-014: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (Total Vaccinated Cohort)

		15-25 N=229	26-45 N=226	46-55 N=211
Primary System Organ Class	**Preferred term**	**n (%)**	**n (%)**	**n (%)**
At least one NOCD		3 (1.3%	1 (0.4%)	0 (0.0%)
Nervous system disorders	Multiple sclerosis Optic neuritis	1 (0.4%) 0 (0.0%)	0 (0.0%) 1 (0.4%)	0 (0.0%) 0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	1 (0.4%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Urticaria	1 (0.4%)	0 (0.0%)	0 (0.0%)

[15-25] = HPV-16/18 (15 years≤Age≤25 years); [26-45] = HPV-16/18 (26 years≤Age≤45 years)
[46-55] = HPV-16/18 (46 years≤Age≤55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
Source: STN 125259/0, CSR 014, Supplement 57, p. 166

The subjects who developed NOCD's Month 0-7 are as follows :

- Subject no. 1024 (15-25 year age group) experienced severe urticaria 7 days post-Dose 2. The event lasted 2 days and was considered as causally related to vaccination by the investigator.
- Subject no. 1321 (15-25 year age group) experienced mild allergic rhinitis 18 days post-Dose 3. The event was still ongoing at the time of reporting.
- Subject no. 1264 (15-25 year age group) suffered from a multiple sclerosis of moderate intensity appearing 25 days post-Dose 2. This event was also reported as an SAE.
- Subject no. 704 (26-45 year age group) had an optic neuritis of moderate intensity 9 days post-Dose 1. This event was considered as causally related to vaccination by the investigator and was also reported as an SAE.

Medically Significant Adverse Events:
Reviewer's Comment: Bronchitis was the most commonly reported medically significant AE, reported by 3 (1.3 %), 2 (0.9 %) and 3 (1.4 %) subjects in the 15–25, 26–45 and 46–55 years age groups, respectively. All other medically significant AEs were reported with a frequency of <1.0%, and all 95% CIs overlap.

Concomitant medications/vaccinations: Overall, the percentage of subjects having received concomitant medications and/or concomitant vaccinations in the 30 day post-vaccination period during the study was equal to 24.0%, 22.6% and 17.5% in groups 1, 2 and 3, respectively. Antipyretics were taken by 15.3%, 14.2% and 5.2% of subjects in groups 1, 2 and 3, respectively. Antibiotics were taken by 6.1%, 5.3% and 7.6% of subjects in groups 1, 2 and 3, respectively. No concomitant medication was taken prophylactically.

Pregnancy: No subject became pregnant during the study.

Reveiwer's Comment: CBER will await the results of the efficacy study underway in older women and review efficacy data ----------b(4)----------

IMMUNOGENICITY RESULTS OF INTEREST
GSK also presented *post-hoc* analyses of immunogenicity of the HPV 16/18 vaccine stratified by different categories such as smoking status, hormonal contraceptive status, and hormone replacement therapy. In these exploratory analyses:

- Non-smokers and ex-smokers had higher GMTs as compared to smokers.
- There was no apparent impact of menopausal status on GMTs in women 46-55 years of age.
- Use of hormonal contraception did not impact on the immune responses induced by the vaccine for all age groups and for both antibodies.
- There was no apparent impact of the use of HRT on the immunogenicity induced by the vaccine, although the number of subjects in each analysis was relatively small.

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For HPV-16 and HPV-18 Pseudovirion Neutralizing antibodies: The seropositvity rates are 100% in all age groups.

- **The GMTs for HPV-16** are highest in the youngest age group and lowest in the oldest age group in the 3 age group analysis (26-45 years of age analyzed together) and all 95% CIs overlap. (Source: STN 125259/0, CSR 014, Annex 2, Table 5, p. 24, not shown here).
- **The GMTs for HPV-18** are highest in the youngest age group and lowest in the oldest age group in the 3 age group analysis and all 95% CIs overlap. (Source: STN 125259/0, CSR 014, Annex 2, Table 6, p. 24, not shown here).

Safety and immunogenicity were assessed out to Month 12 and out to Month 24.

STUDY HPV-014: SAFETY RESULTS TO MONTH 12

Number and distribution of subjects in the Extended Follow-up period (Month 12)

The EFU Vaccinated cohort included 635 (95.3 %) subjects (213, 221 and 201 subjects in the 15-25, 26-45 and 46-55 years age groups, respectively). The EFU ATP immunogenicity cohort included 617 (92.6 %) subjects (208, 214 and 195 subjects in the 15-25, 26-45 and 46-55 years age groups, respectively).

Table 310-Study-014: Number of subjects enrolled into the study as well as the number excluded from the EFU Vaccinated cohort analyses with reasons for exclusion

	Total			[15–25]		[26–45]		[46–55]	
Title	n	s	%	n	s	n	s	n	s
Total Enrolled cohort	**667**								
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1							
Total Vaccinated cohort	**666**		**100**	**229**		**226**		**211**	
Subject who could not be contacted during the extended follow-up period (after Month 7 visit) (code 3000)	31	32		16	16	5	5	10	10
EFU Vaccinated cohort	**635**		**95.3**	**213**		**221**		**201**	

[15–25] = HPV-16/18 VLP (15–25 years)
[26–45] = HPV-16/18 VLP (26–45 years)
[46–55] = HPV-16/18 VLP (46–55 years)
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated cohort
BS = blood sampling
EFU = extended follow-up
Source: STN 125259/0, CSR 014, Annex 3, Table 2, p. 27

The reasons for subjects being excluded from analyses are shown in Table 311 below.

Table 311-Study HPV-014: Number of subjects enrolled into the study and the number excluded from the EFU ATP cohort for immunogenicity analyses with reasons for exclusion

	Total			[15–25]		[26–45]		[46–55]	
Title	n	s	%	n	s	n	s	n	s
Total Enrolled cohort	**667**								
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1*							
Total Vaccinated cohort	**666**		**100**	**229**		**226**		**211**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	2	2		1	1	1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	3	3		0	0	2	2	1	1
Administration of any medication forbidden by the protocol (code 2040)	3	4		1	1	1	2	1	1
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	2	2		0	0	1	1	1	1
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	5	5		1	1	1	1	3	3
Essential serological data missing (code 2100)	7	8		2	3	1	1	4	4
Subject who could not be contacted during the extended follow-up period (after Month 7 visit) (code 3000)	21	31		12	16	4	5	5	10
Non compliance with blood sampling schedules (date of BS not corresponding to adapted protocol interval or unknown BS date) (code 3090)	5	5		4	4	1	1	0	0
Serological result not available at extended follow-up visit (code 3100)	1	33		0	16	0	5	1	11
EFU ATP cohort for immunogenicity	**617**		**92.6**	**208**		**214**		**195**	

[15–25] = HPV-16/18 VLP (15–25 years)
[26–45] = HPV-16/18 VLP (26–45 years)
[46–55] = HPV-16/18 VLP (46–55 years)
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated cohort
BS = blood sampling
EFU = extended follow-up
Note: Codes 1030, 1040, 1070, 2040, 2080, 2090 and 2100 were attributed at the time of the Month 7 database freeze. Codes 3000, 3090 and 3100 were attributed at the time of the Month 12 database freeze.
This subject also received a 3000 elimination code.
Source: STN 125259/0, CSR 014, Annex 3, Table 3, p. 28

Safety Results
EFU vaccinated cohort results (Month 7 to Month 12)
Serious adverse events: There was one SAE in the extended follow-up period.

Table 312-Study HPV-014, Subjects with SAE (Month 7-12)
(CBER generated)

Case number, age	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to vaccination per investigator
0742, 50 years old	Vestibular neuronitis	63 days after dose 3	2 days	Resolved	Unrelated

Reviewer's Comment: The vestibular neuronitis was of short duration and occurred app. 2 months after the subject received dose 3 of vaccine. Vestibular neuronitis is believed to be related to a viral infection of the vesrtibular nerve, but is also associated with localized ischemia. The causative mechanism is not certain. It usually resolves within a few weeks. The subject was taking an herbal treatment for menopausal symptoms, black cohosh, which may be associated with dizziness (although liver toxicity may also be seen).

Fatal events: No subject died during the study through Month 12.

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study: No subjects withdrew from the extended follow-up period of the study due to an AE.

New onset of chronic diseases: There were no reports of NOCDs during the extended follow-up period of the study.

Other medically significant adverse events: The percentage of subjects reporting medically significant AEs prompting emergency room visits or physician visits during the extended follow-up period are shown in Table 313 below. None of the medically significant AEs reported were considered by the investigator to be related to vaccination.

Table 313-Study HPV-014: Percentage of subjects reporting the occurrence of medically significant AEs classified by MedDRA Primary System Organ Class and Preferred Term, during the extended follow-up phase (Month 7 to Month 12) (EFU Vaccinated cohort)

	Preferred Term	15-25 N=213	26-45 N=221	46-55 N=201
Primary System Organ Class		**n (%)**	**n (%)**	**n (%)**
At least one MSAE		**1 (0.5%)**	**3 (1.4%)**	**1 (0.5%)**
Blood and lymphatic system disorders	Iron deficiency anemia	0 (0.0%)	1 (0.5%)	0 (0.0%)
Ear and labyrinth disorders	Vestibular neuronitis	0 (0.0%)	0 (0.0%)	1 (0.5%)
Gastrointestinal disorders	Tooth diosrder	0 (0.0%)	2 (0.9%)	0 (0.0%)
Infections and Infestations	Otitis media	1 (0.5%)	0 (0.0%)	0 (0.0%)

[15–25] = HPV-16/18 VLP (15–25 years); [26–45] = HPV-16/18 VLP (26–45 years)
[46–55] = HPV-16/18 VLP (46–55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95 % CI= exact 95 % confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 014, Annex 3, Table 10, p. 39

Pregnancy: During the extended follow-up period of the present study (Months 7 to 12) two pregnancies (both in the 26–45 years age group) were reported in 635 subjects.

- **One subject** was reported to be pregnant 6 months after the third dose of HPV-16/18 vaccine. After 41 weeks of pregnancy, this 32-year-old subject gave birth to a healthy female infant by normal vaginal delivery.
- **One subject** was reported to be pregnant 6 months after the third dose of HPV-16/18 vaccine. After 41 weeks of pregnancy, this 28-year-old subject gave birth to a healthy female infant by normal vaginal delivery.

Safety Results in the Total vaccinated cohort results (Month 0 to Month 12)
SAEs, Fatal events: No subject died through Month 12.
SAEs, Non-fatal events: During the twelve months of follow-up, a total of seven SAEs were reported for seven subjects. These are presented in Table 314.

Table 314-Study HPV-014: Percentage of subjects reporting the occurrence of Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, reported during the entire follow-up period (Month 0 to Month 12) (Total Vaccinated cohort)

	Preferred Term	15-25 N=213	26-45 N=221	46-55 N=201
Primary System Organ Class		**n (%)**	**n (%)**	**n (%)**
At least one SAE		**3 (1.3%)**	**1 (0.4%)**	**3 (1.4%)**
Ear and labyrinth disorders	Vestibular neuronitis	0 (0.0%)	0 (0.0%)	1 (0.5%)
Gastrointestinal disorders	Irritable bowel syndrome	0 (0.0%)	0 (0.0%)	1 (0./5%)
Injury, poisoning and procedural complications	Thermal burn	1 (0.4%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	Multiple sclerosis Optic neuritis	1 (0.4%) 0 (0.0%)	0 (0.0%) 1 (0.4%)	0 (0.0%) 0 (0.0%)
Psychiatric disorders	Depression	0 (0.0%)	0 (0.0%)	1 (0.5%)
Reproductive system and breast disorders	Ovarian cyst	1 (0.4%)	0 (0.0%)	0 (0.0%)

[15–25] = HPV-16/18 VLP (15–25 years)
[26–45] = HPV-16/18 VLP (26–45 years)
[46–55] = HPV-16/18 VLP (46–55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95 % CI= exact 95 % confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 014, Annex 3, Table 11, p. 41

New onset of chronic diseases: A total of four NOCDs were reported by four subjects through Month 12. Three in the 15–25 years age group (multiple sclerosis, rhinitis allergic and urticaria) and one in the 26–45 years age group (optic neuritis). Two of these NOCDs (multiple sclerosis and optic neuritis) were also considered to be SAEs.

Other medically significant adverse events: A total of 85 medically significant AEs were reported by 64 subjects through Month 12. The percentage of subjects reporting these medically significant AEs was 9.2, 9.7 and 10.0 % in the 15–25, 26–45 and 46–55 years age groups, respectively. The most commonly reported symptom was bronchitis, which was reported by 1.3, 0.9 and 1.4 % of subjects in the 15–25, 26–45 and 46–55 years age groups, respectively. All other symptoms were reported with a frequency of <1 %.

Pregnancy: A total of two pregnancies (both in the 26–45 years age group) were reported during the study (Month 0 to Month 12). Both pregnancies resulted in healthy babies.

Table 315-Study HPV-014: Outcome of reported pregnancies (Month 0 to Month 12) (Total Vaccinated cohort)

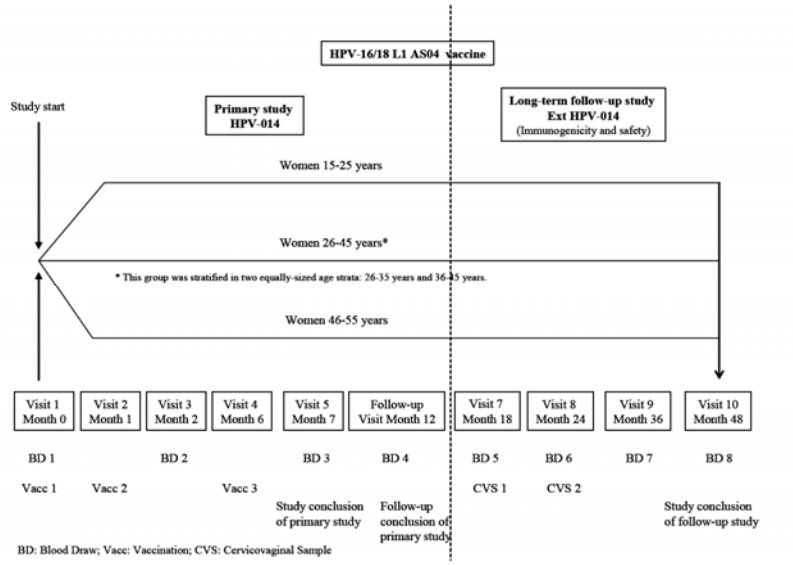
Outcome	[15-25]	[26-45]	[46-55]	All
Pregnancy ongoing	0	0	0	0
Healthy baby	0	2	0	2
Miscarriage/spontaneous abortion/foetal death	0	0	0	0
Elective abortion	0	0	0	0
Neonatal death	0	0	0	0
Unknown	0	0	0	0
Total	**0**	**2**	**0**	**2**

[15–25] = HPV-16/18 VLP (15–25 years)
[26–45] = HPV-16/18 VLP (26–45 years)
[46–55] = HPV-16/18 VLP (46–55 years)
Source: STN 125259/0, CSR 014, Annex 3, Table 15, p. 45

STUDY HPV-014: SAFETY RESULTS TO MONTH 18

Additional long-term follow-up was reported at Month 18 and Month 24. The study overview for this long-term follow-up is shown in Figure 35 below.

Figure 35-Study EXT HPV-014: Overview of Study and Long Term Follow-Up



Primary endpoint: Anti-HPV-16 and anti-HPV-18 antibody titers assessed by ELISA in all subjects at Month 18.

Secondary endpoints
Immunogenicity

- Anti-HPV-16 and anti-HPV-18 antibody titers assessed by ELISA at each time point (Months 0, 7, 12 and 18).
- Anti-HPV-16 and anti-HPV-18 antibody titers from subjects enrolled in studies HPV-001/HPV-007 subjects assessed by ELISA at each time point.
- Anti-HPV-16 and anti-HPV-18 antibody titers in cervical secretion samples at Month 18 in subjects who had cervicovaginal secretion samples collected (subset of subjects).

Reviewer's Comment: As the immunogenicity assessments and comparisons in this protocol did not contribute to the ultimate decision-making process concerning licensure of this vaccine product, the review of this product will focus on the safety data.

Safety: Occurrence of pregnancies, serious adverse events (SAEs), new onset chronic diseases (NOCDs) and other medically significant conditions prompting emergency room visits or physician visits that were not related to common diseases or routine visits for physical examination or vaccination, or SAEs that were not related to common diseases throughout the study period (including the period from Month 12 follow-up visit of the primary HPV-014 study until visit 7 [Month 18] of the Ext HPV-014 study).

Interim analysis: An interim analysis is planned after each phase of the long-term follow-up : Ext HPV-014 Month 18; Ext HPV-014 Month 24; Ext HPV-014 Month 36; Ext HPV-014 Month 48).

Protocol amendments/modifications
The original HPV-014 study protocol dated 7/26/04 was amended on 3/3/06 to allow for long-term follow-up. The long-term follow-up was designed to assess the immunogenicity and safety of the HPV-16/18 vaccine up to 36 months after the end of the HPV-014 study (48 months after the first vaccine dose).

Study Population Results for Month 18
Study dates: Visit 7 (Month 18) took place between 4/3/06 and 7/11/06 for all subjects. The date of the data lock point was 11/3/06.

Subject eligibility and attrition from study
Number and distribution of subjects: A total of 524 subjects attended visit 7 (Month 18) and were enrolled in this extension study, of whom 169, 175 and 180 subjects were in the 15-36, 26-45 and 46-55 year age groups, respectively.

Study completion and withdrawal from study: A total of 524 subjects attended visit 7 (Month 18), i.e., the only scheduled visit of this follow-up phase of the extension study. The number of subjects excluded from analysis are shown below.

Table 316-Study EXT HPV-014: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion (Month 18)

	Total			[15-25]		[26-45]		[46-55]	
Title	n	s	%	n	s	n	s	n	s
Total enrolled cohort (Active phase)	667								
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1							
Total Vaccinated Cohort (Active Phase)	666		100	229		226		211	
Subject missed all extension Month 18 visits (code 4000)	142	143		60	60	51	51	31	31
Total Vaccinated Cohort (Extension Month 18)	524		78.7	169		175		180	
Administration of vaccine(s) forbidden in the protocol (code 1040)	1	2		0	1	1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	0	3		0	0	0	2	0	1
Administration of any medication forbidden by the protocol (code 2040)	2	4		0	1	1	2	1	1
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	1	2		0	0	1	1	0	1
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	3	5		0	1	0	1	3	3
Essential serological data missing (code 2100)	0	8		0	3	0	1	0	4
ATP Cohort for immunogenicity	517		77.6	169		172		176	

[15-25] = HPV 16/18 VLP (15-25 years); [26-45] = HPV 16/18 VLP (26-45 years)
[46-55] = HPV 16/18 VLP (46-55 years)
Note: Subjects may have more than one elimination code assigned
Note: code 1030, 1040, 1070, 2040, 2080, 2090 and 2100 were attributed at the Month 7 database freeze; code 4000 was attributed at the Month 18 database freeze.
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Source: STN 125259/0, CSR 014, Month 18 extenstion,. Table 4, p. 45

Safety Results
Month 12-Month 18
Data sets analyzed: The main analysis of safety was performed on the Total Vaccinated cohort of the extension follow-up phase using 3 age groups (15-25, 26-45 and 46-55 years) for the period of Month 0 to Month 18. This analysis included safety data from all 666 subjects of the primary HPV-014 study collected from Month 0 through Month 18. The safety data from the 524 subjects of the extension study collected from Month 12 through Month 18 were included in this analysis. Safety results for the Total Vaccinated cohort of the extension follow-up phase divided in 3 age groups for the period of Month 12 to Month 18 are presented in Tables 317 and 318.

Reviewer' Comment: These events occurred ≥ 5 months after dose 3, and there was no apparent temporal relationship.

Table 317-EXT Study HPV-014, Subjects with SAE (Month 12-18) (CBER generated)

Case number, age	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to vaccination per investigator
85, 46-55 years	Depression and carotid artery dissection	7 months after dose 3	14 days	Recovered	Unrelated
160, 46-55 years	Venous thrombosis limb	11 months after dose 3	7 days	Recovered	Unrelated
240, 46-55 uears	Uterine prolapse	10 months after dose 3	2 days	Recovered	Unrelated
1271, 26-45 years	Cervical polyp	7 months after dose 3	33 days	Recovered	Unrelated
1338, 15-25 years	Gastroduodenitis	9 months after dose 3	Ongoing	Ongoing	Unrelated
1626, 46-55 years	Abdominal hernia	5 months after dose 3	166 days	Recovered	Unrelated

Source: STN 125259/0, CSR 014 Month 18 extension, Supplement 38, p. 134

Table 318-Study EXT HPV-014: Percentage of subjects reporting NOCDs (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the extension follow-up Month 12 to 18 (Total Vaccinated Cohort)

		[15-25] N = 169				[26-45] N = 175				[46-55] N = 180			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		1	0.6	0.0	3.3	1	0.6	0.0	3.1	2	1.1	0.1	4.0
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	1	0.6	0.0	3.3	0	0.0	0.0	2.1	0	0.0	0.0	2.0
Metabolism and nutrition disorders (10027433)	Diabetes mellitus non-insulin-dependent (10012613)	0	0.0	0.0	2.2	0	0.0	0.0	2.1	1	0.6	0.0	3.1
Psychiatric disorders (10037175)	Depression (10012378)	0	0.0	0.0	2.2	1	0.6	0.0	3.1	1	0.6	0.0	3.1

[15-25] = HPV 16/18 VLP (15-25 years); [26-45] = HPV 16/18 VLP (26-45 years); [46-55] = HPV 16/18 VLP (46-55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 014 Month 18 extension, Supplement 42, p. 136

Table 319-Study EXT HPV-014: Percentage of subjects reporting medically significant AEs classified by MedDRA Primary System Organ Class and Preferred Term, during the extension follow-up Month 12 to 18 (Total Vaccinated Cohort)

		[15-25] N = 169				[26-45] N = 175				[46-55] N = 180			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		3	1.8	0.4	5.1	5	2.9	0.9	6.5	6	3.3	1.2	7.1
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	1	0.6	0.0	3.3	0	0.0	0.0	2.1	0	0.0	0.0	2.0
Gastrointestinal disorders (10017947)	Abdominal hernia (10060954)	0	0.0	0.0	2.2	0	0.0	0.0	2.1	1	0.6	0.0	3.1
	Gastroduodenitis (10048714)	1	0.6	0.0	3.3	0	0.0	0.0	2.1	0	0.0	0.0	2.0
	Tongue eruption (10052002)	1	0.6	0.0	3.3	0	0.0	0.0	2.1	0	0.0	0.0	2.0
Metabolism and nutrition disorders (10027433)	Diabetes mellitus non-insulin-dependent (10012613)	0	0.0	0.0	2.2	0	0.0	0.0	2.1	1	0.6	0.0	3.1
	Lipid metabolism disorder (10061227)	0	0.0	0.0	2.2	0	0.0	0.0	2.1	1	0.6	0.0	3.1
Nervous system disorders (10029205)	Carotid artery dissection (10050403)	0	0.0	0.0	2.2	0	0.0	0.0	2.1	1	0.6	0.0	3.1
Psychiatric disorders (10037175)	Depression (10012378)	0	0.0	0.0	2.2	2	1.1	0.1	4.1	1	0.6	0.0	3.1
Reproductive system and breast disorders (10038604)	Cervical dysplasia (10008263)	0	0.0	0.0	2.2	1	0.6	0.0	3.1	0	0.0	0.0	2.0
	Cervical polyp (10008297)	0	0.0	0.0	2.2	1	0.6	0.0	3.1	0	0.0	0.0	2.0
	Uterine prolapse (10046814)	0	0.0	0.0	2.2	0	0.0	0.0	2.1	1	0.6	0.0	3.1
Vascular disorders (10047065)	Hypertension (10020772)	0	0.0	0.0	2.2	1	0.6	0.0	3.1	1	0.6	0.0	3.1
	Venous thrombosis limb (10061408)	0	0.0	0.0	2.2	0	0.0	0.0	2.1	1	0.6	0.0	3.1

[15-25] = HPV 16/18 VLP (15-25 years)
[26-45] = HPV 16/18 VLP (26-45 years)
[46-55] = HPV 16/18 VLP (46-55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 014 Month 18 extension, Supplement 44, p. 138

Month 0-18
Serious adverse events
Fatal events: None of the subjects died during the study period from Month 0 to Month 18.

Non-fatal SAEs:
A total of 7 SAEs were reported by 6 subjects during the Month 12 to Month 18 reporting period. Overall, 13 subjects reported a total of 14 SAEs during the study period from Month 0 to Month 18, of whom 4 subjects in the 15-25 year age group, 2 subjects in the 26-45 year age group and 7 subjects in the 46-55 year age group. Except for one event of optic neuritis, none of these SAEs were considered as potentially causally related to vaccination by the investigator.

Table 320-Study EXT HPV-014: Percentage of subjects reporting SAEs classified by MedDRA Primary System Organ Class and Preferred Term, reported during the entire study period (Month 0 to Month 18) (Total Vaccinated Cohort - Extended phase Month 18

	Preferred Term	15-25 N=229	26-45 N=226	46-55 N=211
Primary System Organ Class		**n (%)**	**n (%)**	**n (%)**
At least one SAE		**4 (1.7%)**	**2 (0.9%)**	**7 (3.3%)**
Ear and labyrinth disorders	Vestibular neuronitis	0 (0.0%)	0 (0.0%)	1 (0.5%)
Gastrointestinal disorders	Abdominal hernia	0 (0.0%)	0 (0.0%)	1 (0.5%)
	Gastroduodenitis	1 (0.4%)	0 (0.0%)	0 (0.0%)
	Irritable bowel syndrome	0 (0.0%)	0 (0.0%)	1 (0.5%)
Injury, poisoning and procedural complications	Thermal burn	1 (0.4%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	Carotid artery dissection	0 (0.0%)	0 (0.0%)	1 (0.5%)
	Multiple sclerosis	1 (0.4%)	0 (0.0%)	0 (0.0%)
	Optic neuritis	0 (0.0%)	1 (0.4%)	0 (0.0%)
Psychiatric disorders	Depression	0 (0.0%)	0 (0.0%)	2 (0.9%)
Reproductive system and breast disorders	Cervical polyp	0 (0.0%)	1 (0.4%)	0 (0.0%)
	Ovarian cyst	1 (0.4%)	0 (0.0%)	0 (0.0%)
	Uterine prolapse	0 (0.0%)	0 (0.0%)	1 (0.5%)
Vascular disorders	Venous thrombosis limb	0 (0.0%)	0 (0.0%)	1 (0.5%)

[15-25] = HPV 16/18 VLP (15-25 years); [26-45] = HPV 16/18 VLP (16-45 years); [46-55] = HPV 16/18 VLP (46-55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 014 Month 18 extension, Table 14, p. 68-69

New onset chronic diseases: 4 subjects experienced each one NOCD during the period from Month 12 to Month 18. Over the complete reporting period (Month 0 to Month 18), 8 subjects reported each one NOCD: 4 subjects in the 15-25 year age group and 2 subjects in each of the 26-45 and 46-55 year age groups. Two cases of NOCD (urticaria and optic neuritis) were considered as potentially causally related to vaccination by the investigator.

- Subject no. 27 (46-55 year age group) experienced non-insulin-dependent diabetes mellitus (mild intensity) at Month 18, or 12 months after the third vaccine dose. The subject was not yet recovered from this event at the time of reporting.
- Subject no. 85 (46-55 year age group) experienced depression of mild intensity at Month 13, at 7 months after the third vaccine dose. The subject recovered from this event 30 days later.
- Depression (moderate intensity) was experienced by subject no. 1285 (26-45 year age group) at Month 14, i.e., 8 months after the third vaccine dose. The subject was still recovering from this event at the time of reporting.
- Subject no. 254 (15-25 year age group) developed autoimmune thyroiditis (mild intensity) at Month 13, at 7 months after the third vaccine dose. The subject had not yet recovered from this event at the time of reporting.

Reviewer's Comment: There were 4 additional NOCDs reported since Month 12. These are the first 4 listed above. All NOCDs are listed in Table 321 below.

Table 321-Study EXT HPV-014: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases classified by MedDRA Primary System Organ Class and Preferred Term, reported during the entire follow-up period (Month 0 to Month 18) (Total vaccinated cohort – Active phase)

		15-25 N=229	26-45 N=226	46-55 N=211	Total N=666
Primary System Organ Class	**Preferred term**	**n (%)**	**n (%)**	**n (%)**	
At least one NOCD		4 (1.7%)	2 (0.9%)	2 (0.9%)	8 (1.2%)
Endocrine disorders	Autoimmune thyroiditia	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Metabolism and nutrition disorders	Diabetes mellitus non-insulin dependent	0 (0.0%)	0(0.0%)	1 (0.5%)	1 (0.2%)
Nervous system disorders	Multiple sclerosis Optic neuritis	1 (0.4%) 0 (0.0%)	0 (0.0%) 1 (0.4%)	0 (0.0%) 0 (0.0%)	1 (0.2%) 1 (0.2%)
Psychiatric disorders	Depression	0 (0.0%)	1 (0.4%)	1 (0.4%)	2 (0.3%)
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Skin and subcutaneous tissue disorders	Urticaria	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

[26-45] = HPV 16/18 VLP (16-45 years)
[46-55] = HPV 16/18 VLP (46-55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 014 Month 18 extension, Table 16, p. 72

Medically Significant AEs: At least one medically significant AE was reported by 8.9%, 9.1% and 12.2% of subjects in the 15-25, 26-45 and 46-55 year age groups, respectively. The most common medically significant events were depression and bronchitis:

- Depression was reported for 6 subjects, of whom 1, 2 and 3 subjects in the 15-25, 26-45, and 46-55 year age groups, respectively.
- Bronchitis was reported for 5 subjects, of whom 2 subjects in the 15-25 year age group and 3 subjects in the 46-55 year age group.

All other medically significant events were reported for at most 2 subjects in any age group during the study period from Month 0 to Month 18.

Pregnancy: During the study period from Month 12 to Month 18, 7 pregnancies were reported. Over the complete reporting period (Month 0 to Month 18), a total of 9 pregnancies were reported. For 6 subjects, the pregnancy resulted in normal birth. For the other 3 subjects, the pregnancy was ongoing or the outcome was unknown at the time of database freezing.

STUDY HPV-014, MONTH 24 REPORT: This report presents the results of the interim analysis of data collected during the study period up to Month 24 (Ext HPV-014 Mth 24)after vaccination. Data collected beyond Month 24 were not submitted to the BLA at present.

Primary Objective for Month 24 interim analysis: To evaluate the long-term immunogenicity of the HPV-16/18 vaccine in all subjects by enzyme-linked immunosorbent assay (ELISA) up to Month 24.

Reviewer's Comment: As the immunogenicity assessments and comparisons in this protocol did not contribute to the ultimate decision-making process concerning licensure of this vaccine, the review of this protocol will focus on the safety data.

Secondary Objectives for Month 24 interim analysis
Safety: To evaluate the long-term safety of the HPV-16/18 vaccine up to approximately 24 months after administration of the first vaccine dose.

Study Population Results
Study dates: The first subject attended Visit 8 (Month 24) on 8/28/06 and the last subject on 1/16/07. The date of the data lock point was 6/25/07.

Number and distribution of subjects: In the primary study HPV-014, of the 667 subjects enrolled, 666 subjects received at least one dose of the HPV-16/18 L1 VLP AS04 vaccine. A total of 531 subjects attended Visit 8 (Month 24): 169 subjects in the 15 - 25 year age group and 181 subjects in each of the 26 - 45 and 46 - 55 year age groups.

Study completion and withdrawal from study: No withdrawals were reported. A total of 531 subjects completed Visit 8 (Month 24), which was the second scheduled visit of this follow-up phase of the extension study. See Table 322 for number of subjects excluded from the ATP analyses with reasons for exclusion.

Table 322-Study EXT HPV-014: Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion (Month 24)

Title	Total			[15 - 25]		[26 - 45]		[46 - 55]	
	N	s	%	n	s	n	s	n	s
Total enrolled cohort (active phase)	**667**								
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1							
Total vaccinated cohort (active phase)x	**666**		**100**	**229**		**226**		**211**	
Subjects not present at M24 visit (code 5000)	135	136		60	60	45	45	30	30
Total Vaccinated Cohort Extension Month 24	**531**		**79.7**	**169**		**181**		**181**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	2	2		1	1	1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	0	3		0	0	0	2	0	1
Administration of any medication forbidden by the protocol (code 2040)	2	4		0	1	1	2	1	1
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	0	2		0	0	0	1	0	1
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	4	5		0	1	1	1	3	3
Essential serological data missing (code 2100)	0	8		0	3	0	1	0	4
Administration of any medication forbidden by the protocol at visit M24 (code 5040)	1	1		1	1	0	0	0	0
Essential serological data missing at M24 (code 5100)	1	1		1	1	0	0	0	0
ATP Cohort for immunogenicity Extension Month 24	**521**		**78.2**	**166**		**178**		**177**	

[15 - 25] = HPV-16/18 L1 AS04 (15 - 25 years); [26 - 45] = HPV-16/18 L1 AS04 (26 - 45 years)
[46 - 55] = HPV-16/18 L1 AS04 (46 - 55 years)
Note: Subjects may have more than one elimination code assigned
Note: code 1030, 1040, 1070, 2040, 2080, 2090 and 2100 were attributed at the Month 7 database freeze and kept through the study; code 5000, 5040 and 5100 were attributed at the Month 24 database freeze.
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort for immunogenicity Extension Month 24 relative to the Total vaccinated cohort
Source: STN 125259.30, CSR 014 Month 24 report, Table 4, p. 49

According-To-Protocol analysis

Safety Results
Total vaccinated cohort Extension Month 24 analysis [Month 18 - Month 24]
Serious adverse events: One additional SAE was reported by one subject in the 26 - 45 year age group during the Month 18 to Month 24 period. This is shown in Table 323.

Table 323-Study EXT HPV-014: SAEs (Month 18-24)

Case number, age	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to vaccination per investigator
741, 47 years	Shoulder ligament rupture (injury) – surgery	>18 months after dose 3	Ongoing	Unresolved	Unrelated

Adverse events leading to premature discontinuation of study vaccine and/or study: No subjects were withdrawn from the extension follow-up period from Month 18 to Month 24 due to an AE.

Fatal events: There were no fatalities during the extension follow-up period from Month 18 to Month 24.

Medically significant adverse events: During Month 18-24 time period, the percentages of subjects reporting at least one medically significant AE were similar across all age groups: 1.8% of subjects in the 15 - 25 year age group, 1.7% of subjects in the 26 – 45 year age group and 1.1% of subjects in the 46 - 55 year age group.

Table 324-Study EXT HPV-014: Percentage of subjects reporting the occurrence of medically significant AEs classified by MedDRA Primary System Organ Class and Preferred Term, during the extension follow-up Month 18 to 24 (Total Vaccinated Cohort Extension Month 24)

		[15 - 25] N = 169				[26 - 45] N = 181				[46 - 55] N = 181			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one medically significant AE		3	1.8	0.4	5.1	3	1.7	0.3	4.8	2	1.1	0.1	3.9
Gastrointestinal disorders (10017947)	Haemorrhoids (10019022)	1	0.6	0.0	3.3	0	0.0	0.0	2.0	0	0.0	0.0	2.0
Infections and infestations (10021881)	Cystitis (10011781)	1	0.6	0.0	3.3	0	0.0	0.0	2.0	0	0.0	0.0	2.0
Injury, poisoning and procedural complications (10022117)	Ligament rupture (10065433)	0	0.0	0.0	2.2	1	0.6	0.0	3.0	0	0.0	0.0	2.0
Investigations (10022891)	Smear cervix abnormal (10041206)	0	0.0	0.0	2.2	1	0.6	0.0	3.0	0	0.0	0.0	2.0
Musculoskeletal and connective tissue disorders (10028395)	Arthropathy (10003285)	0	0.0	0.0	2.2	0	0.0	0.0	2.0	1	0.6	0.0	3.0
	Intervertebral disc protrusion (10050296)	0	0.0	0.0	2.2	1	0.6	0.0	3.0	0	0.0	0.0	2.0
Psychiatric disorders (10037175)	Panic attack (10033664)	0	0.0	0.0	2.2	1	0.6	0.0	3.0	0	0.0	0.0	2.0
Skin and subcutaneous tissue disorders (10040785)	Acne (10000496)	1	0.6	0.0	3.3	0	0.0	0.0	2.0	0	0.0	0.0	2.0
Vascular disorders (10047065)	Hypertension (10020772)	0	0.0	0.0	2.2	0	0.0	0.0	2.0	1	0.6	0.0	3.0

[15 - 25] = HPV-16/18 L1 VLP AS04 (15 - 25 years); [26 - 45] = HPV-16/18 L1 VLP AS04 (26 - 45 years)
[46 - 55] = HPV-16/18 L1 VLP AS04 (46 - 55 years)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.30, CSR 014, Month 24, Table 13, p. 69

New onset of chronic diseases: During the extension follow-up period [Month 18 - 24], there were no NOCDs identified based on GSK assessment.

Pregnancy: During the extension follow-up period Month 18 to Month 24, six pregnancies and one pregnancy outcome were reported. None of these pregnancies or pregnancy outcomes was reported as SAEs or AEs.

Table 325-Study EXT HPV-014: Outcome of reported pregnancies Month 18 to 24 (Total Vaccinated Cohort Extension Month 24)

Outcome	[15 - 25]	[26 - 45]	[46 - 55]	Total
Abnormal infant / congenital anomaly	0	0	0	0
Ectopic pregnancy	0	0	0	0
Elective termination	0	1	0	1
Lost to follow-up	0	0	0	0
Missed abortion	0	0	0	0
Normal infant	1	2	0	3
Ongoing	1	2	0	3
Premature birth	0	0	0	0
Spontaneous abortion / Miscarriage	0	0	0	0
Still birth	0	0	0	0
Therapeutic abortion	0	0	0	0
Total	2	5	0	7

Source: STN 125259.30, CSR 014, Month 24, Table 14, p. 70

No pregnancies were reported in the 46 - 55 year age group. The outcome of all ongoing pregnancies will be followed up.

Total vaccinated cohort analysis [Month 0 - Month 24]
Serious adverse events: During the entire study period (Month 0 to Month 24), a total of 14 subjects reported 15 SAEs: 4 subjects in the 15 - 25 year age group, 3 subject in the 26 - 45 year age group and 8 subjects in the 46 - 55 year age group. None of the reported SAEs were considered related to vaccination by the investigator, except the occurrence of optic neuritis experienced by Subject no. 704 during the active phase of the study (Month 0 to Month 7) (already described).
Reviewer's Comment: As compared to the Month 0-18 table, 1 additional subject was added to the Injury System Organ Class in the 46-55 year old age group.

Medically significant adverse events: During the entire study period (Month 0 to month 24), a total of 110 medically significant AEs were reported by 79 subjects: 24 subjects reported 33 medically significant AEs in the 15 - 25 year age group, 29 subjects reported 38 medically significant AEs in the 15 -25 year age group and 26 subjects reported 39 medically significant AEs in the 15 – 25 year age group. The most frequently reported medically significant AEs were bronchitis, depression and hypertension:

- Bronchitis was reported by 8 subjects: 3 subjects in the 15 - 25 year age group, 2 subjects in the 26 - 45 year age group and 3 subjects in the 46 - 55 year age group.
- Depression was reported by 6 subjects: 1 subject in the 15 - 25 year age group, 2 subjects in the 26 - 45 year age group and 3 subjects in the 46 - 55 year age group.
- Hypertension was reported by 5 subjects: 1 subject in the 26 - 45 year age group and 4 subjects in the 46 - 55 year age group.

All other medically significant AEs were reported for at most 2 subjects in any age group.

New onset of chronic disease: During the entire study period (Month 0 to Month 24), 8 events were identified as NOCDs based on GSK assessment. Eight subjects reported 8 events that were classified as NOCDs: 4 subjects reported 4 events in the 15 - 25 year age group (autoimmune thyroiditis, multiple sclerosis, rhinitis allergic and urticaria), 2 subjects reported 2 events in each of the 26 - 45 year age group (optic neuritis and depression) and 46 - 55 year age group (diabetes mellitus non-insulin dependent and depression). These events are described in HPV-014 EXT (Month 18) section of this review.

CONCLUSIONS FOR STUDY HPV-014:

- Immune responses were age dependent, in that younger women (15-25 years of age) had higher anti-HPV-16 and anti-HPV-18 IgG levels by ELISA as compared to females >26 years of age.
- Safety profiles were generally comparable across age groups, although younger females had a somewhat higher frequency of solicited local and general adverse events.
- Two adverse events related to neuroinflammatory process occurred in 2 subjects in this study within 30 days of vaccination (one optic neuritis case assessed as related to vaccine and one multiple sclerosis event assessed as not related to vaccine). Events such as these were reviewed across studies in a meta-analysis requested by CBER and conducted by GSK (with CBER statistical review of methodology prior to conductng the meta-analysis). A discussion of these events are provided in the Overview of Safety section of this review.

8.10 HPV-016 (Trial #10): A phase III, double-blind, randomized study to assess the consistency of the immunogenicity of three production lots of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects aged 18 – 25 years and to demonstrate non-inferiority of the candidate HPV vaccine manufactured at -b(4)- scale compared with a --b(4)--- manufacturing scale.
Study Dates: 10/28/05-9/8/06
Study Sites: Nine centers in three countries: Denmark, Lithuania, and Poland.

STUDY OBJECTIVES
Primary Objectives
First primary objective: To demonstrate lot-to-lot consistency in terms of immunogenicity between three industrial production lots (-b(4)- scale) of the HPV-16/18 L1/AS04 vaccine one month after the third dose (Month 7). Criteria for consistency: one month after the third dose, the two sided 95 % confidence intervals (CI) of the geometric mean titer (GMT) ratio between all pairs of lots are within [0.5, 2].
If consistency is demonstrated, the three lots will be pooled and non-inferiority of the -b(4)- scale lot vaccine versus the -b(4)- scale lot vaccine will be evaluated as a second primary objective. (If consistency is not demonstrated, non-inferiority cannot be tested.)

Second primary objective: To demonstrate that the HPV vaccine produced at -b(4)- manufacturing scale is noninferior in terms of immunogenicity to the HPV vaccine produced at b(4)- scale one month after the third dose (Month 7). Two criteria for non-inferiority will be assessed sequentially (if the first one is not demonstrated, the second one cannot be tested):
- One month after the third dose, the upper limit of the 95% CI for the difference between the percentage of subjects who seroconverted after administration of the -b(4)- scale lot vaccine versus the pooled -b(4)- scale vaccine lots is below 5%;
- One month after the third dose, the upper limit of the 95% CI for the GMT ratio between the b(4)- scale vaccine and pooled -b(4)- scale vaccine lots is below two.

Secondary Objectives
- Evaluation of immunogenicity in terms of seroconversion rates of three industrial scale vaccine production lots (-b(4)- scale) one month after the third dose (Month 7).
- Evaluation of immunogenicity in terms of GMTs of three industrial scale vaccine production lots (-b(4)- scale) one month after the second dose (Month 2).
- Evaluation of immunogenicity in terms of seroconversion rates and GMTs of the vaccine produced at -b(4)- manufacturing scale compared with b(4) scale one month after the second dose (Month 2).
- To evaluate the safety and reactogenicity of all study vaccines after each dose.

Table 326-Study HPV-016: Study Procedures

Visit Timing Sampling timepoint	VISIT 1 Day 0 Pre vacc	VISIT 2 Month 1 Post vacc I	VISIT 3 Month 2 Post vacc II	VISIT 4 Month 6 Post vacc II	VISIT 5 Month 7 Post vacc III	TELEPHONE CONTACT† Month 12
Informed consent	●					
Check inclusion criteria	●					
Check exclusion criteria	●					
Check elimination criteria		●	●	●	●	
Check contraindications		●		●		
Collect demographic data	●					
Medical history	●					
History-directed physical examination	○					
Pre-vaccination body temperature	●	●		●		
Internet randomization	●					
Blood sampling: for HPV-16/18 antibody determination (5 mL)	●		●		●	
Urine sampling for pre-vaccination pregnancy test	●	●		●		
Vaccination	●	●		●		
Daily post vaccination recording of solicited symptoms (Days 0-6) by subjects	○	○		○		
Daily post vaccination recording of unsolicited symptoms (Days 0–29) by subjects	○	○		○		
Safety follow-up telephone contact						●
Reporting of all pregnancies and pregnancy outcomes		●	●	●	●	●
Counselling	○					
Return of diary cards		○	○		○	
Diary card transcription		●	●		●	
Record any concomitant medication/vaccination	●	●	●	●	●	
Reporting of SAEs, new onset chronic diseases and other medically significant conditions	●	●	●	●	●	●
Study Conclusion					●	
Safety follow-up conclusion						●

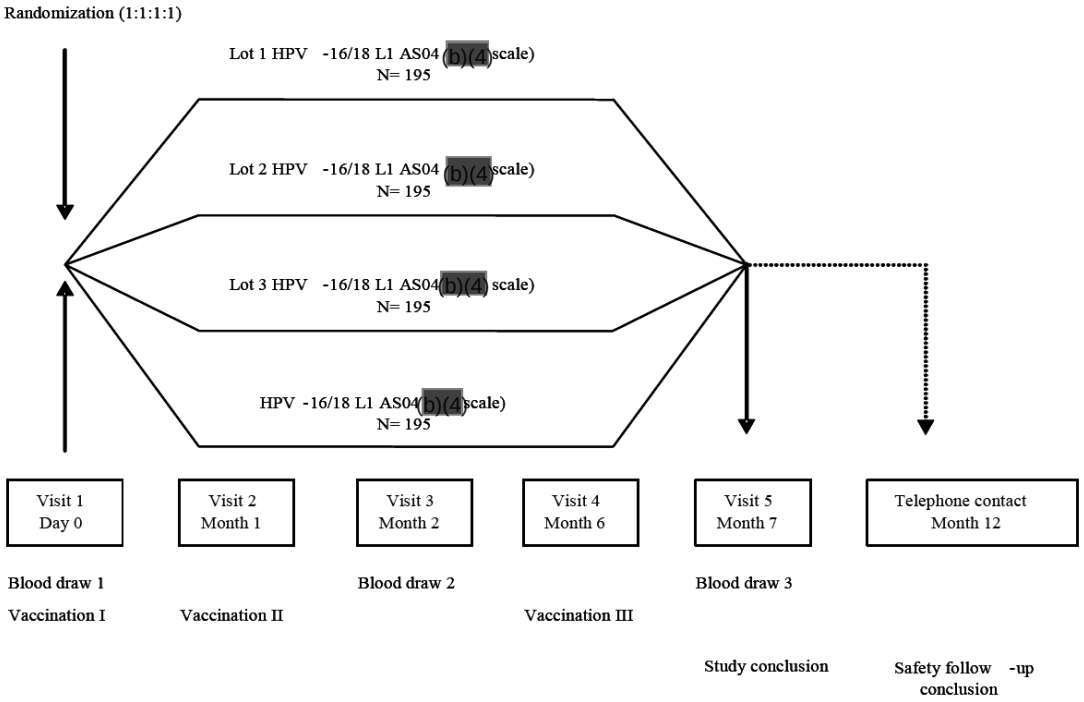
● is used to indicate a study procedure that required documentation in the individual eCRF.
○ is used to indicate a study procedure that did not require documentation in the individual eCRF.
† The study was concluded, and final report written, after all subjects completed visit 5 (Month 7) and all results are available. However, a safety follow-up telephone contact is planned for all subjects at Month 12. The results of the Month 12 safety follow-up telephone contact will be reported in an annex report.
Source: STN 125259/0, CSR 016, Table 1, p. 43

Selection of study population: This study was conducted in healthy female subjects between 18 and 25 years of age. The aim was to enrol approximately 780 subjects in multiple centers located in three European countries (Denmark, Lithuania and Poland).

Inclusion criteria:

- Healthy female 18-25 years of age
- Written informed consent.
- Subjects were to have a negative urine pregnancy test.

Figure 36-Study HPV-016: Study Design



This study was conducted under US IND. This was a phase III, multi-country, double-blinded, randomized (1:1:1:1) trial with four parallel groups. The duration of the study for each subject was 12 months with a telephone contact at Month 12.

Treatment allocation groups:

- Three groups of subjects were to receive one of the three -b(4)- scale production lots of the HPV-16/18 L1 AS04 vaccine.
- The fourth group of subjects was to receive the b(4) scale production lot of the HPV-16/18 L1 AS04 vaccine.
- Treatments were allocated to subjects using internet based randomization system (-b(4)-).
- Remote Data Entry (RDE) was used for data collection.
- Vaccination schedule: Three doses of vaccine were administered intramuscularly according to a 0, 1, 6-month schedule.
- There were five scheduled visits at Months 0, 1, 2, 6 and 7 (+ telephone contact at Month 12).
- Blood sampling schedule: Blood samples were collected from all subjects at Months 0, 2 and 7 (i.e., visits 1, 3 and 5).
- The safety and the reactogenicity of the different lots of the HPV-16/18 vaccine were monitored as follows:
  - Solicited signs and symptoms occurring on the day of vaccination and on the six follow-up days were self-reported in all subjects, using a diary card.
  - Unsolicited signs and symptoms occurring within 30 days after each vaccination were reported in all subjects.
  - Serious adverse events occurring throughout the study period [up to Month 7] (and up to the Month 12 telephone contact) were reported in all subjects.
  - New onset chronic diseases and other medically significant conditions occurring throughout the study [up to Month 7] (and up to the Month 12 telephone contact) were reported in all subjects regardless of causal relationship to vaccination and intensity.

least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Randomization of subjects: A targeted number of approximately 780 subjects aged 18 – 25 years were to be enrolled with approximately 195 subjects in each group. The treatment allocation at the investigator site was performed using a central randomization system on Internet (-b(4)-).

Blinding: All subjects were blinded to the individual subject treatment (HPV vaccine manufacturing lot). Study personnel and GSK Biologicals' personnel directly involved in the conduct of the study were blinded to the individual subject treatment given. Blinding was maintained for the whole study period (until the last subject enrolled completes the last visit at Month 7) and until the database was frozen.

Assessment of immunogenicity variables
Laboratory assays and time points: Blood samples were collected at Months 0, 2 and 7 (i.e., visits 1, 3 and 5). Serological assays for the determination of antibodies against HPV-16 and HPV-18 were performed by ELISA.

Assessment of safety variables: Follow-up of adverse events were similar to the follow-up in study HPV-012 and HPV-014.

STATISTICAL CONSIDERATIONS
Primary endpoints
- Anti-HPV-16/18 seroconversion rates and antibody titers in subjects receiving the three -b(4)- scale lots of the HPV-16/18 L1/AS04 vaccine assessed by ELISA at Month 7.
- Anti-HPV-16/18 seroconversion rates and antibody titers in subjects receiving the -b(4)- scale lot HPV vaccine assessed by ELISA at Month 7.

Secondary endpoints
- Anti-HPV-16/18 seroconversion rates and antibody titers in subjects receiving the three -b(4)- scale lots of the HPV-16/18 L1/AS04 vaccine assessed by ELISA at Month 2.
- Anti-HPV-16/18 seroconversion rates and antibody titers in subjects receiving the b(4) scale lot HPV vaccine assessed by ELISA at Month 2.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms, and occurrence and intensity of solicited local symptoms within 7 days (Days 0 – 6) after each and any vaccination.
- Occurrence, intensity and causal relationship to vaccination of unsolicited symptoms within 30 days (Days 0 – 29) after any vaccination.
- Occurrence and relationship to vaccination of SAEs throughout the study period (up to Month 7).
- Occurrence of new onset chronic diseases and other medically significant conditions prompting emergency room visits or physician visits that are not related to common diseases throughout the study period (up to Month 7) regardless of causal relationship to vaccination and intensity.
- Occurrence of SAEs, new onset chronic diseases and other medically significant conditions up to Month 12 (extended safety follow-up).

Determination of sample size: A sample size of 624 evaluable subjects was needed (156 subjects for each of the three -b(4)- scale production lots and 156 subjects for the b(4) scale lot vaccine) to demonstrate both primary objectives of this study. Assuming 20% non-evaluable

- Subject was to be of non-childbearing potential or on appropriate contraception for 30 days prior to vaccination and to have agreed to continue such precautions for two months after completion of the vaccination series.

Exclusion criteria:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days) of immune-modifying drugs within six months prior to the first vaccine dose.
- Planned administration/ administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after (i.e. Days 0 – 29) the first dose of vaccine. (Administration of routine vaccines as per described)
- A women planning to become pregnant, likely to become pregnant up to two months after the last vaccine dose (up to Month 8)
- Pregnant or breastfeeding women
- Previous vaccination against HPV
- Previous administration of MPL or AS04 adjuvant
- Hypersensitivity to latex (found in syringe-tip cap and plunger)
- Known acute or chronic, clinically significant neurologic, hepatic or renal functional abnormality
- Cancer or autoimmune disease under treatment
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine (e.g. aluminum, MPL).
- Any confirmed or suspected immunosuppressive or immunodeficient condition
- Acute disease at the time of enrolment. All vaccines could be administered to persons with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile illness, i.e. oral temperature <37.5°C (99.5°F) / axillary temperature <37.5°C (99.5°F)).
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or was to be exposed to an investigational or a non-investigational product (pharmaceutical product or device).

Products Used

Table 327-Study HPV-016: Vaccines, formulation, lot numbers and allocation

Vaccine	Formulation	Lot number	Group
HPV-16/18 L1/AS04 vaccine (b)(4) scale lot)	20 µg HPV-16 L1 protein 20 µg HPV-18 L1 protein 50 µg MPL 500 µg aluminium as $Al(OH)_3$	DHPVA014A	(b)(4) L1
		DHPVA017A	L2
		DHPVA016A	L3
HPV-16/18 L1/AS04 vaccine (b)(4) scale lot)	20 µg HPV-16 L1 protein 20 µg HPV-18 L1 protein 50 µg MPL 500 µg aluminium as $Al(OH)_3$	DHPVA004A	

Source: STN 125259/0, CSR 016, Table 3, p. 49

Dosage and administration: The HPV-16/18 vaccine was supplied as liquid in individual pre-filled syringes to be administered (0.5 mL) intramuscularly (IM) into the deltoid (D) of the nondominant arm on a 0, 1, 6-month schedule. The vaccinees were to be observed closely for at

subjects (10% dropout rate and 10% seropositive for both HPV-16 and -18), 780 subjects were needed to be enrolled:

- 195 subjects per group were needed to conclude consistency between the three -b(4)- scale production lots with at least 94% power,
- 195 subjects were needed for the b(4) scale lot vaccine group to rule out the null hypothesis that the pooled -b(4)- production lot is inferior to the b(4) production lot with at least 96% power.

In order to have at least 90% power to achieve both primary objectives, the sample size was derived by ensuring beta less than 6% and 4%, respectively, for the two primary objectives (Bonferroni adjustment of beta). No adjustment was needed for the type I error of each primary comparison since one wanted to reject simultaneously the null hypothesis of non consistency between the -b(4)-lots and non-inferiority between the pooled b(4) and b(4) produced HPV vaccines.

With 156 evaluable subjects enrolled per group, the study had enough power to demonstrate lot-to-lot consistency between the b(4) lots and non-inferiority between the pooled b(4) and b(4) lots. The overall power was greater than 90%.

Study cohorts/data sets analyzed

Total Vaccinated cohort: The Total Vaccinated cohort included all vaccinated subjects. The Total Vaccinated cohort for analysis of safety included all subjects with at least one vaccine administration documented and the Total Vaccinated cohort for analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

According-To-Protocol (ATP) cohort for analysis of safety: The ATP cohort for analysis of safety included all subjects: who had received at least one dose of study vaccine according to their random assignment; with sufficient data to perform an analysis of safety (at least one dose with safety follow-up); for whom administration site of study vaccine was known; who had not received a vaccine not specified or forbidden in the protocol; for whom the randomization code had not been broken.

ATP cohort for analysis of immunogenicity: The ATP cohort for analysis of immunogenicity included all evaluable subjects.

Analysis of immunogenicity: The primary analysis was based on the ATP cohort for analysis of immunogenicity. A second analysis based on the Total Vaccinated cohort was performed to complement the ATP analysis. The analysis of immunogenicity was only performed on subjects seronegative at Day 0 (subjects seropositive for one antigen were eliminated from the analysis of that antigen but were still evaluable for the analysis of the other antigen).

Analysis of immunogenicity: between group comparisons

First primary objective: Lot-to-lot consistency of -b(4)-vaccine lots in terms of geometric mean titers (GMTs)

- 95% CIs of anti-HPV-16 and anti-HPV-18 GMT ratios, one month post Dose 3, were computed for each pair among the three b(4) vaccine lots, using an ANOVA model on the log10 transformation of the titers. The ANOVA model included the vaccine group as fixed effect.

The primary objective was reached if the 95% CIs of the GMT ratios between each pair lie within [0.5; 2] for both anti-HPV-16 and anti-HPV-18 antibodies.

Second primary objective: Non-inferiority of pooled b(4) vaccine lot versus b(4) vaccine lot

- The standardized asymptotic 95% CIs for the difference in seroconversion rate to anti-HPV-16 and anti-HPV-18 (------b(4)----------) one month post Dose 3 were computed using Proc StatXact 5.0.

This objective was reached if the Upper Limit of the 95% CIs of the difference in seroconversion rates for both anti-HPV-16 and anti-HPV-18 antibodies was below 5%.

- 95% CIs of anti-HPV-16 and anti-HPV-18 GMT ratios (b(4) lot GMT divided by -b(4)- lot GMT), one month post Dose 3, were computed using an ANOVA model on the log10 transformation of the titers. The ANOVA model included the vaccine group as fixed effect (pooled -b(4)- lot versus b(4) lot).

This objective was reached if the upper limit of the 95% CIs of the GMT ratios for both anti-HPV-16 and anti-HPV-18 antibodies were below 2.

Secondary objective: Evaluation of immunogenicity of -b(4)- vaccine lots in terms of seroconversion rates

- The standardized asymptotic 95% CIs for the difference in seroconversion rate to anti-HPV-16 and anti-HPV-18, one month post Dose 3, were computed for each pair among the three -b(4)- vaccine lots.

Analysis of immunogenicity: within group comparisons: For each treatment group (pooled -b(4)- lot and b(4) lot if consistency was shown; if consistency was not shown, the three -b(4) lots were to be shown separately), at each time point that a blood sample result was available (Months 0, 2 and 7):

- Seroconversion rate and antibody titers for anti-HPV-16 and anti-HPV-18 (with exact 95% CI) were calculated by group,
- GMT with 95% CI and range of antibody titers were tabulated for antibodies for each antigen.

The distribution of antibody titers for each antigen at Month 7 was displayed using reverse cumulative distribution curves.

Analysis of safety: The primary analysis was based on the Total Vaccinated cohort. A second analysis based on the ATP cohort was performed to complement the Total analysis. All safety/reactogenicity analyses were performed by group. No formal comparisons were made between groups.

Interim analysis: No interim analysis was performed.

STUDY POPULATION RESULTS

Number and distribution of subjects: A total of 798 subjects were enrolled at 9 centres located

Study completion and withdrawal from study: Compliance with completion of the 3-dose vaccination schedule was very high in all vaccine lot groups: 96.7% subjects in the -b(4)- Pooled vaccine lots group (96.0% subjects in the -b(4)- L1 vaccine lot group, 97.0% subjects in the -b(4)- L2 vaccine lot group and 97.0% subjects in the -b(4)- L3 vaccine lot group) and 94.5% subjects in the -b(4)- vaccine lot group.

The number of subjects vaccinated, completed and withdrawn with reason for withdrawal is presented in Table 328 below.

Table 328-Study HPV-016: Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

	Group					
	(b)(4)	L1	(b)(4)	L2	(b)(4) L3	Pooled (b)(4)	Total
Number of subjects vaccinated	199		198		201	598	200	798
Number of subjects completed	182		177		182	541	181	722
Number of subjects withdrawn	17		21		19	57	19	76
Reasons for withdrawal :								
Serious Adverse Event	0		0		1	1	0	1
Non-serious adverse event	2		0		0	2	2	4
Protocol violation	0		1		0	1	0	1
Consent withdrawal (not due to an adverse event)	1		2		3	6	2	8
Migrated/moved from study area	3		0		2	5	7	12
Lost to follow-up (subjects with incomplete vaccination course)	1		3		1	5	2	7
Lost to follow-up (subjects with complete vaccination course)	10		15		12	37	6	43
Others	0		0		0	0	0	0

b(4) L1 = HPV b(4) - DHPVA014A; b(4) L2 = HPV b(4) - DHPVA017A
b(4) L3 = HPV b(4) - DHPVA016A
Pooled = Pooled (b(4))
b(4) = HPV b(4) - DHPVA004A
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Source: STN 125259/0, CSR 016, Table 12, p. 71

Four subjects (subjects no. 160 and 189 in the b(4) L1 vaccine lot group; subjects no. 57 and 149 in the b(4) vaccine lot group) reported non-serious adverse events which led to their withdrawal from the study. One subject (subject no. 4582 in the b(4) L3 vaccine lot group) was withdrawn because of prolapsed vertebral disc which was reported as a SAE.

Protocol deviations leading to exclusion of subjects from an analysis: All enrolled subjects received at least one dose of HPV vaccine. The Total vaccinated cohort included 798 subjects: 598 subjects in the -b(4)- Pooled vaccine lots group (199 subjects in the -b(4)-- L1 vaccine lot group, 198 subjects in the b(4) L2 vaccine lot group and 201 subjects in the b(4) L3 vaccine lot group) and 200 subjects in the b(4) vaccine lot group.

The number of subjects enrolled as well as the number of subjects excluded from ATP analyses are shown in Table 329.

Table 329-Study HPV-016:Number of subjects enrolled into the study as well as the number excluded from ATP anal s r ons for exclusion

	Total			(b)(4) L1		(b)(4) L2		(b)(4) L3		Pooled		(b)(4)	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**	**n**	**s**	**n**	**s**
Total enrolled cohort	798												
Total vaccinated cohort	798		100	199		198		201		598		200	
Administration of vaccine(s) forbidden in the protocol (code 1040)	6	6		2	2	3	3	0	0	5	5	1	1
Study vaccine dose not administered according to protocol (code 1070)	4	4		1	1	0	0	2	2	3	3	1	1
ATP safety cohort	788		98.7	196		195		199		590		198	
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	20	20		2	2	5	5	6	6	13	13	7	7
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	32	39		7	8	8	9	5	6	20	23	12	16
Essential serological data missing (code 2100)	67	77		14	17	17	21	17	19	48	57	19	20
ATP immunogenicity cohort	669		83.8	173		165		171		509		160	

b(4) L1 = HPV b(4) - DHPVA014A; b(4) L2 = HPV b(4) - DHPVA017A; b(4) L3 = HPV b(4) - DHPVA016A; Pooled = Pooled (b(4)); b(4) = HPV b(4) - DHPVA004A; Note: Subjects may have more than one elimination code assigned; n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number; s = number of subjects with the elimination code assigned; % = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Source: STN 125259/0, CSR 016, Table 14, p. 75

Demographic characteristics

ATP cohort for immunogenicity: The demographic profiles of the three -b(4)------ vaccine lot groups subjects and the b(4) vaccine lot group subjects were similar with respect to mean age and racial distribution. The mean age ranged from 21.9 years in the three b(4) vaccine lot groups to 22.0 years in the b(4) vaccine lot group. The study population was predominantly White-Caucasian/European heritage (98.1%). The demographic characteristics of the ATP cohort for immunogenicity are detailed in Table 330.

Table 330-Study HPV-016: Summary of demographic characteristics (ATP cohort for immunogenicity)

	b(4) N=173	b(4) L2 N=165	b(4) L3 N=171	Pooled N=509	b(4) N=160	Total N=669
Age						
Mean (SD)	21.9 (2.11)	21.9 (2.12)	21.9 (2.02)	21.9 (2.08)	22.0 (2.02)	21.9 (2.07)
Median	22.0	22.0	22.0	22.0	22.0	22.0
Min-Max	18-25	18-25	18-25	18-25	18-25	18-25
Race/Ethnicity						
African heritage/African American	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Asian-central/south Asian heritage	0 (0.0%)	0 (0.0%)	2 (1.2%)	2 (0.4%)	0 (0.0%)	2 (0.3%)
Asian-east Asian heritage	0 (0.0%)	1 (0.6%)	1 (0.6%)	2 (0.4%)	0 (0.0%)	2 (0.3%)
Asian-southesast Asian heritage	1 (0.6%)	0 (0.0%)	1 (0.6%)	2 (0.4%)	2 (1.3%)	4 (0.6%)
White-Arabic/north African heritage	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
White-Caucasian/European heritage	171 (98.8%)	162 (98.2%)	165 (96.5%)	498 (97.8%)	158 (98.8%)	656 (98.1%)

b(4) L1 = HPV b(4) - DHPVA014A; b(4) L2 = HPV b(4) - DHPVA017A; b(4) L3 = HPV b(4) - DHPVA016A
Pooled = Pooled (b(4)); b(4) = HPV b(4) - DHPVA004A
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Source: STN 125259/0, CSR 016, Table 15, p. 76

Total vaccinated cohort: The demographic profiles of the Total vaccinated cohort were similar with respect to mean age and racial distribution for the three b(4) vaccine lot groups subjects and the b(4) vaccine lot group subjects. The mean age ranged from 21.8 years (b(4)---- L1 and L2 vaccine lots groups) to 22.0 years in the b(4) vaccine lot group with a mean age of 21.9 years in the b(4) L3 vaccine lot group. The study population was predominantly white (97.9%). (Source: STN 125259/0, CSR 016, Supplement 4, p. 132, not shown here).

ATP cohort for safety: The demographic characteristics of the ATP cohort for safety are comparable to those of the Total vaccinated cohort. (Source: STN 125259/0, CSR 016, Supplement 5, p. 133, not shown here).

IMMUNOGENICITY RESULTS

Data sets analyzed: Analysis of immunogenicity was performed on the ATP cohort (primary analysis) and on the Total vaccinated cohort only for subjects seronegative at Day 0 (subjects seropositive for one antigen were eliminated for the analysis of that antigen but were still evaluable for the analysis of the other antigen).

According-To-Protocol analysis: The ATP cohort for immunogenicity included 669 subjects: 509 subjects in the b(4) Pooled vaccine lots group (173 subjects in the b(4) L1 vaccine lot group, 165 subjects in the b(4) L2 vaccine lot group and 171 subjects in the b(4) L3 vaccine lot group) and 160 subjects in the b(4) vaccine lot group.

First primary objective: lot-to-lot consistency of the three industrial production b(4) **scale lots in terms of geometric mean titers (GMTs)**

The anti-HPV-16 and the anti-HPV-18 GMT ratios following the administration of the third vaccine dose between the three b(4) vaccine lots at Month 7 are presented in Table 331.

The two-sided 95% confidence intervals (CI) of the GMT ratio of anti-HPV-16 and anti-HPV-18 antibodies between each pair among the three -b(4)-- vaccine lot groups at Month 7 were within the pre-defined limits [0.5, 2].

- GMT ratios for anti-HPV-16 antibodies ranged from 1.04 [0.81; 1.34] (b(4) L1 vaccine lot group/ b(4) L2 vaccine lot group) to 1.26 [0.98; 1.63] (b(4) L1 vaccine lot group/ b(4) L3 vaccine lot group).
- GMT ratios for anti-HPV-18 antibodies ranged from 1.19 [0.95; 1.49] (b(4) L1 vaccine lot group/ b(4) L2 vaccine lot group) to 1.48 [1.18; 1.85] (b(4) L1 vaccine lot group/ b(4) L3 vaccine lot group).

Te three b(4) vaccine lots were shown to be consistent for both anti-HPV-16 and anti-HPV-18 antigens.

Table 331-Study HPV-016: GMT ratios between the three (b)(4) lots for anti-HPV-16/18, Post Dose III, Month 7 (ATP cohort for im genicity)

								GMT ratio†				
											95% CI	
Antibody	Group description	N	GMT†	Group description	N	GMT†	Ratio order			Value	LL	UL
HPV-16 IGG (EL.U/mL)	(b)(4) L1	118	9073.6	(b)(4) L2	127	8687.9	(b)(4) L1	(b)(4)	L2	1.04	0.81	1.34
	L1	118	9073.6	L3	126	7176.6	L1		L3	1.26	0.98	1.63
	L2	127	8687.9	L3	126	7176.6	L2		L3	1.21	0.94	1.55
HPV-18 IGG (EL.U/mL)	L1	129	4348.9	L2	143	3652.1	L1		L2	1.19	0.95	1.49
	L1	129	4348.9	L3	135	2941.8	L1		L3	1.48	1.18	1.85
	L2	143	3652.1	L3	135	2941.8	L2		L3	1.24	1.00	1.55

†: Calculation rmed on subjects seronegat or dose 1.
-b(4)- L1 = HPV -b(4)- - DHPVA014A
-b(4)- L2 = HPV -b(4)- - DHPVA017A
-b(4)- L3 = HPV -b(4)- - DHPVA016A
IGG = Immunoglobulin G
GMT = geometric mean antibody titer
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance with more than 2 groups); LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 016, Table 16, p. 78

Second primary objective: non-inferiority assessment between the HPV vaccine produced at -b(4)- manufacturing scale and the HPV vaccine produced at b(4) scale: As the first primary objective was reached, the three -b(4)- vaccine lots were pooled in order to assess sequentially the second primary objective based on two criteria.

Non-inferiority in terms of seroconversion rates: The difference in seroconversion rates between the -b(4)- scale vaccine (pooled lots) and the b(4) scale vaccine for HPV-16 and HPV-18 antibodies is presented in Table 332. One month after the third vaccine dose (Month 7), the upper limit of the 95% CI for the difference between the percentages of subjects who seroconverted after being administered the b(4) scale vaccine versus the-b(4)- scale vaccine (pooled lots) is less than the pre-defined clinical limit of 5% (1.02 for anti-HPV-16 antibodies and 0.94 for the HPV-18 antibodies). The HPV vaccine produced at-b(4)- manufacturing scale was non-inferior to the HPV vaccine produced at b(4) scale in terms of seroconversion.

Table 332-Study HPV-016: Non-inferiority assessment in terms of seroconversion rates between the-b(4)- lot and the pooled-b(4)- lots for anti-HPV-16/18, Post Dose III, Month 7 (ATP cohort for immunogenicity)

							Difference in seroconversion rate (Group 2 - Group 1)			
									95 % CI	
Antibody	Group 1	N	%	Group 2	N	%	Difference†	%	LL	UL
HPV-16 IGG	Pooled	371	100	(b)(4)	102	100	(b)(4) - Pooled	0.00	-3.63	1.02
HPV-18 IGG	Pooled	407	100		117	100		0.00	-3.18	0.94

†: Calculation performed on subjects seronegative prior dose 1.
Pooled = Pooled -b(4)-
b(4) = HPV b(4) - DHPVA004A
IGG = Immunoglobulin G
N = number of subjects with available results
% = percentage of subjects with HPV-16 IGG titer ≥ 8 EL.U/mL or with HPV-18 IGG titre ≥ 7 EL.U/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 016, Table 17, p. 79

Since the non-inferiority in terms of seroconversion between the -b(4)- scale vaccine and the b(4) scale vaccine was reached, non-inferiority in terms of GMTs was assessed.

Non-inferiority in terms of GMTs: The GMTs ratio between the-b(4)- scale vaccine and the -b(4)- scale vaccine (pooled lots) for HPV-16 and HPV-18 antibodies are detailed in Table 333. The upper limits of the two-sided 95% CIs of the GMT ratio of anti-HPV-16 and anti-HPV-18 antibodies at Month 7 between the-b(4)- scale vaccine and the-b(4)- scale vaccine (pooled lots) were less than the pre-defined clinical limit of 2 (1.08 for anti-HPV-16 antibodies and 0.97 for anti-HPV-18 antibodies). It was concluded that the HPV vaccine produced at-b(4)- manufacturing scale was non-inferior to the HPV vaccine produced at-b(4)- scale in terms of GMTs.

Table 333-Study HPV-016: Non-inferiority assessment in terms of GMT ratios between the b(4) lot and the pooled -b(4)- lots for anti-HPV-16/18, Post Dose III, Month 7 (ATP cohort for immunogenicity)

Antibody	(b)(4)		Pooled		GMT ratio (b)(4) / Pooled)†		
						95% CI	
	N	GMT	N	GMT	Value	LL	UL
HPV-16 IGG (EL.U/mL)	102	7190.8	371	8255.2	0.87	0.70	1.08
HPV-18 IGG (EL.U/mL)	117	2891.8	407	3592.7	0.80	0.66	0.97

†: Calculation performed on subjects seronegative prior dose 1
Pooled = Pooled (b(4))
b(4) = HPV b(4) - DHPVA004A
GMT = geometric mean antibody titer
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 016, Table 18, p. 79

Secondary objectives: evaluation of immunogenicity of the three industrial production -b(4) scale lots in terms of seroconversion rates: The difference in seroconversion rates between the three -b(4)- vaccine lots for HPV-16 and HPV-18 antibodies are presented respectively in Tables 334 and 335. One month after the third dose (Month 7), the difference between each pair among the percentages of subjects who seroconverted after being administered one of the three -b(4)- vaccine lots was equal to 0%. This result confirms the consistency showed between the three -b(4)-vaccine lots in terms of GMTs in the primary objective.

Table 334-Study HPV-016: Consistency assessment in terms of seroconversion rates between the three b(4) lots for anti-HPV-16 IGG, Post Dose III, Month 7 (ATP cohort for immunogenicity)

							Difference in seroconversion rate (Group 2 - Group 1)			
									95 % CI	
Group 1	N	%	Group 2	N	%	Difference†		%	LL	UL
(b)(4)	L1	118	100	L2	127	100	(b)(4) L2 - (b)(4) L1	0.00	-2.94	3.15
(b)(4)	L1	118	100	L3	126	100	(b)(4) L3 - (b)(4) L1	0.00	-2.96	3.15
(b)(4)	L2	127	100	L3	126	100	(b)(4) L3 - (b)(4) L2	0.00	-2.96	2.94

†: Calculation performed on subjects seronegative prior dose 1
b(4) L1 = HPV b(4) - DHPVA014A; b(4) L2 = HPV b(4) - DHPVA017A; b(4) L3 = HPV b(4) - DHPVA016A
IGG = Immunoglobulin G
N = number of subjects with available results
% = percentage of subjects with HPV-16 IGG titer ≥ 8 EL.U/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 016, Table 19, p. 80

Table 335-Study HPV-016: Consistency assessment in terms of seroconversion rates between the three b(4) lots for anti-HPV-18 IGG, Post Dose III, Month 7 (ATP cohort for immunogenicity)

							Difference in seroconversion rate (Group 2 - Group 1)†			
									95 % CI	
Group 1	N	%	Group 2	N	%	Difference		%	LL	UL
(b)(4)	L1	129	100	L2	143	100	(b)(4) L2 - (b)(4) L1	0.00	-2.62	2.89
(b)(4)	L1	129	100	L3	135	100	(b)(4) L3 - (b)(4) L1	0.00	-2.77	2.89
(b)(4)	L2	143	100	L3	135	100	(b)(4) L3 - (b)(4) L2	0.00	-2.77	2.62

†: Calculation performed on subjects seronegative prior dose 1
b(4) L1 = HPV b(4) - DHPVA014A; b(4) L2 = HPV b(4) - DHPVA017A; b(4) L3 = HPV b(4) - DHPVA016A
IGG = Immunoglobulin G
N = number of subjects with available results
% = percentage of subjects with HPV-18 IGG titer ≥ 7 EL.U/mL; 95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit; STN 125259/0, CSR 016, Table 20, p. 80

Secondary objectives: summary of anti-HPV-16 and anti-HPV-18 antibody levels

Seropositivity by pre-vaccination status: One month after the second vaccine dose (Month 2), 100% of the initially seronegative subjects had already seroconverted for both antigens. At Month 7, all initially seronegative subjects had seroconverted with high GMT values for both anti-HPV-16 (9073.6 EL.U/mL in the b(4) L1 vaccine lot group; 8687.9 EL.U/mL in the b(4) L2 vaccine lot group; 7176.6 EL.U/mL in the b(4) L3 vaccine lot group; 7190.8 EL.U/mL in the b(4) vaccine lot group) and anti-HPV-18 antibodies (4348.9 EL.U/mL in the b(4) L1 vaccine lot group; 3652.1 EL.U/mL in the b(4) L2 vaccine lot group; 2941.8 EL.U/mL in the b(4) L3 vaccine lot group; 2891.8 EL.U/mL in the b(4) vaccine lot group) regardless of the vaccine lot used.

Reviewer's Comment: All subjects, regardless of baseline serostatus, had seroconverted by 1 month post dose 3 for each anti-HPV 16 and anti-HPV 18. The GMTs are higher in subjects who were initially seronegative as compared to those who were initially seropositive. (Source: STN 125259/0, CSR 016, Table 21, p. 82-83 and Table 22, p. 84-85, not shown here)

Analysis of Total vaccinated cohort: The immunogenicity data obtained from the analysis of the Total vaccinated cohort were consistent with those obtained from the analysis of immunogenicity in the ATP cohort.

SAFETY RESULTS

Safety Results: Compliance in terms of returning local and general symptom sheets overall was very high in the four vaccine lots groups (> 97%). (Source: STN 125259/0, CSR 016, Table 23, p. 87, not shown here). Compliance with safety data capture presented was also high in all vaccine lot groups (> 97% of all doses). (Source: STN 125259/0, CSR 016, Supplement 17, p. 144, not shown here).

Data sets analyzed: The analysis of safety and reactogenicity was performed on the Total vaccinated cohort (primary analysis). Analyses based on the ATP cohort for safety were performed to supplement the primary analysis.

Total vaccinated cohort analysis: The Total vaccinated cohort was comprised of 798 subjects with 199 subjects in the b(4) L1 vaccine lot group, 198 subjects in the b(4) L2 vaccine lot group, 201 subjects in the b(4) L3 vaccine lot group and 200 subjects in the b(4) vaccine lot group.

Overall incidence of adverse events

Solicited and unsolicited symptoms: The percentages of any solicited and unsolicited symptoms, solicited and unsolicited local symptoms, solicited and unsolicited general symptoms reported following each dose in each vaccine lot group during the 30-day (Days 0 - 29) post-vaccination period were reviewed. The percentages for lota are comparable to each other.

Reviewer's Comment: The proportions of subjects with local reactions are higher as compared to the proportions of subjects with general reactions. The proportions of subjects with an adverse reaction per subject are similar for all lots tested. (Source: STN 125259/0, CSR 016, Table 24, p. 89, not shown here)

Reviewer's Comment: The proportions of Grade 3 reactions across lots were fairly comparable. The subjects in the Lot b(4) L1 group experienced a numerically higher proportion of adverse reactions as compared to the other lots, but the 95% CIs overlapped for all groups. There was no increase in Grade 3 adverse events with subsequent dosing. (Source: STN 125259/0, CSR 016, Table 25, p. 90, not shown here)

Solicited local adverse events: Overall, the percentages of doses with local solicited symptoms reported during the 7-day (Days 0 - 6) follow-up period after each dose were similar across all vaccine lot groups. In all vaccine lot groups, the most frequently reported solicited local symptom during the 7-day post-vaccination period was pain at the injection site followed by redness and swelling. The percentages of redness and swelling tended to increase from Dose 2 to Dose 3 in all vaccine lot groups whereas there was no increase in the incidence of pain at the injection site.

Table 336-Study HPV-016: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following overall/subject (b(4) Pooled and b(4) vaccine lots) (Total vaccinated cohort)

	Pooled	-b(4)-
Symtpom	n/N (%)	n/N (%)
Pain		
All	576/594 (97.0%)	192/197 (97.5%)
Grade 3	108/594 (18.2%)	30/197 (15.2%)
Redness		
All	373/594 (62.8%)	126/197 (64.0%)
Grade 3	21/594 (3.5%)	6/197 (3.0%)
Swelling		
All	341/594 (57.4%)	107/197 (54.3%)
Grade 3	27/594 (4.5%)	10/197 (5.1%)

Pooled = Pooled (b(4))
b(4) = HPV b(4) - DHPVA004A
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
For Overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 016, Table 27, p. 94

Reviewer's Comment: The comparison of solicited local adverse events showed similar proportions of subjects with such events in all three b(4) lots (although there was a slightly higher numeric proportion of subjects with Grade 3 swelling for the L1 lot, the 95% CIs for all groups overlapped. (Source: STN 125259/0, CSR 016, Table 26, p. 93, not shown here). There was no apparent difference in proportion of subjects with solicited local adverse events when comparing the pooled b(4) lots and the b(4) lots. (See Table 336 above).

Duration of pain and swelling during the 7-day post-vaccination follow-up period were similar across all groups, around 3.0 days in all -b(4)- vaccine lot groups and in the b(4) vaccine lot group. Redness lasted around 2.0 days in the b(4) L3 vaccine lot group and around 3.0 days in the three other vaccine lots groups. There were few subjects with solicited local symptoms beyond 7 day period. (Source: STN 125259/0, CSR 016, Supplement 26, p. 157, not shown here).

Solicited general adverse events: The incidence of solicited general symptoms reported during the 7-day (Days 0 - 6) follow-up period after each vaccine dose and overall is presented in Table 337. The percentage of doses with solicited general symptoms was similar across all vaccine lot groups with respect to incidence and severity. There was no increase in the events observed with subsequent doses of each vaccine lot. The most frequently solicited general symptoms during the 7-day (Days 0 - 6) postvaccination period were fatigue, headache, myalgia, gastrointestinal symptoms and arthralgia. The reporting of fever, rash and urticaria was less frequent in all vaccine lot groups.
The incidence of Grade 3 solicited general symptoms followed the same pattern. The most frequently Grade 3 solicited general symptoms were fatigue, headache, and myalgia.

Reviewer's Comment: The incidence of rates of solicited general symptoms were similar across b(4) lots and across doses, and when calculated per subject, and 95% CIs were overlapping in each category (all and Grade 3). (Source: STN 125259/0, CSR 016, Table 28, p. 97-100, not shown here). In addition, when the pooled -b(4)- lots were compared to the b(4) lot, the incidence rates of all solicited general adverse events were similar after each dose, when calculated per dose, and per subject, with 95% CIs overlapping in each category. The results are shown for the rate per subject in Table 337 below.

Table 337-Study HPV-016: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Pooled lot and b(4) lot) (Total vaccinated cohort)

	Pooled b(4)		**b(4)**	
	Overall/subject			
Symptom	n/N	%	n/N	%
Arthralgia				
All	110/594	18.5%	35/197	17,8%
Grade 3	5/594	0.8%	0/197	0.0%
Fatigue				
All	340/594	57.2%	105/197	53.3%
Grade 3	27/594	4.5%	12/197	6.1%
Fever (º C) Axilla				
All	48/594	8.1%	15/197	7.6%
>39.0	1/594	0.2%	0/197	0.0%
Gastrointestinal				
All	173/594	29.1%	49/197	24.9%
Grade 3	9/594	1.5%	5/197	2.5%
Headache				
All	297/594	50.0%	93/197	47.2%
Grade 3	31/594	5.2%	5/197	2.5%
Myalgia				
All	230/594	38.7%	66/197	33.5%
Grade 3	17/594	2.9%	2/197	1.0%
Rash				
All	40/594	6.7%	15/197	7.6%
Grade 3	0/594	0.0%	0/197	0.0%
Urticaria				
All	19/594	3.2%	10/197	5.1%
Grade 3	0/594	0.0%	0/197	0.0%

Pooled = Pooled (b(4))
b(4) = HPV b(4) - DHPVA004A
For overall/subject: N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 016, Table 29, p. 101-104

The duration (median number of days) of fatigue, headache, arthralgia and myalgia was similar and lasted a median of 2.0 days in all vaccine lot groups. Fever lasted a median of 1.0 day in all vaccine lot groups. Gastrointestinal symptoms and rash lasted a median of 2.0 days in all vaccine lot groups except in the b(4) L2 vaccine lot group where these symptoms lasted respectively a median of 1.0 and 4.0 days. Urticaria lasted a median of 2.5 days in the -b(4) L1 vaccine lot group, 2.0 days in the b(4) L2 vaccine lot group, 4.0 days in the -b(4) L3 vaccine lot group and 3.0 days in the b(4) vaccine lot group. (Source: STN 125259/0, CSR 016, Supplement 24, p. 151-155, not shown here).

There was no urticaria/rash within the 30 minutes following the administration of any vaccine dose to subjects reported by the investigator. (Source: STN 125259/0, CSR 016, Supplement 27, p. 158, not shown here).

The number of solicited general symptoms ongoing beyond the 7-day (Days 0 - 6) postvaccination period are similar across all vaccine lot groups. (Source: STN 125259/0, CSR 016, Supplement 29, p. 162-164, not shown here).

Unsolicited adverse events: The percentages of doses with at least one unsolicited symptom (classified by MedDRA Primary System Organ Class and Preferred Term) reported within the 30-day (Days 0-29) post-vaccination period were similar across all vaccine lot groups: 13.6% of doses in the -b(4)- Pooled vaccine lots group (12.9%, 11.9% and 16.0% in each b(4) vaccine lot group) and 13.8% of doses in the b(4) vaccine lot group. The percentage of subjects reporting at least one unsolicited symptoms were also similar across all vaccine groups.
The percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class within the 30-day (Days 0-29) post-vaccination period were presented. The most frequently reported unsolicited symptoms under Primary System Organ Class were:

- Infections and infestations (nasopharyngitis reported after 1.7% of doses in the b(4) Pooled vaccine lots group [1.5%, 1.7% and 1.8%, in each b(4) vaccine lot group] and after 1.2% of doses in the b(4) vaccine lot group; Cystitis reported after 0.8% of doses in the b(4) Pooled vaccine lots group [1.2%, 0.5% and 0.7%, in each b(4) vaccine lot group] and after 0.7% of doses in the b(4) vaccine lot group.
- General disorders and administration site conditions (injection site pruritus reported after 0.8% of doses in the b(4) Pooled vaccine lots group [1.2%, 0.5% and 0.7%, in each b(4) vaccine lot group] and after 2.2% of doses in the b(4) vaccine lot group; injection site induration reported after 0.6% of doses in the b(4) Pooled vaccine lots group [0.9%, 0.5% and 0.5%, in each b(4) vaccine lot group] and after 0.3% of doses in the b(4) vaccine lot group; injection site reaction reported after 0.5% of doses in the b(4) Pooled vaccine lots group [0.2%, 0.9% and 0.5%, in each b(4) vaccine lot group] and after 0.5% of doses in the b(4) vaccine lot group.

Reviewer's Comment: Table 338 compares unsolicited AEs in recipients of the pooled b(4) lots and b(4) lot. The 95% CIs overlap when comparing the b(4) lots. (Source: STN 125259/0, CSR 016, Table 31, 106, not shown here).

Table 338-Study HPV-016: Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class within the 30-day (Days 0-29) post-vaccination period (Pooled and b(4) vaccine lot groups) (Total vaccinated cohort)

	Pooled N = 1768				(b)(4) N = 585			
			95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL
At least one unsolicited symptom	241	13.6	12.1	15.3	81	13.8	11.2	16.9
Blood and lymphatic system disorders (10005329)	4	0.2	0.1	0.6	4	0.7	0.2	1.7
Cardiac disorders (10007541)	0	0.0	0.0	0.2	1	0.2	0.0	0.9
Ear and labyrinth disorders (10013993)	1	0.1	0.0	0.3	0	0.0	0.0	0.6
Endocrine disorders (10014698)	1	0.1	0.0	0.3	1	0.2	0.0	0.9
Eye disorders (10015919)	2	0.1	0.0	0.4	0	0.0	0.0	0.6
Gastrointestinal disorders (10017947)	16	0.9	0.5	1.5	6	1.0	0.4	2.2
General disorders and administration site conditions (10018065)	53	3.0	2.3	3.9	28	4.8	3.2	6.8
Immune system disorders (10021428)	5	0.3	0.1	0.7	0	0.0	0.0	0.6
Infections and infestations (10021881)	106	6.0	4.9	7.2	34	5.8	4.1	8.0
Injury, poisoning and procedural complications (10022117)	7	0.4	0.2	0.8	1	0.2	0.0	0.9
Investigations (10022891)	1	0.1	0.0	0.3	0	0.0	0.0	0.6
Musculoskeletal and connective tissue disorders (10028395)	18	1.0	0.6	1.6	1	0.2	0.0	0.9
Nervous system disorders (10029205)	24	1.4	0.9	2.0	6	1.0	0.4	2.2
Psychiatric disorders (10037175)	2	0.1	0.0	0.4	0	0.0	0.0	0.6
Renal and urinary disorders (10038359)	1	0.1	0.0	0.3	0	0.0	0.0	0.6
Reproductive system and breast disorders (10038604)	10	0.6	0.3	1.0	1	0.2	0.0	0.9
Respiratory, thoracic and mediastinal disorders (10038738)	19	1.1	0.6	1.7	6	1.0	0.4	2.2
Skin and subcutaneous tissue disorders (10040785)	10	0.6	0.3	1.0	7	1.2	0.5	2.4
Vascular disorders (10047065)	2	0.1	0.0	0.4	1	0.2	0.0	0.9

Pooled = Pooled (b(4))
b(4) = HPV b(4) - DHPVA004A
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of administered doses
n/% = number/percentage of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 016, Table 32, p. 107

Overall, 32 subjects reported 35 Grade 3 unsolicited symptoms within the 30-day (Days 0 - 29) post-vaccination period. The percentage of doses followed by at least one Grade 3 unsolicited symptom was reported after 1.5% of doses in the b(4) Pooled vaccine lots group (0.9%, 1.0% and 2.5%, in each b(4) vaccine lot group) and after 1.2% of doses in the b(4) vaccine lot group.

Table 339-Study HPV-016: Percentage of subjects reporting the occurrence of Grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) postvaccination period (Pooled and b(4) vaccine lot groups) (Total vaccinated coho

		Pooled N = 598				(b)(4) N = 200			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one unsolicited symptom		25	4.2	2.7	6.1	7	3.5	1.4	7.1
Blood and lymphatic system disorders (10005329)	Lymphadenitis (10025188)	0	0.0	0.0	0.6	1	0.5	0.0	2.8
Gastrointestinal disorders (10017947)	Tooth disorder (10044034)	0	0.0	0.0	0.6	1	0.5	0.0	2.8
	Toothache (10044055)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
General disorders and administration site conditions (10018065)	Chills (10008531)	0	0.0	0.0	0.6	1	0.5	0.0	2.8
	Injection site haematoma (10022066)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Oedema peripheral (10030124)	0	0.0	0.0	0.6	1	0.5	0.0	2.8
	Pyrexia (10037660)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Infections and infestations (10021881)	Appendicitis (10003011)	0	0.0	0.0	0.6	1	0.5	0.0	2.8
	Cystitis (10011781)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Erysipelas (10015145)	0	0.0	0.0	0.6	1	0.5	0.0	2.8
	Hand-foot-and-mouth disease (10019113)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Herpes zoster (10019974)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Influenza (10022000)	3	0.5	0.1	1.5	0	0.0	0.0	1.8
	Laryngitis (10023874)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Nasopharyngitis (10028810)	3	0.5	0.1	1.5	0	0.0	0.0	1.8
	Otitis media (10033078)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Pharyngitis (10034835)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Pneumonia (10035664)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Sinusitis (10040753)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Tonsillitis (10044008)	0	0.0	0.0	0.6	1	0.5	0.0	2.8
	Upper respiratory tract infection (10046306)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Injury, poisoning and procedural complications (10022117)	Injury (10022116)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Joint injury (10060820)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Musculoskeletal and connective tissue disorders (10028395)	Intervertebral disc protrusion (10050296)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Nervous system disorders (10029205)	Dizziness (10013573)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Headache (10019211)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Somnolence (10041349)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Psychiatric disorders (10037175)	Depression (10012378)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Respiratory, thoracic and mediastinal disorders (10038738)	Pharyngolaryngeal pain (10034844)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.2	0.0	0.9	0	0.0	0.0	1.8
	Hyperhidrosis (10020642)	0	0.0	0.0	0.6	1	0.5	0.0	2.8

Pooled = Pooled (b(4)); b(4) = HPV b(4) - DHPVA004A; At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term); N = number of subjects with at least one administered dose; n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 016, Supplement 39, p. 184

New onset of chronic diseases: Seventeen subjects reported 17 events identified as NOCDs. The most frequently events identified as NOCD were hypersensitivity and seasonal allergy.

Table 340-Study HPV-016: Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (up to Month 7) (Total vaccinated cohort)

	Preferred Term	Pooled N=598	-b(4)- N=200
Primary System Organ Class		**n (%) [95% CI]**	**n (%) [95% CI]**
At least one symptom		**14 (2.3%) [1.3, 3.9%)**	**3 (1.5%) [0.3, 4.3%]**
Endocrine disorders	Hyerthyroidism	1(0.2%)	0 (0.0%)
Gastrointestinal disorders	Gastritis erosive	0 (0.0%)	1 (0.5%)
Immune system disorders	Allergy to arthropod sting	1 (0.2%)	0 (0.0%)
	Hypersensitivity	5 (0.8%)	0 (0.0%)
	Seasonal allergy	4 (0.7%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Arthritis	1 (0.2%)	0 (0.0%)
	Arthritis reactive	1 (0.2%)	1 (0.5%)
Skin and subcutaneous tissue disorders	Dermatitis allergic	1 (0.2%)	0 (0.0%)
	Urticaria	0 (0.0%)	1 (0.5%)

At least one NOCD = at least one NOCD experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 016, Table 35, p. 110)

New onset of autoimmune diseases: Among the 17 NOCDs according to GSK assessment, 4 events were classified as autoimmune diseases by a GSK physician. The percentages of subjects reporting NOADs were similar across all vaccine lot groups: one subject in each vaccine lot group.

Table 341-Study HPV-016: Percentage of subjects reporting the occurrence of New Onset Autoimmune Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (up to Month 7) (Total vaccinated cohort)

	Preferred Term	Pooled N=598	-b(4)- N=200
Primary System Organ Class		**n (%) [95% CI]**	**n (%) [95% CI]**
At least one symptom		**3 (0.5%) [0.1, 1.5%]**	**1 (0.5%) [0.0, 2.8%]**
Endocrine disorders	Hyperthyroidism	1 (0.2%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Arthitis	1 (0.2%)	0 (0.0%)
	Arthritis reactive	1 (0.2%)	1 (0.5%)

Pooled = Pooled (-b(4)-)
b(4) = HPV b(4) - DHPVA004A
At least one NOAD = at least one NOAD experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the NOAD
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 016, Table 36, p. 111

Reviewer's Comment: In this study, 3 events of arthritis and reactive arthritis occurred in subjects who received HPV vaccine trhough Month 7. These events were part of an overall review of musculoskeletal events of potential autoimmune etiology. The events in these subjects included one subject with a diagnosis of a viral syndrome 106 days after dose 2 (considered not related to an immune mediated event by a panel of rheumatology experts), a subject with arthritis associated with knee ligament rupture (uncertain etiology) and one additional subjects with reactive arthritis at 63 days after dose 2 (also of uncertain etiology). The events were reviewed by an expert panel of rheumatologists assembled by GSK. Please see conclusions regarding these

events in the overview of safety section. Events such as these will be collected during the post-marketing period (part of a post-marketing commitment) in a large managed care organization. Final details of the study protocol are being finalized at the time of the approval.

Medically significant adverse events: The percentages of subjects reporting at least one medically significant AE (classified by MedDRA Primary System Organ Class and Preferred Term) during the entire follow-up period (up to Month 7) are similar in the pooled b(4) group (11.9%) and the b(4) group (11.5%). The most frequently events reported was cystitis in all vaccine lot groups (3.0% of subjects in the b(4) L1 vaccine lot group, 2.0% of subjects in the b(4) L2 vaccine lot group, 1.5% of subjects in the b(4) L3 vaccine lot group and 1.5% of subjects in the b(4) vaccine lot group). (Source: STN 125259/0, CSR 016, Table 38, p. 115-116, not shown here)

Serious adverse events
Fatal events: There were no fatalities reported during the study.

Non-fatal events: Overall, 7 subjects experienced and reported 8 SAEs. None of the SAEs reported were considered as related to vaccination by the investigator. Among the 8 SAEs reported throughout the study, one SAE led to the withdrawal from the study of subject no. 4582 (b(4) L3 vaccine lot group).

Table 342-Study EXT HPV-016: SAEs (Month 0-7)

Case number, age	Event (treatment, possible etiology)	Time to Event	Duration of Event	Outcome	Relationship to vaccination per investigator
197, 23 years	Hit by car	46 days after dose 2	1 day	Recovered	Unrelated
205, 19 years	Pelvic inflammation (Chlamydia)	89 days after dose 2	2 days	Recovered	Unrelated
2227, 20 years	Appendicitis	82 days after dose 2	2 days	Recovered	Unrelated
4508, 23 years	SVT, syncope (counted as 2 SAEs)	117 days aftare dose 2	7 days	Recovered	Unrelated
4572, 22 years	Appendicitis	25 days after dose 1	6 days	Recovered	Unrelated
4582, 23 years	Prolapsed vertebral disc	19 days after dose 1	Ongoing	Withdrew from study	Unrelated
5023, 23 years	Femur fracture (ski accident)	30 days after dose 2	35 days	Recovering	Unrelated

There were no SAEs reported by subjects in the b(4) L2 vaccine lot group.
Reviewer's Comment: The safety reports for these SAEs were reviewed. None of the events was considered related to study vaccine.

Table 343-Study HPV-016: Summary of Serious Adverse Events reported (Total vaccinatedcohort)

	Group				Total
	(b)(4)	L1	(b)(4)	L3 Pooled	(b)(4)
Number of subjects with at least one SAE reported	2	2	4	3	7
Number of doses followed by at least one SAE	2	2	4	3	7
Number of SAEs classified by MedDRA Preferred Term*	2	2	4	4	8
Number of SAEs reported	2	2	4	4	8

b(4) L1 = HPV b(4) - DHPVA014A; b(4) L2 = HPV b(4) - DHPVA017A
b(4) L3 = HPV b(4) - DHPVA016A
Pooled = Pooled (b(4)); b(4) = HPV b(4) - DHPVA004A
* SAEs symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted Once
Source: STN 125259/0, CSR 016, Table 39, p. 118

Table 344-Study HPV-016: Percentage of subjects reporting the occurrence of Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (up to Month 7) (Pooled and b(4) vaccine lot groups) (Total vaccinated cohort)

	Preferred Term	Pooled N=598	b(4) N=200
Primary System Organ Class		**n (%) [95% CI]**	**n (%) [95% CI]**
At least one SAE		**4 (0.7%) [0.2, 1.7%]**	**3 (1.5%) [0.3, 4.3%]**
Cardiac disorders	Supraventricular tachycardia	0 (0.0%)	1 (0.5%)
Infections and infestations	Appendicitis PID	0 (0.0%) 1 (0.2%)	2 (1.0%) 0 (0.0%)
Injury, poisoning and procedural complications	Femur fracture Road traffic accident	1 (0.2%) 1 (0.2%)	0 (0.0%) 0 (0.0%)
Musculskeletal and connective tissue disorders	Intervertebral disc protrusion	1 (0.2%)	0 (0.0%)
Nervous system disorders	Syncope	0 (0.0%)	1 (0.5%)

Pooled = Pooled (b(4)); b(4) = HPV b(4) - DHPVA004A
At least one SAE = at least one SAE experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the SAE
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: Table 41, p. 120

Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study
Four subjects withdrew from the study due to non-serious AEs:

- Subject no. 57 who suffered from swollen glands discontinued the study before receiving the third dose of HPV-16/18 vaccine (b(4) vaccine lot).
- Subject no. 149 who experienced erysipelas discontinued the study before receiving the second dose of HPV-16/18 vaccine (b(4) vaccine lot).
- Subject no. 160 who suffered from reactive arthritis discontinued the study before receiving the third dose of HPV-16/18 vaccine (b(4) L1 vaccine lot).
- Subject no. 189 who suffered from herpes zoster discontinued the study before receiving the second dose of HPV-16/18 vaccine (b(4) L1 vaccine lot).

There were no withdrawals due to non-serious AEs in the b(4) L2 and the b(4) L3 vaccine lot groups.

Concomitant medications/vaccinations: The percentages of doses after which any concomitant medication was taken were similar across all vaccine lot groups. Overall, subjects received concomitant medication after 13.3% of doses in the b(4) Pooled vaccine lots group (12.3%, 11.6% and 16.0%, in each b(4) vaccine lot group) and after 14.9% of doses in the b(4) vaccine lot group. The use of antipyretics was rare [after 5.0% of doses in the b(4) Pooled vaccine lots group (4.3%, 3.9% and 6.7%, in each b(4) vaccine lot group) and after 4.1% of doses in the b(4) vaccine lot group] and there were no subjects taking antipyretics prophylactically in anticipation of post-vaccination adverse events.
Reviewer's Comment: The tables reviewed demonstrated similar proportions of subjects across lots taking any medication, any anti-pyretic or any antibiotic in the 30 days after any dose , and per subject. It is noted that a slightly higher proportion of subjects took any medication after dose 1, but 95% CIs were overlapping across doses. (Source: STN 125259/0, CSR 016, Tables 42-43, p. 121-122, not shown here).

Pregnancy: During the active phase of the study (up to Month 7), four pregnancies were reported.

Table 345-Study HPV-016: Outcome of reported pregnancies (Months 0 - 7) (Total vaccinated cohort)

Outcome	(b)(4) L1	(b)(4) L2	(b)(4) L3	(b)(4) L
Healthy baby	1	1	-	0
Miscarriage/spontaneous abortion/foetal death	0	0	0	0
Elective abortion	0	1	0	0
Neonatal death	0	0	0	0
Unknown	0	0	1	0
Total	1	2	1	0

b(4) L1 = HPV b(4) - DHPVA014A; b(4) L2 = HPV b(4) - DHPVA017A
b(4) L3 = HPV b(4) - DHPVA016A; b(4) = HPV b(4) - DHPVA004A
Source: STN 125259/0, CSR 016, Table 44, p. 122

- One subject was reported to be pregnant 60 days after receiving the second dose of HPV-16/18 vaccine (-b(4)- L2 vaccine lot) and underwent elective abortion for personal reasons. She received the last vaccine dose and completed the active phase of the study (up to Month 7).
- One subject was reported to be pregnant 4 months after receiving the second dose of HPV-16/18 vaccine (-b(4)- L2 vaccine lot). This subject was withdrawn from the study because of this pregnancy without receiving the third vaccine dose and gave birth to a healthy baby in October 2007.
- One subject was reported to be pregnant 4 months after receiving the second dose of HPV-16/18 vaccine (-b(4)- L3 vaccine lot). This subject completed the safety evaluation of the active phase of the study (up to Month 7) but did not receive any further vaccine dose. This subject is expected to deliver in January 2007. (See extension report).
- One subject was reported to be pregnant 4 months after receiving the second dose of HPV-16/18 vaccine (-b(4)- L1 vaccine lot) and subsequently gave birth to a healthy baby. This subject completed the safety evaluation of the active phase of the study (up to Month 7) but did not receive any further vaccine dose.

No pregnancies were reported in the -b(4)- vaccine lot group.

Reviewer's Comment: The safety reports were reviewed. The outcomes were as noted in the clinical narratives.

According-to-protocol cohort analysis: The analyses based on the ATP safety cohort were also provided, and the results are consistent with those obtained for the Total vaccinated cohort and presented in the previous section. (Source: STN 125259/0, CSR 016, Suppplements 45-89, p. 194-268, not shown here).

STUDY HPV-016 CONCLUSIONS:

- The immune responses and safety profiles of the -b(4)-and -b(4)-lot formulations were similar. Lot consistency was demonstrated for the two formulations.
- Safety issues identified in several subjects (neuroinflammatory events and musculoskeletal events of potential autoimmune nature) were noted and are included in part of a broader discussion of these events in the Overview of Safety section.

OVERVIEW OF EFFICACY

9.1.1

Indication: Prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine (16, and 18):

Cervical Cancer
Cervical intraepithelial neoplasia (CIN) grade 2 or worse and Adenocarcinoma in situ
Cervical intraepithelial neoplasia (CIN) grade 1

Population: Females 10-25 years of age

The clinical data used to support efficacy for cervical lesion indication came from Studies 008 and 001/007.

9.1.2 General Discussion of Efficacy Endpoints

HPV 16/18 related Cervical cancer, cervical AIS, Cervical Intraepithelial Neoplasia Grades 2 and 3: The use of the CIN 2+ with HPV detection to support a cervical cancer indication was discussed at the VRBPAC meeting in November 2001. Members agreed that histopathologic lesions were clinically relevant and feasible endpoints to evaluate for evidence of efficacy of Gardasil against squamous cell or adenocarcinoma of the cervix.

9.1.3 Efficacy Endpoints

The analyses from Study HPV-008 for indications sought are next reviewed. Analyses from Study HPV 001/007 provided supportive data for the indication sought, as well as evidence of duration of action. Analyses from individual studies were discussed earlier in the review within the specific study. The results from HPV-008 support approval of the indications.

Primary Efficacy Endpoint

- **HPV 16/18 related Cervical cancer, CIN 2+ lesions:** The endpoint CIN2+ included cases of CIN 2, CIN 3, AIS, and invasive cervical cancer. There were no cases of cervical cancer in study HPV-008 or study HPV-001/007. As noted above, CIN 2+ lesions are used as surrogate endpoints for indication of prevention of squamous cell cancer and adenocarcinoma of the cervix. This endpoint was the primary endpoint in Study 008 (discussed previously in Section 8.6, Efficacy Outcomes). An interim analysis for 16/18 related CIN 2+ was performed in 2007, and at that time, 23 cases had accrued in Protocol 008. CBER reviewed this application, and because additional information was required, a Complete Response letter was issued on 12/14/07. In addition to provision of additional safety and CMC data, GSK proposed to submit the results of the study at the time 36 cases of HPV 16/18 related CIN2+ in the ATP cohort for efficacy was reached. The final analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 and/or HPV-18 cervical infection were detected in the ATP cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection. At the time of the final analysis, 60 cases (48 cases related to HPV-16, 17 cases related to HPV-18, and 5 cases related to both HPV- 16 and HPV-18.

Additional Secondary Endpoints Evaluated (Study HPV-008)

- 12-month persistent infection with HPV 16 and/or 18: This was also exploratory endpoint in study HPV-001/007.
- 6-month persistent infection with HPV 16 and/or 18: This was secondary endpoint in study HPV-001/007.
- 6-month persistent infection with 14 oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 anf 68 (by PCR). This was also a secondary endpoint in study HPV-001/007.
- CIN2+ associated with 14 oncogenic HPV types (combined endpoint).

- CIN1+ associated with HPV 16/18
- CIN1+ associated with 14 oncogenic HPV types.

Additional Exploratory Endpoints Evaluated (Study HPV-008)

- VIN1+ or VaIN1+ associated with HPV 16/18
- Definitive treatments for cervical dysplasias
- Any cytological abnormality associated with HPV 16/18 or oncogenic HPV types
- Incident infection with HPV 16/18- This was primary endpoint in study HPV-001/007.

Several analysis populations were used to assess efficacy of Cervarix against pre-defined and exploratory histopathological endpoints. The vast majority of subjects in study 008 were sexually active at the time of enrollment. The primary analysis was conducted in the According to Protocol (ATP) population. Subjects in this cohort had a normal or low-grade cytology, were seronegative for the relevant HPV type at baseline, were PCR negative for the relevant HPV type through Month 6, and had no protocol violations. Cases were counted from 1 day after dose 3. It is important to note that **the applicant's primary analyses were specific to the HPV type.**

Cohorts similar to the ATP cohort for efficacy included the Total Vaccinated Cohort-1 (TVC-1) (protocol violators included, seronegative for the relevant HPV type at baseline, PCR negative for the relevant HPV type at baseline, cases counted after day 1) and TVC-2 (had normal cytology and otherwise same as TVC-1 cohort). (Results were generally similar to those in the ATP cohort for efficacy since subjects were seronegative and PCR negative for the relevant HPV type, although cases were counted after dose 1). Results from these analyses are not presented in this overview.

The **Total Vaccinated cohort (TVC)** included all subjects regardless of baseline status for whom data was available, and cases were counted 1 day after dose 1.

In order to provide and estimate of efficacy in young females who have not yet had sexual experience, a subset of subjects who were seronegative for both HPV 16 and 18 at baseline, had a normal cytology at baseline, were naïve for all **14** tested oncogenic HPV types by PCR at baseline, did not have protocol violations, received all 3 doses, and were naïve for the relevant HPV type through Month 6 were considered. This cohort was the **ATP-naïve population**, and cases were counted 1 day after dose 3. A similar cohort, the **TVC naïve population,** included a subset of subjects who may have been protocol violators, had a normal cytology at baseline, were seronegative for HPV 16 and 18 at baseline, were PCR negative for any oncogenic HPV type at baseline, with cases counted 1 day after dose 1. In this overview of efficacy, efficacy results are presented for the ATP cohort (primary analysis), the TVC, and the TVC-naïve so as to present the expected impact on generally naïve subjects as well as subjects who have been infected with one or more vaccine (or non-vaccine) HPV type. Numbers of subjects included in each analysis may vary depending on analysis being conducted (e.g., whether type specific, if data available).

In the ATP cohort for efficacy, baseline characteristics were considered for HPV 16 and HPV 18 when analyzing the results for the specific vaccine HPV type. Therefore, although there are 8093 Cervarix recipients and 8069 Havrix recipients in this cohort, when HPV 16 endpoints are analyzed, only those seronegative and PCR negative for HPV 16 through Month 6 are considered. Likewise, when HPV 18 endpoints are analyzed, only those seronegative and PCR negative for HPV 18 through Month 6 are considered. That explains the different number of subjects considered for specific analyses presented.

9.1.4

Study Design HPV-008

18,665 subjects were enrolled in Study HPV-008, and 18,644 subjects received at least one dose of either Cervarix (N=9319) or the active control Havrix (N=9325).

- This was a double-blind, randomized, active-controlled study. The study was conducted in 14 countries in Asia Pacific, Europe, Latin America, and North America.
- The vaccine was administered using a 0, 1 and 6 months schedule.
- Ten scheduled visits per subject at Months 0, 1, 6, 7, 12, 18, 24, 30, 36 and 48.
- Gynecological examination was performed in all subjects at Months 0, 12, 24, 36 and 48.
- Cytology testing was conducted at Months 0, 12, 24, 36, and 48 and HPV DNA typing by PCR was collected and performed at Months 0, 6, 12, 18, 24, 30, 36 and 48.
- Blood for serology was collected in all subjects at Months 0, 7, and 24, and in a subset of subjects, also collected at Months 6, 12, 36, and 48.

9.1.5

Subject Demographics: Table 346 provides the proportions of subjects enrolled into Study HPV-008 by mean age, region, and ethinicity for the Total Vaccinated Cohort. These are similar to those in the ATP cohort for efficacy. Approximately 30% of subjects in each group were smokers, approximately 60% of subjects were taking hormonal contraceptives, and approximately 92-93% of subjects had < 3 partners in the past year. The demographics of the Cervarix and Havrix groups were comparable, with 54% white, 31% Asian, 7% Hispanics and 4% black.

Table 346-Study HPV-008: Pap Test Abnormalities at Baseline (TVC and ATP populations)

	HPV	**HAV**	**Total**
TVC			
Characteristics at Visit 1	**%**	**%**	**%**
Subjects with normal cytology	90.1%	90.6%	90.3%
Subjects with low-grade cytology	9.3%	8.8%	9.0%
Subjects with high-grade cytology	0.5%	0.5%	0.5%
ATP			
Subjects with normal cytology	90.6%	91.4%	91.0%
Subjects with low-grade cytology	9.4%	8.6%	9.0%
Subjects with high-grade cytology	0.0%	0.0%	0.0%

Source: STN 125259/48, CSR 008. Tables 22 and 23, p. 203-204

The proportions of subjects with normal cytology were generally comparable, although there was a slightly higher proportion of subjects with low-grade abnormality in the HPV group as compared to the HAV group.

Vaccine HPV Status at Baseline: Overall, 26% of subjects were seropositive and/or PCR positive to one or more of the vaccine HPV types at baseline.

Table 347-Study HPV-008: Baseline serostatus and PCR status for HPV 16/18 at baseline (Total Vaccinated cohort)

		HPV N=9319	HAV N=9325	Total N=18644
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
HPV-16 serostatus and DNA status	DNA-, S-	7448 (80.0%)	7430 (80.7%)	14878 (80.7%)
	DNA-, S+	1258 (13.6%)	1302 (14.1%)	2560 (13.9%)
	DNA+,S-	230 (2.5%)	228 (2.5%)	458 (2.5%)
	DNA+,S+	286 (3.1%)	250 (2.7%)	536 (2.9%)
	Missing	97	115	212
HPV-18 serostatus and DNA status	DNA-, S-	8035 (87.0%)	8057 (87.2%)	16092 (87.1%)
	DNA-, S+	988 (10.7%)	968 910.5%)	1956 (10.6%)
	DNA+,S-	127 (1.4%)	114 (1.2%)	241 (1.3%)
	DNA+,S+	88 (1.0%)	102 (1.1%)	190 (1.0%)
	Missing	81	84	165

Source: STN 125259/48, CSR 008. Tables 25, p. 206

Subject follow-up: For each of the endpoints, efficacy was calculated using incidence in person-year rate. [T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group.] The mean duration of follow-up in study HPV-008 was 39 months after dose 1, and 34.5 months after dose 3.

9.1.6 Vaccine Efficacy

The primary endpoint was met, as were histologic and virologic secondary endpoints shown below in Table 348. Each are briefly described in the overview.

Table 348-Study HPV-008: Overview of the Assessment of Primary and Secondary Efficacy Endpoints at the Final Analysis

	Power	Results
Primary endpoint		
CIN2+ associated with HPV 16/18	94%	Objective met
Secondary endpoints		
Virological		
12-month persistent infection with HPV 16/18	99%	Objective met
6-month persistent infection with HPV 16/18	99%	Objective met
6-month persistent infection with oncogenic HPV types	99%	Objective met
Histopathological		
CIN2+ associated with oncogenic HPV types	62%	Objective met
CIN1+ associated with HPV 16/18	99%	Objective met
CIN1+ associated with oncogenic HPV type	91%	Objective mer

Source: STN 125259.0048, CSR 008, Table 28, p. 211

Cervical Intraepithelial Neoplasia 2+ (includes CIN 2, CIN 3, AIS and invasive cervical cancer)

Efficacy in Prevention of CIN 2+ related to HPV 16 and/or 18 in females 15-25 years of age naïve for the relevant vaccine HPV type-Prophylactic Efficacy: In the protocol-specified primary endpoint analysis the objective was met with vaccine efficacy against CIN2+ associated with HPV-16/18 of 92.9% [96.1% CI: 79.9, 98.3] (4 cases in the HPV group versus 56 cases in the HAV group). Statistically significant vaccine efficacy was observed individually for CIN2+ associated with HPV-16 (VE=95.7% [96.1% CI: 82.9, 99.6]) and HPV-18 (VE=86.7% [96.1%

CI: 39.7, 98.7]). Please note that the lower and upper bound of the 96.1% CI were used in analyses (adjustment taken in view of interim analysis). These analyses were conducted in women naïve (seronegative at baseline and PCR negative through Month 6) for the relevant vaccine HPV type, with a normal or low-grade cytology, and with cases counted 1 day after receipt of dose 3. There were no cases of invasive cervical cancer.

Table 349-Study HPV-008: Incidence rates and vaccine efficacy against *CIN2+* associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (year)**	**(n/T) per 100 [95% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7344	4	17689.6	0.02 [0.01, 0.06]	92.9% [79.9, 98.3%]
	HAV	7312	56	17663.32	0.32 [0.24, 0.42]	-
HPV 16	**HPV**	6303	2	15193.63	0.01 [0.00, 0.05]	95.7% [82.9, 99.6%]
	HAV	6165	46	14911.49	0.31 [0.22, 0.42]	-
HPV 18	**HPV**	6794	2	16377.95	0.01 [0.00, 0.05]	86.7% [39.7, 98.7%]
	HAV	6746	15	16310.82	0.09 [0.05, 0.16]	-

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type); n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048. CSR 008, Table 31, p. 237

An additional endpoint of interest was the vaccine efficacy in prevention of HPV 16 and/or 18 related CIN3+ in the ATP cohort for efficacy, and the point estimate for this endpoint was 80%; 96.1% CI: 0.3, 98.1%. There were too few cases of AIS identified in the dataset to reach statistical significance individually. In subjects who were naïve for the relevant HPV type at baseline, there were 3 cases in the HAV group (1 subjects also had CIN3) and 2 with AIS alone. As noted earlier, the 4 cases identified in the HPV group were infected with other HR HPV types at baseline and these other non-vaccine HPV types were detected in the lesions as well.

When cases are counted after day 1 in subjects who were naïve at baseline for the relevant vaccine HPV type and a normal or low-grade cytology (TVC-1 cohort), high efficacy [94.5%; 86.2, 98.4%] for the combined HPV 16 and/or 18 CIN2+ cases was also demonstrated. In this population, there were 96 cases of CIN2+ associated with HPV-16/18 in subjects who were HPV DNA negative and seronegative for the corresponding type at baseline. (The point estimates for efficacy analyses in this cohort reached statistical significance for HPV 16 and 18 individually). In this same TVC-1 cohort, where cases were counted after day 1, vaccine efficacy against CIN3+ associated with HPV-16/18 was statistically significant at 90.9% [60.8, 99.1%].

In the TVC-naive cohort, (subjects who were naïve for all tested HPV types, PCR negative all tested HR HPV types, seronegative for HPV 16 and 18, cytology negative, cases counted after day 1), the point estimates of efficacy for these endpoints were nearly 100% for all analyses.

Efficacy Against HPV Types 16 and 18, Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18: In The Total Vaccinated Cohort includes subjects who received at least one dose of vaccine, and could be either naïve or non-naïve for the relevant HPV type. In this cohort, the point estimates were lower than those in the ATP cohort for efficacy. The positive impact in this analysis may be related to the impact of subjects naïve to the relevant HPV type at the time of vaccination.

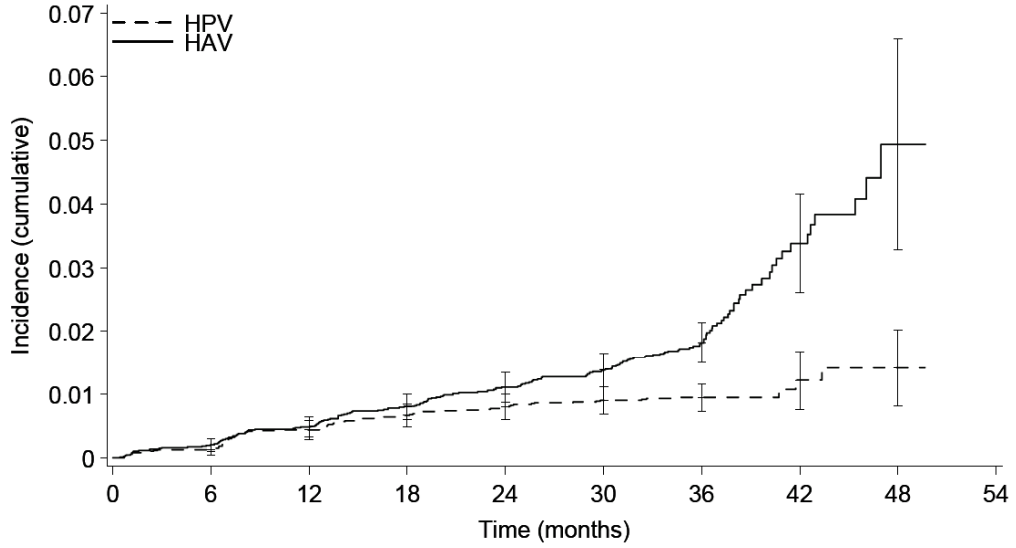
Table 350-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in all subjects, irrespective of their baseline HPV DNA and serostatus, using conditional exact method (Total Vaccinated cohort)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (yesr)**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8667	82	24825.41	0.33 [0.26, 0.41]	**52.8% [37.5, 64.7%]**
	HAV	8682	174	24846.52	0.70 [0.60, 0.82]	-
HPV 16	**HPV**	8667	75	24837.48	0.30 [0.23, 0.38]	**50.6% [33.5, 63.6%]**
	HAV	8682	152	24878.73	0.61 [0.51, 0.72]	-
HPV 18	**HPV**	8667	8	24958.28	0.03 [0.01, 0.06]	**75.7% [44.4, 90.8%]**
	HAV	8682	33	25027.68	0.13 [0.09, 0.19]	-

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
All subjects included, irrespective of their baseline HPV DNA status; n=number of subjects reporting at least one event in each group; T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 192 p. 10391

The cumulative incidence curve for CIN2+, associated with HPV-16/18 in all subjects irrespective of their baseline HPV DNA and serostatus in the Total Vaccinated cohort was also presented.

Figure 37-Study HPV-008: Cumulative incidence curve for CIN2+ associated with HPV-16/18 irrespective of baseline HPV DNA and serostatus (Total Vaccinated cohort)



Number at risk										
HPV	8667	8634	8453	8255	7880	7414	3469	645	76	0
HAV	8682	8642	8450	8221	7869	7409	3452	727	67	0
Number of cases (cumulative)										
HPV	0	11	38	57	68	76	79	81	82	82
HAV	0	18	42	69	94	114	143	168	174	174

Source: STN 125259.0048. CSR 008, Supplement 193, p. 10392

***Efficacy in prevention of CIN2+ associated with HPV 16 and/or 18 in subjects non-naïve (seropositive and/or PCR positive) for the relevant vaccine HPV type*:** Results for vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 in subjects who were HPV DNA positive at baseline indicated a lack of therapeutic effect and point estimates were not statistically

significant. In subjects who were HPV DNA positive and/or seropositive at baseline the vaccine efficacy against CIN2+ with HPV-16/18 was 1.5% [96.1% CI: -43.3, 32.3]), in TVC-1.

When considering subjects who were HPV DNA positive at baseline, there was an apparent imbalance in number of CIN2+ lesions associated with HPV-16/18 in subjects who were HPV DNA positive and seropositive at baseline in subjects with a normal or low-grade cytology [TVC-1] (43 cases versus 31 cases in HPV and HAV groups, respectively), although this imbalance was slightly less than observed at the interim analysis (33 cases versus 18 cases in HPV and HAV groups, respectively). This may indicate greater accrual of cases in the HAV group than in the HPV group between the interim and final analyses. There was little difference observed for CIN1+ associated with HPV-16/18 in the same subset of subjects (44 cases versus 40 cases in HPV and HAV groups, respectively). The analysis of HPV DNA positive subjects was 12- month and 6-month persistent infections for the relevant HPV types were assessed as secondary endpoints. There is no accepted definition of HPV persistence which is clinically relevant, although it has been reported that persistent infection over 1 year (and especially 2 years) may predict higher risk of progression to pre-cancer or cancer (at least in women 30 years of age or younger). [8,9]

The sponsor notes that the randomization scheme used in this study did not take into account the HPV DNA status at baseline. It was already noticed at the interim analysis that the distribution of subjects with low-grade cytology at baseline was not exactly balanced between groups. As noted, there was a slightly higher proportion of subjects with low-grade cytology in the HPV group in both the ATP cohort (9.4% HPV, 8.6% HAV) as compared to the TVC cohort (9.3% vs. 8.8%). This may help explain the numerical imbalance in cases of CIN2+ in the subgroup of subjects that had abnormal cytology and were HPV DNA positive and seropositive at baseline. Other factors such as coinfections with other HPV types are not known, nor can the exact duration of infection be determined (since these women were PCR positive at baseline).

In addition, the sponsor also notes that when considering the overall number of subjects with abnormal cytology at entry progressing to CIN2+ (a total of 1484 subjects had abnormal cytology at baseline), there were 103 subjects in HPV group (13.6%) and 101 in the HAV group (13.9%) with progression to CIN2+, so there was no apparent increase in risk of development of CIN2+ if a subject had an abnormal cytology at baseline.

From all study panel-ascertained CIN2+cases, CBER assessed the breakdown by treatment group in subjects seropositive and PCR positive for the relevant HPV types regardless of baseline cytology (i.e., included all such cases). The numerical imbalance was seen in this comparison as well. It appears that 11 additional cases were added to the HPV group and 13 cases were added to the HAV group when including subjects with higher grade baseline cytological abnormalities as compared to when subjects with low-grade or normal cytology are considered.

Efficacy Against Any CIN 2+ irrespective of HPV Type, Regardless of Current Infection with or Without Prior Exposure to Vaccine or Non-Vaccine Types: The point estimate of efficacy for prevention of CIN 2+ associated with ANY HPV type is 30.4% [16.4, 42.1%] in the Total Vaccinated Cohort. This analysis includes all subjects (both naïve and non-naïve) and with varying Pap tests.

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[8] Schiffman M et al. Human papillomavirus and cervical cancer. The Lancet (2007); 370: 890-907

[9] Rodriguez C et al. JNCI 2008;100:513-517.

Table 351 - HPV-008: Incidence rates and vaccine efficacy against CIN2+, irrespective of HPV DNA results, irrespective of subjects HPV DNA and serostatus at baseline using conditional exact method (Total Vaccinated cohort)

				Person-year rate	VE
Group	**N**	**n**	**T (year)**	**n/T (per 100)**	**% [96.1% CI]**
HPV	8667	224	24627.29	0.91 [0.79, 1.04]	30.4% [16.4, 42.1%]
HAV	8682	322	24658.87	1.31 [1.16.1.46]	

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
All subjects included, irrespective of their baseline HPV DNA status; n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.48, CSR 008, Table 87, p. 332

Positive point estimates of efficacy were also noted in the Total Vaccinated Cohort for CIN 3+ related to ANY HPV type (VE=33.4% [9.1, 51.5%]) and for CIN 1+ related to ANY HPV type (VE=21.7% [10.7, 31.4%]).

In an exploratory analysis, a reduction in rates of local cervical therapy was noted in the Total Vaccinated Cohort (VE=24.7% [7.4, 38.9%]).

Efficacy in prevention of CIN2+ associated with ANY HPV type who had normal cytology and were not infected with any tested HPV at baseline: There was a 70% reduction in CIN 2+ related to any HPV type in this cohort of uninfected subjects (see Table 352 below).

Table 352 - HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with ANY HPV DNA results, in HPV naïve subjects at baseline, using conditional exact method (Total cohort of HPV naïve women)

				Person-year rate	VE
Group	**N**	**n**	**T (yesr)**	**(n/T) per 100 [95% CI]**	**% [96.1% CI]**
HPV	5449	33	15771.51	0.21 [0.14, 0.30]	70.2% [54.7, 80.9%]
HAV	5436	110	15690.39	0.70 [0.57, 0.85]	-

CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer; N=number of subjects included in each group
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
n=number of subjects reporting at least one event in each group; T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group; Follow-up period started at day after Dose 1; n/T=Incidence rate of subjects reporting at least one event; VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.48, CSR 008, Supplement 290, p. 10485

Point estimates of efficacy for prevention of CIN3+ related to any HPV type (VE=87% [96.1% CI: 54.9, 97.7%] and CIN1+ related to any HPV type (VE=50.1% [96.1%: 35.9, 61.4%] were also reported in the TVC-naïve cohort.

CIN1+ with HPV-16/18 in subjects naïve for the relevant vaccine HPV type: The results for prevention of CIN1+ lesions (include CIN 1, CIN 2, CIN 3, AIS, and invasive cervical cancer) are presented for subjects naive for the relevant vaccine HPV type in Table 353 below. The point estimates of efficacy in the ATP cohort and the TVC-naïve cohort are presented below, and are $\geq$ 91.7% in both populations (LBs $\geq$ 82.4%).

Table 353 - HPV-008: Summary of vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy and TVC-naïve cohort)

				VE
Endpoint	**Group**	**N**	**n**	**% [96.1% CI]**
ATP cohort				
CIN 1+ associated with HPV 16 and/or HPV 18	HPV	7344	8	91.7% [82.4, 96.7%]
	HAV	7312	96	
TVC Naïve cohort				
CIN 1+ associated with HPV 16 and/or HPV 18	HPV	5449	3	96.5% [89.0, 99.4%]
	HAV	5436	85	

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type; For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type); n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048, CSR 0008, Table 90, p. 343

Efficacy Against CIN1+ associated with HPV Types 16 and 18, Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18: The efficacy of Cervarix against CIN1+ associated with HPV-16 and/or HPV-18, regardless of current or prior exposure to vaccine HPV types, is presented in Table 354 below. The point estimate of efficacy is similar to that seen for CIN2+ in the same population (TVC).

Table 354-Study HPV-008: Vaccine Efficacy Against CIN 1+ Associated with HPV-16 and/or HPV-18 (by PCR) in Subjects Regardless of Current or Prior Exposure to Vaccine HPV types

				VE
Endpoint	**Group**	**N**	**n**	**% [96.1% CI]**
ATP cohort				
CIN 1+ associated with HPV 16 and/or HPV 18	HPV	8667	107	55.5% [43.2, 65.3%]
	HAV	8682	240	

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type; For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV
type (subjects were in the analysis of at least one single type); n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits

Efficacy in Prevention of CIN 1+ associated with ANY HPV type in Total Vaccinated Cohort:

Table 355-Study HPV-008: Vaccine Efficacy Against CIN 1+ Associated with ANY HPV Type (by PCR) in Subjects Regardless of Current or Prior Exposure to Vaccine or Non-vaccine HPV types

				VE
Endpoint	**Group**	**N**	**n**	**% [96.1% CI]**
ATP cohort				
CIN 1+ associated with HPV 16 and/or HPV 18	HPV	8667	451	21.7% [10.7, 31.4%]
	HAV	8682	577	-

HPV = HPV-16/18 L1 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
CIN1+ = CIN1, CIN2, CIN3, AIS or invasive cervical cancer; N=number of subjects included in each group
n=number of subjects reporting at least one event in each group
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

As noted for CIN2+ results, there was no apparent impact on reduction of CIN1+ lesions in subjects who were PCR positive (with or without seropositvity) for the relevant HPV type assessed. The point estimates are provided below. All 96.1% CIs include 0.

Table 356-Study HPV-008: Overview of vaccine efficacy against histological lesions associated with HPV-16/18 in HPV DNA positive subjects in TVC-1

				VE
Endpoint	**Group**	**N**	**n**	**% [96.1% CI]**
HPV DNA positive and seronegative subjects at baseline				
CIN 1+ associated with HPV 16 and/or HPV 18	HPV	303	27	30.5% [-20.9, 60.5%]
	HAV	285	36	-
HPV DNA positive and seropositive subjects at baseline				
CIN 1+ associated with HPV 16 and/or HPV 18	HPV	315	44	-3.0% [-66.0, 35.9%]
	HAV	290	40	-
HPV DNA positive at baseline, regardless of initial serostatus				
	HPV	617	72	13.0% [-23.8, 38.9%]
	HAV	567	76	

HPV = HPV-16/18 L1 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
CIN1+ = CIN1, CIN2, CIN3, AIS or invasive cervical cancer; N=number of subjects included in each group
n=number of subjects reporting at least one event in each group
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048, Table 100, p. 358

The point estimates for HPV 16 and HPV 18 individually are near to those in the combined analyses provided above and reach statistical significance. There are in general fewer cases related to HPV 18 as compared to HPV 16 in all analyses.

Other virological endpoints of interest: Persistent infections by 12-month and 6-month definitions were two secondary endpoints. Incident infection was an exploratory endpoint. These are of interest. As noted in the Executive Summary, the accepted endpoint for prevention of cervical cancer is prevention of CIN 2/3 or worse associated with virology identification. The duration of persistent infection has not been universally agreed upon, and may be different for different HPV types. For example, the mean duration of HPV-16 infection had been noted to be approximately 8 months, and it has also been stated that persistent infections > 1 year may be most predictive of development of advanced lesions. These endpoints are nonetheless included here.

Virological endpoints associated with HPV-16/18 in subjects naïve for the relevant vaccine HPV type: The point estimates of efficacy in prevention of persistent infection are reported in the ATP cohort. As discussed, detection of HPV type at one time point may be related to deposition of HPV at the time of intercourse, but an infection of basal epithelium may not occur. That is the reason why persistent infection is a more reliable measure of true infection, which may however still regress spontaneously.

Table 357-Study HPV-008: Summary of vaccine efficacy against virological endpoints associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

				VE
Endpoint	**Group**	**N**	**n**	**% [96.1% CI]**
ATP cohort				
Persistent infection (12-month) HPV 16 and/or HPV 18	HPV	7035	21	91.2% [85.9, 94.8%]
	HAV	6984	233	
Persistent infection (6-month) HPV 16 and/or HPV 18	HPV	7177	32	93.8% [91.0, 95.9%]
	HAV	7122	497	
Incident infection HPV 16 and/or HPV 18	HPV	7346	263	76.7% [73.2, 79.9%]
	HAV	7320	1074	

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type; For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type); n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048, CSR 008, Table 90, p. 343

Virological endpoints associated with HPV-16/18 in subjects irrespective of baseline PCR and serostatus: These are presented to be complete. Again, subjects in these analyses may have been naïve or non-naïve for the relevant HPV types.

Table 358-Study HPV-008: Summary of vaccine efficacy against virological endpoints associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (TVC)

				VE
Endpoint	**Group**	**N**	**n**	**% [96.1% CI]**
Persistent infection (12-month) HPV 16 and/or HPV 18	HPV	8625	331	47.5% [39.5, 54.6%]
	HAV	8648	620	-
Persistent infection (6-month) HPV 16 and/or HPV 18	HPV	8856	503	56.5% [51.4, 61.1%]
	HAV	8859	1115	-
Incident infection HPV 16 and/or HPV 18	HPV	9315	1116	49.8% [45.8, 53.5%]
	HAV	9318	2115	-

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type; For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV
type (subjects were in the analysis of at least one single type); n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048, Response to FDA request 8/25/09

Analyses of Efficacy against CIN2+ Related to Non-Vaccine Oncogenic HPV Types
Secondary histopathological endpoints: CIN2+ cases associated with oncogenic HPV types
CIN2+ cases associated with oncogenic HPV types in subjects who were HPV DNA negative for the corresponding type at baseline, regardless of initial HPV serostatus: Considering the multiple oncogenic HPV types with which a woman may be infected and assessing the impact of Cervarix in reducing CIN2+ related to these non-vaccine HPV types is very complicated.
One of 6 secondary analyses which were pre-specified in protocol HPV-008 is as follows: "Histopathologically-confirmed CIN2+ associated with the following oncogenic HPV types (or combination of types): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR) detected within the lesional component of the cervical tissue specimen (by PCR)." As noted by our statistician, this is a composite endpoint including 14 HPV types. None of these types was pre-specified as an individual endpoint. Individual analyses on these 12 non-vaccine HPV types would be considered post-hoc. In addition, multiplicity adjustments for the Type I error

probability have not been been considered in the evaluation of each of the 12 non-vaccine HPV types. Therefore, results from these analyses by HPV type that are presented in the BLA should be considered as exploratory, not confirmatory.

Analyses were performed on subjects who were HPV DNA negative for the corresponding type at baseline, regardless of initial serostatus, and vaccine efficacy was determined using the conditional exact method. The analyses for HR-HPV included cases related to HPV 16/18. The analyses of HRW-HPV may include lesions with multiple HPV types, which although associated with another oncogenic type besides HPV-16/18 may also contain HPV-16/18 within the lesion and therefore the analysis of vaccine efficacy for histopathological endpoints with HRW-HPV may be confounded by the presence of HPV-16/18. GSK also presented an analysis of lesions which did not include HPV 16/18.

The incidence rates and vaccine efficacy of CIN2+ associated with oncogenic (high-risk) HPV types in HPV DNA negative subjects at baseline in the ATP cohort for efficacy are presented in Table 359. The point estimate of vaccine efficacy against CIN2+ associated with HR-HPV was 61.9% [96.1% CI: 46.7, 73.2] with 54 cases in the HPV group versus 142 cases in the HAV group. This analysis considered HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. In consideration of cases related to the high-risk HPV tested (except 16 and 18), the vaccine efficacy against CIN2+ associated with HRW-HPV was 54.0% [96.1% CI: 34.0, 68.4]) with 50 cases in the HPV group versus 109 cases in the HAV group. It should be noted that the analyses of HRW-HPV may have included lesions with multiple HPV types, including HPV 16 and/or 18. It was possible that the analysis of vaccine efficacy for histopathological endpoints with HRW-HPV may be confounded by the presence of HPV-16/18.

For analyses of vaccine efficacy against oncogenic HPV types other than HPV-16/18, efficacy against CIN2+ (in which point estimates were positive and LBs around the CIs were >0) was observed for HPV-31, HPV-51 and HPV-58 in the ATP cohort for efficacy. Point estimates for these types were 92.0%, 62.9% and 64.5%, respectively. Of note the point estimate was 100% for vaccine efficacy against CIN2+ associated with HPV-45, but this analysis did not reach statistical significance since there were few cases, with 0 cases in the HPV group and 4 cases in the HAV group. The vaccine efficacy against CIN2+ associated with HPV-45 in subjects HPV-45 DNA negative at baseline was statistically significant in the broader Total Vaccinated cohort, which includes all vaccinated subjects (VE=100% [96.1% CI: 7.0, 100], p=0.0312), with 0 cases in the HPV group and 6 in the HAV group.

Table 359-Study HPV-008: Incidence rates and vaccine efficacy of CIN2+ associated with oncogenic HPV types (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method (ATP cohort for efficacy)

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16	HPV	7372	4	17726.34	0.02	0.01	0.06	92.7	79.3	98.2	<0.0001
	HAV	7276	54	17520.68	0.31	0.23	0.41	-	-	-	-
HPV-18	HPV	7645	2	18388.48	0.01	0.00	0.04	87.6	44.1	98.8	0.0007
	HAV	7583	16	18312.59	0.09	0.05	0.15	-	-	-	-
HPV-31	HPV	7583	2	18220.46	0.01	0.00	0.04	92.0	66.0	99.2	<0.0001
	HAV	7599	25	18339.26	0.14	0.09	0.20	-	-	-	-
HPV-33	HPV	7720	12	18546.95	0.06	0.03	0.12	51.9	-2.9	78.9	0.0332
	HAV	7706	25	18596.46	0.13	0.08	0.20	-	-	-	-
HPV-35	HPV	7768	1	18674.74	0.01	0.00	0.03	83.3	-49.1	99.7	0.0702
	HAV	7764	6	18761.90	0.03	0.01	0.07	-	-	-	-
HPV-39	HPV	7609	3	18291.41	0.02	0.00	0.05	69.8	-24.2	95.2	0.0921
	HAV	7614	10	18414.11	0.05	0.02	0.10	-	-	-	-
HPV-45	HPV	7782	0	18715.82	0.00	0.00	0.02	100	-67.8	100	0.0619
	HAV	7745	4	18732.22	0.02	0.01	0.06	-	-	-	-
HPV-51	HPV	7363	10	17691.42	0.06	0.03	0.11	62.9	18.0	84.7	0.0050
	HAV	7352	27	17732.77	0.15	0.10	0.23	-	-	-	-
HPV-52	HPV	7461	12	17934.23	0.07	0.03	0.12	14.3	-108.1	65.4	0.7000
	HAV	7414	14	17925.16	0.08	0.04	0.13	-	-	-	-
HPV-56	HPV	7646	4	18388.52	0.02	0.01	0.06	59.9	-47.1	91.5	0.1181
	HAV	7638	10	18457.65	0.05	0.02	0.10	-	-	-	-
HPV-58	HPV	7709	6	18512.03	0.03	0.01	0.07	64.5	1.5	89.2	0.0225
	HAV	7702	17	18607.82	0.09	0.05	0.15	-	-	-	-
HPV-59	HPV	7720	1	18558.42	0.01	0.00	0.03	74.9	-178.6	99.6	0.3749
	HAV	7723	4	18663.51	0.02	0.01	0.06	-	-	-	-
HPV-66	HPV	7592	4	18249.66	0.02	0.01	0.06	60.0	-46.7	91.6	0.1176
	HAV	7564	10	18268.55	0.05	0.03	0.10	-	-	-	-
HPV-68	HPV	7633	5	18352.82	0.03	0.01	0.07	54.4	-49.8	88.4	0.1428
	HAV	7614	11	18396.00	0.06	0.03	0.11	-	-	-	-
HRW-HPV	HPV	7863	50	18848.93	0.27	0.19	0.35	54.0	34.0	68.4	<0.0001
	HAV	7853	109	18897.20	0.58	0.47	0.70	-	-	-	-
HR-HPV	HPV	7863	54	18842.44	0.29	0.21	0.38	61.9	46.7	73.2	<0.0001
	HAV	7853	142	18871.92	0.75	0.63	0.89	-	-	-	-

HPV = HPV-16/18 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
HRW-HPV = All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18
HR-HPV= High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Table 43, p. 270

CBER reviewed datasets for cases associated with non-vaccine HPV types in both treatment groups. Many of the CIN2+ cases were associated with multiple HPV types. CBER requested that GSK provide a post-hoc analysis after excluding cases which also included HPV 16 and/or 18. This is provided in Table 360. The LB of the 96.1% CI around the point estimate of efficacy is > 0% for HPV-31 alone and for the combined analysis for all oncogenic HPV types when HPV 16 and/or 18 are excluded from analysis (VE=37.4%, 96.1% CI: .7.4, 58.2%). When analyzing specific non-vaccine HPV types, the point estimate of efficacy for HPV-31 has LB > 0%. CBER notes that these lesions could have also contained other non-vaccine HPV types.

Table 360-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with oncogenic HPV types without co-infections with HPV=16 or HPV-18 (by PCR) in HPV DNA negative at baseline, using conditional exact method (ATP cohort for efficacy)

				Vaccine Efficacy	96.1% CI		
Event Type	Group	N	n	%	LL	UL	P-value
HPV-16	HPV	7372	0	.	.	.	-
	HAV	7276	0	-	-	-	-
HPV-18	HPV	7645	0	.	.	.	-
	HAV	7583	0	-	-	-	-
HPV-31	HPV	7583	2	89.4	53.7	99.0	0.0002
	HAV	7599	19	-	-	-	-
HPV-33	HPV	7720	12	42.7	-26.4	75.4	0.1207
	HAV	7706	21	-	-	-	-
HPV-35	HPV	7768	1	74.9	-178.3	99.6	0.2186
	HAV	7764	4	-	-	-	-
HPV-39	HPV	7609	3	39.6	-235.1	91.5	0.7265
	HAV	7614	5	-	-	-	-
HPV-45	HPV	7782	0	100.0	-4933.4	100.0	0.4988
	HAV	7745	1	-	-	-	-
HPV-51	HPV	7363	9	35.5	-67.0	76.6	0.3067
	HAV	7352	14	-	-	-	-
HPV-52	HPV	7461	12	-50.0	-346.2	46.2	0.5032
	HAV	7414	8	-	-	-	-
HPV-56	HPV	7646	4	49.8	-98.9	89.8	0.2664
	HAV	7638	8	-	-	-	-
HPV-58	HPV	7709	6	39.7	-93.0	83.1	0.3318
	HAV	7702	10	-	-	-	-
HPV-59	HPV	7720	1	49.7	-1011.9	99.3	1.0000
	HAV	7723	2	-	-	-	-
HPV-66	HPV	7592	4	33.3	-201.3	87.3	0.5480
	HAV	7564	6	-	-	-	-
HPV-68	HPV	7633	4	49.9	-98.7	89.8	0.2661
	HAV	7614	8	-	-	-	-
HPV-HRW	HPV	7863	48	37.4	7.4	58.2	0.0092
	HAV	7853	77	-	-	-	-
HPV-HR	HPV	7863	48	37.4	7.4	58.2	0.0092
	HAV	7853	77	-	-	-	-

HPV= HPV-16/18 vaccine (three lots); HAV =Hepatitis A vaccine (three lots) = Control group
N=number of subjects included in each group
Subjects not accounted as case in CIN2+ associated with HPV types 16/18; For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6 (subjects are in the analysis of at least one single type); n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for the corresponding HPV type at Month 0 and Month 6
HPV-HRW = All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18
HPV-HR = High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: Response to FDA request 9/21/09

Because the subjects in the ATP cohort could have been non-naïve for other HPV types, CBER reviewed in detail the cases of CIN2+ which occurred in the TVC naïve population.

Table 361-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with oncogenic HPV types (by PCR) in HPV naïve subjects at baseline using conditional exact method (Total cohort of HPV naïve women)

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16	HPV	5449	1	15810.77	0.01	0.00	0.04	98.2	89.1	100	<0.0001
	HAV	5436	56	15732.25	0.36	0.26	0.47	-	-	-	-
HPV-18	HPV	5449	0	15812.40	0.00	0.00	0.02	100	61.3	100	0.0002
	HAV	5436	12	15761.28	0.08	0.04	0.14	-	-	-	-
HPV-31	HPV	5449	0	15812.40	0.00	0.00	0.02	100	78.3	100	<0.0001
	HAV	5436	20	15758.82	0.13	0.08	0.20	-	-	-	-
HPV-33	HPV	5449	5	15804.70	0.03	0.01	0.08	72.3	19.1	92.5	0.0065
	HAV	5436	18	15757.89	0.11	0.07	0.18	-	-	-	-
HPV-35	HPV	5449	1	15811.06	0.01	0.00	0.04	75.1	-176.3	99.6	0.2181
	HAV	5436	4	15769.13	0.03	0.01	0.07	-	-	-	-
HPV-39	HPV	5449	3	15808.83	0.02	0.00	0.06	66.8	-41.4	94.8	0.0917
	HAV	5436	9	15767.50	0.06	0.02	0.11	-	-	-	-
HPV-45	HPV	5449	0	15812.40	0.00	0.00	0.02	100	-19.5	100	0.0310
	HAV	5436	5	15768.25	0.03	0.01	0.08	-	-	-	-
HPV-51	HPV	5449	2	15809.41	0.01	0.00	0.05	88.3	47.9	98.9	0.0004
	HAV	5436	17	15760.92	0.11	0.06	0.18	-	-	-	-
HPV-52	HPV	5449	7	15802.95	0.04	0.02	0.09	36.5	-88.4	80.3	0.3583
	HAV	5436	11	15764.34	0.07	0.03	0.13	-	-	-	-
HPV-56	HPV	5449	0	15812.40	0.00	0.00	0.02	100	-67.1	100	0.0622
	HAV	5436	4	15766.14	0.03	0.01	0.07	-	-	-	-
HPV-58	HPV	5449	3	15807.28	0.02	0.00	0.06	72.8	-8.9	95.6	0.0348
	HAV	5436	11	15766.43	0.07	0.03	0.13	-	-	-	-
HPV-59	HPV	5449	0	15812.40	0.00	0.00	0.02	100	-514.5	100	0.2494
	HAV	5436	2	15770.57	0.01	0.00	0.05	-	-	-	-
HPV-66	HPV	5449	1	15810.44	0.01	0.00	0.04	83.4	-48.0	99.7	0.0699
	HAV	5436	6	15767.25	0.04	0.01	0.09	-	-	-	-
HPV-68	HPV	5449	2	15807.74	0.01	0.00	0.05	71.5	-60.3	97.5	0.1088
	HAV	5436	7	15766.42	0.04	0.02	0.09	-	-	-	-
HRW-HPV	HPV	5449	21	15782.25	0.13	0.08	0.21	68.8	47.1	82.4	<0.0001
	HAV	5436	67	15725.85	0.43	0.33	0.55	-	-	-	-
HR-HPV	HPV	5449	22	15780.62	0.14	0.09	0.22	77.7	63.5	87.0	<0.0001
	HAV	5436	98	15698.87	0.62	0.50	0.77	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: STN 125259.0048. CSR 008, Supplement 273, p. 10469

Reviewer's Comment : In a *post-hoc* analysis, the number of cases included in Table 362 above also included HPV 16 and/or 18. If those lesions were excluded, the case splits would decrease.

Table 362-Study HPV-008: CIN2+ Cases Associated with Non-Vaccine HPV Types in TVC Naïve Population

	Cervarix N=5449	Havrix N=5436
HPV type	Total Cases	Total cases excluding lesions with HPV 16 and/or 18
31	0	20-7=13
33	5	18-3=15
35	1	4-2=2
39	3	9-5=4
45	0	5-4=1
51	2	17-14=3
52	7	11-8*=3
56	0	4-4=0
58	3	11-6*=5
59	0	2-1*=1
66	1	6-3=3
68	2	7-5=2

*HPV types may have been in two lesions at same time

Reviewer's Comment: For HPV-31, after excluding lesions which also include 16 and 18, there are 0 cases in the Cervarix group and 13 cases in the Havrix group related to HPV 31. For the lesions associated with HPV 45, 4 of these lesions were also associated with HPV 16, and one other was associated with HPV 58. For HPV 33, the case split decreases to 15:5 after exclusion of cases which also include HPV 16/18. For HPV 51, the majority of lesions in the Havrix group also include HPV 16 and/or 18. This observation demonstrates the difficulty of teasing HPV types apart. Given the results for the combined endpoint, we want to better understand the impact the vaccine is having on prevention of non-vaccine HR HPV types. It is not clear as to how different HPV types present in one lesion impact on other HPV types also present in the lesion, and if there is interaction among different HPV types as they relate to CIN2+ development. We do know that in the Cervarix group, none of the CIN2+ lesions in TVC naïve group included HPV 16 or 18 when analyzed for other HR HPV types. CBER requested that GSK conduct a post-hoc analysis and provide point estimates of efficacy after excluding cases which included HPV 16 and/or 18 from the type specific analysis. These results are provided in Table 363 below. After excluding HPV 16 and/or 18 containing lesions, the point estimate of efficacy is maintained for HPV-31 alone, and not for others.

Table 363-Study HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with oncogenic HPV types without co-infections with HPV=16 or HPV-18 (by PCR) in HPV DNA negative at baseline, using conditional exact method (TVC Naïve)

Event Type	Group	N	n	%	LL	UL	P-value
HPV-16	HPV	5449	0	.	.	.	-
	HAV	5436	0	-	-	-	-
HPV-18	HPV	5449	0	.	.	.	-
	HAV	5436	0	-	-	-	-
HPV-31	HPV	5449	0	100.0	64.7	100.0	0.0001
	HAV	5436	13	-	-	-	-
HPV-33	HPV	5449	5	66.8	-0.8	91.2	0.0263
	HAV	5436	15	-	-	-	-
HPV-35	HPV	5449	1	50.1	-1002.8	99.3	0.6245
	HAV	5436	2	-	-	-	-
HPV-39	HPV	5449	3	25.2	-381.9	90.1	0.7262
	HAV	5436	4	-	-	-	-
HPV-45	HPV	5449	0	100.0	-4915.1	100.0	0.4994
	HAV	5436	1	-	-	-	-
HPV-51	HPV	5449	2	33.5	-544.5	95.2	0.6871
	HAV	5436	3	-	-	-	-
HPV-52	HPV	5449	7	-132.9	-1442.1	50.2	0.3435
	HAV	5436	3	-	-	-	-
HPV-56	HPV	5449	0	.	.	.	-
	HAV	5436	0	-	-	-	-
HPV-58	HPV	5449	3	40.2	-232.0	91.6	0.5072
	HAV	5436	5	-	-	-	-
HPV-59	HPV	5449	0	100.0	-4915.0	100.0	0.4994
	HAV	5436	1	-	-	-	-
HPV-66	HPV	5449	1	66.8	-361.1	99.5	0.3743
	HAV	5436	3	-	-	-	-
HPV-68	HPV	5449	2	0.2	-1481.1	93.7	1.0000
	HAV	5436	2	-	-	-	-
HPV-HRW	HPV	5449	21	40.1	-8.7	67.9	0.0618
	HAV	5436	35	-	-	-	-
HPV-HR	HPV	5449	21	40.1	-8.7	67.9	0.0618
	HAV	5436	35	-	-	-	-

HPV= HPV-16/18 L1 vaccine; HAV = Hepatitis A vaccine
N=number of subjects included in each group
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
* Subjects not accounted as case in CIN2+ associated with HPV types 16/18
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Source: Response to FDA Request, 9/21/09

Reviewer's Comment: In addition, as noted, multiple non-vaccine HPV types may have been detected in some of these lesions (after exclusion of HPV 16 and/or 18 from the lesion). There were discussions as to strength of the data for efficacy in prevention of non-vaccine HPV types at the September 9, 2009 VRBPAC meeting. At the VRBPAC meeting, there was a general consensus that there was additional impact on non-vaccine HPV types overall in addition to prevention of HPV-16 and HPV-18, and the best data appeared to be presented for HPV-31. In

the analyses of prevention of CIN2+ irrespective HPV type detected in the lesion in subjects in the TVC naïve population, the point estimate of efficacy was approximately 70%. It is estimated that 50% of CIN2+ is associated with HPV 16 and/or 18, and approximately 70% CIN3+ are associated with these typesn (so the estimate of combined CIN2 and CIN3 probably falls between those estimates). Analyses for some HPV types demonstrated negative point estimates of efficacy when HPV 16 and/or 18 were excluded. Since the combined endpoint was pre-specified and LB around the CIs did not include 0, and because the analyses were considered to provide important information (no evidence of replacement and additional cases were being prevented on to of those related to HPV 16 and/or 18) it was considered appropriate to include these analyses in the package insert. Although some members of the committee believed that there was impact on HPV-31, one member advised caution in interpreting data as to impact on non-vaccine HPV types, and another noted that the prevalence of these non-vaccine HPV types may have impact on the point estimates of efficacy which are noted. The smaller number of cases related to the non-vaccine HPV types likely impacts on the ability to ascertain a more definitive assessment of individual non-vaccine HPV types. The issue of efficacy or cross-protection against the non-vaccine oncogenic HPV types is complex. Even though there was observed nearly 60% efficacy against HPV-31, the reasons for this effect is unclear. The finding should be interpreted with caution based on several considerations: 1)possible confounding effect from possible residual undetected co-infection with HPV-16, even after excluding those with PCR(+) HPV-16 or 18, since HPV-16 and HPV-31 coinfections are common; 2)HPV-16 and HPV-31 are phylogenetically closely related and PCR distinguishing the two may not be sufficiently specific; 3) antibody induced by vaccine-types may be cross-protective, either inherently ot due to adjuvant effect.

The immune response is mentioned here for the non-vaccine HPV types. GSK provided data for types HPV-31 and HPV-45 in a small number of subjects in earlier phase studies. Even though the seroresponse to HPV-31 and HPV-45 were 69% and >92.3%, respectively, at Month 51-56, the seroresponses as measured by pseudovirion neutralization assay were not as robust (47.6%-69.6% for HPV-31 and 9.5%-34.8% for HPV-45 at Month 7 and 14% for HPV-31 and 0% for HPV-45 at Month 45-50). The protection may not be as durable as that provided for HPV-16 and/or HPV-18.

Exploratory analysis: reduction in rates of cervical therapy in the TVC and TVC-naïve population: In an exploratory analysis, a reduction in rates of local cervical therapy was noted in the Total Vaccinated Cohort (VE=24.7% [7.4, 38.9%]). In an exploratory analysis, a reduction in local cervical therapy in the TVC naïve subset was also noted (68.8% [96.1%: 50.0, 81.2%]).

Efficacy against VIN1+ and/or VaIN 1: VIN 2/3 or VaIN 2/3 were not assessed as endpoints, although efficacy was assessed in prevention of VIN1+ and/or VaIN1+ associated with HPV 16/18 in subjects who were naïve for the relevant vaccine HPV type. In the clinical study report for study HPV-008, the sponsor presents the few cases which have occurred within Study HPV-008, and although vaccine efficacy is estimated at 100% for each of the combined HPV 16 and/or 18 VIN 1+ or VaIN 1+ composite endpoints, these point estimates do not reach statistical significance. Endpoints related to vulvar and vaginal dysplasias which are considered clinically releavant include VIN 2/3 and VaIN 2/3.

The incidence rates and vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 (by PCR) in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy are presented. There were 12 cases of VIN1+/VaIN1+ associated with HPV-16/18 included in this analysis. The vaccine efficacy against VIN1+/VaIN1+ associated with HPV-16/18 was statistically significant (VE=80.0% [96.1% CI: 0.3, 98.1]), with 2 cases in the HPV

group versus 10 cases in the HAV group. There were 2 cases of VIN1+/VaIN1+associated with HPV-16 in the HPV group and 6 in the HAV group. There were only 4 cases of VIN1+/VaIN1+ associated with HPV-18, which were all in the HAV group.

The incidence rates and vaccine efficacy against VIN1+ or VaIN1+, irrespective of HPV DNA type detected in the lesion, in subjects who were DNA negative for all HPV types at baseline, regardless of initial serostatus, in the ATP cohort for efficacy are presented. The vaccine efficacy was statistically significant at 60.3% [96.1% CI: 11.3, 83.7]), with 10 cases in the HPV group versus 25 in the HAV group.

9.1.7 Evidence of Duration of Effect: From study HPV-008, the mean follow-up time was 39 months after dose 1 and approximately 34.5 months after dose 3. From the data presented in study HPV-008, the duration of prevention of CIN2+ associated with HPV 16/18 extends out to Month 39 after Dose 1. Study HPV-001 and its extension study HPV-007 enrolled females 15-25 years of age who were naïve for oncogenic HPV types (DNA negative for 14 oncogenic HPV types and cytology negative and seronegative for HPV 16 and/or 18) provided evidence of prevention of incident HPV 16 and/or 18 infection (primary endpoint), 6-month (secondary endpoint) and 12-month (other endpoint) persistent HPV-16 and/or 18 infection, and CIN2+ related to HPV-16 and/or 18 (secondary endpoint) in women naïve for the relevant HPV type for a time period up to 6.4 years. The results for study HPV-007 (subjects who continued follow-up through entire time period) at up to 6.4 years after dose 1 in study HPV-001 are presented in Table 364.

Table 364-Study HPV-001/007: Efficacy of HPV-16/18 L1 AS04 vaccine against virologicaland histopathological lesions associated with HPV-16/18 using conditional exact method (ATP Cohort for Efficacy andTotal Cohort)

Event type	Group	N	n	Vaccine efficacy 95% CI	N*	n*	Vaccine efficacy 98.67% CI
ATP Cohort							
Incident infection	Vaccine	303	2	96.7% (87.4, 99.6%)			
	Alum Control	267	47				
6-month persistent infection	Vaccine	304	0	100% (85.9, 100%)	401	0	100% (86.2, 100%)
	Alum Control	277	24		372	34	
12-month persistent infection	Vaccine	304	0	100% (75.0, 100%)	401	0	100% (74.4, 100%)
	Alum Control	285	15		372	20	
Total Cohort							
CIN1+	Vaccine	358	0	100% (52.6, 100%)	481	0	100% (62.1, 100%)
	Alum Control	339	9		470	15	
CIN2+	Vaccine	358	0	100% (19.7, 100%)	481	0	100% (28.4, 100%)
	Alum Control	342	6		470	9	

Vaccine = HPV-16/18 (DVLP017A); Placebo = Aluminum hydroxide (DVLP018A)
N=number of subjects in each group (007)
n=number of subjects reporting at least one event in each group (007)
N*=number of subjects from combined analysis (001 and 007)
n*=number of cases from combined analysis (001 and 007)
ATP Cohort = Subjects with an event are DNA negative for HPV-16 and HPV-18 at Month 0 and Month 6 in HPV-001
Total Cohort=subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001
Follow-up period starts at Month 0 for HPV-001 (ATP cohort)
Follow-up period starts at Month 0 for HPV-001 and pooled HPV-001/007, interval period between end of HPV-001 and beginning of HPV-007 is censored (TVC Cohort)
Subjects with an event who did not report the same event in HPV-001
Source: STN 125259.0048, CSR 007 M36, Table 13, p. 86; Table 16, p. 93; Table 19, p. 98; Table 37, p. 121; Table 40, p. 125; and CSR 007 M36, Annex 1 report, Table 1, p. 9 and Table 3, p. 12

9.1.8 Efficacy Conclusions

There is evidence of efficacy of Cervarix in the prevention of HPV-16 and HPV-18 cervical dysplastic lesions (CIN 2/3, AIS, or worse). HPV types 16 and 18 have been reported to be associated with approximately 70% of cervical cancers. There is evidence of efficacy against vaccine HPV type related CIN 1 as well.

Highest efficacy rates are noted in subjects who have not been previously exposed to the specific vaccine HPV type prior to administration of Cervarix. In subjects who have been previously infected with a specific vaccine HPV type, there is no evidence of efficacy in reducing cervical dysplasia associated with that vaccine type. However, it appears that efficacy was noted against cervical dysplasia associated with vaccine HPV types to which the subject was naïve.

There is evidence of some protection against the combined incidence of CIN 2+ lesions associated with HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 66, and 68 in those naïve for the relevant HPV type, as well as those naïve for all tested HPV types. When lesions which also contain HPV-16 and HPV-18 were excluded from the analyses, there was a more modest impact on prevention of CIN2+ lesions related to a non-vaccine HPV type (VE=37.4% [96.1% CI: 7.4, 58.2%]. From the data presented, CBER could not differentiate defintively effectiveness on specific non-vaccine HPV types, and CBER also notes that in analyses, the trend in prevention may have been positive for some types (HPV-31 and HPV-33) while being negative for other types (e.g., HPV-52).

Because of the apparent high efficacy in those naïve to the relevant vaccine HPV types, subjects who are naïve to HPV-16 and HPV-18 types will likely benefit most from the vaccine. There is some evidence that this group may be protected against disease related to other non-vaccine HPV types, but to a lesser degree than the protection afforded against lesions related to HPV 16 and/or 18. Since HPV 16 and 18 are associated with approximately 70% of cervical cancers, there is expected to be overall benefit in the reduction of CIN 2/3 or worse related to HPV 16 and 18. Although an efficacy study was not conducted in females 10-14 years of age, immunogenicity bridging (which demonstrated non-inferiority of immune response of younger females compared to the response of females 15-25 years of age who participated in the efficacy trials), as well as safety data in the 10-14 year old female population was provided to support use of Cervarix in younger females. (See Immunogenicity Overview and Safety Overview).

There is no evidence of vaccine efficacy against HPV 16/18 related CIN 2/3 in subjects non-naïve for the relevant vaccine HPV type. In subjects seropositive and PCR positive for a specific vaccine HPV type, there was a negative point estimate of efficacy, but the CI included 0. As discussed, there was a slightly higher proportion of subjects with an a low-grade cytology result at baseline, and the proportions of subjects with prior infection with anyHR HPV type was not perfectly balanced. In addition, the proportions of subjects with an abnormal cytology who went onto develop CIN 2+in either treatment group were balanced among the groups (13.6% HPV, 13.9% HAV group). This negative impact was not noted in the other non-naïve subgroups (seropositive and PCR negative, and seronegative and PCR positive).

Given the fact that there are more than 100 HPV types, and approximately 30-40 of these have been reported to be associated with cervical and genital lesions, not all HPV related disease will be prevented, even in persons naïve to both vaccine HPV types. HPV types included in the vaccine have been reported to be associated with most cases of cervical cancer (approximately 70%). However, because the vaccine does not target all HPV types that have been associated genital disease, females will still require routine gynecological examinations. Duration of efficacy has been estimated from results of prevention of CIN 2/3 or worse in subjects who were

followed for 6.4 years in study HPV-007. In that same long-term study, the immune response as measured by IgG (ELISA) and pseudovirion neutralization assays were long-lasting, with seropositvity rates for both assays at ≥ 98%.
Phase III efficacy studies in older females are currently ongoing. Post-marketing commitments are listed in the approval letter.

Efficacy against HPV related disease outside the genital tract (i.e, aerodigestive tract disease) has not been studied, although efficacy against these diseases would be of interest to follow in the future.

OVERVIEW OF IMMUNOGENICITY

9.1.9 Immunogenicity: Immunogenicity was presented in studies HPV-001/007, HPV-008, HPV-012, HPV-013, and HPV-016. Lot consistency studies were conducted in study HPV-012 (one formulation as compared to newer formulation) and study HPV-016. Please see results of those studies for results as they pertain to lot consistency.

In study HPV-008, immune responses to HPV 16 and HPV 18 IgG as measured by ELISA peaked after dose 3, then decreased and reached a plateau from Month 24 onward. GMTs remained much higher than those noted in the control group, and as compared to subjects with evidence of natural infection. In study HPV-008, immune responses were measured in the immunogenicity subset. CBER notes that the ATP cohort for immunogenicity included subjects who received all three doses of vaccine, had not protocol violations, for whom data was available, and did not develop an endpoint. CBER also notes that very few subjects who received Cervarix developed an endpoint if they were naïve for the relevant HPV type. Further, results in the Total Vaccinated Cohort were very similar to those noted for the ATP cohort of immunogenicity. Table 365 and Table 366 presents ths seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 for subjects in study HPV-008 in the ATP cohort for immunogenicity.

Table 365-Study HPV -008: Seropositivity rates and GMTs for anti-HPV-16 antibody titers (ATP cohort for immunogenicity)

			≥ 8 EL.U/ml					GMT				
						95% CI			95% CI			
Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV	S- and S+	PRE	1029	161	15.6	13.5	18	5.4	5.2	5.7	<8.0	502
		PII(M6)	1020	1018	99.8	99.3	100	698.9	655.4	745.2	<8.0	38767
		PIII(M7)	1021	1016	99.5	98.9	99.8	8698.2	8171.5	9259	<8.0	187703
		PIII(M12)	986	984	99.8	99.3	100	3224.9	3029.6	3432.8	<8.0	87534
		PIII(M24)	936	935	99.9	99.4	100	1588.1	1495.9	1685.9	<8.0	36310
		PIII(M36)	919	919	100	99.6	100	1260.6	1186.7	1339.1	25	23557
HAV	S- and S+	PRE	894	146	16.3	14.0	18.9	5.5	5.2	5.9	<8.0	1055.0
		PII(M6)	874	159	18.2	15.7	20.9	5.7	5.4	6.1	<8.0	2929.0
		PIII(M7)	876	139	15.9	13.5	18.5	5.6	5.3	6.0	<8.0	21663.0
		PIII(M12)	850	130	15.3	12.9	17.9	5.4	5.1	5.8	<8.0	2032.0
		PIII(M24)	807	127	15.7	13.3	18.4	5.6	5.2	5.9	<8.0	1295.0
		PIII(M36)	789	122	15.5	13.0	18.2	5.4	5.1	5.8	<8.0	1388.0

S- = seronegative subjects (antibody titer < 8 EL.U/ML) prior to vaccination; S+ = seropositive subjects (antibody titer ≥ 8 EL.U/ML) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available; n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination
PII(M6) = Post Dose II (Month 6); PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12)
PIII(M24) = Post Dose III (Month 24); PIII(M36) = Post Dose III (Month 36)

Table 366-Study HPV-008: Seropositivity rates and GMTs for anti-HPV-18 antibody titers (ATP cohort for immunogenicity)

			≥ 7 EL.U/ml					GMT				
						95% CI			95% CI			
Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV	S- and S+	PRE	1029	96	9.3	7.6	11.3	4.2	4	4.4	<7.0	1397.0
		PII(M6)	1020	1016	99.6	99	99.9	566.3	533	601.7	<7.0	30703.0
		PIII(M7)	1020	1015	99.5	98.9	99.8	4683.2	4414.7	4967.9	<7.0	142964.0
		PIII(M12)	986	986	100	99.6	100	1521.3	1435.3	1612.4	79.0	62477.0
		PIII(M24)	936	935	99.9	99.4	100	707.4	663.7	754	<7.0	30567.0
		PIII(M36)	920	920	100	99.6	100	537.9	504	574.1	28	20621.0
HAV	S- and S+	PRE	895	108	12.1	10.0	14.4	4.4	4.2	4.6	<7.0	745.0
		PII(M6)	873	119	13.6	11.4	16.1	4.5	4.3	4.8	<7.0	4271.0
		PIII(M7)	874	121	13.8	11.6	16.3	4.6	4.4	4.9	<7.0	9564.0
		PIII(M12)	851	123	14.5	12.2	17.0	4.6	4.4	4.9	<7.0	4060.0
		PIII(M24)	797	119	14.9	12.5	17.6	4.6	4.4	4.9	<7.0	722.0
		PIII(M36)	787	104	13.2	10.9	15.8	4.5	4.3	4.8	<7.0	467.0

S- = seronegative subjects (antibody titer < 8 EL.U/ML) prior to vaccination; S+ = seropositive subjects (antibody titer ≥ 8 EL.U/ML) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available; n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination; PII(M6) = Post Dose II (Month 6); PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M24) = Post Dose III (Month 24); PIII(M36) = Post Dose III (Month 36)

Neutralizing antibodies were also measured in study HPV-008 in a subset of subjects. The results obtained by PBNA are similar to those obtained by ELISA. All evaluated subjects in the HPV group were seropositive for anti-HPV-16 and anti-HPV-18 neutralizing antibodies at Month 24, i.e. up to 18 months after completion of the full vaccination course. After a peak response at Month 7, GMTs for anti-HPV-18 neutralizing antibodies already reached a plateau at Month 12, while GMTs for anti-HPV-16 neutralizing antibodies gradually declined up to Month 24 (with a smaller decline between the Month 12 and 24 timepoints). The data for anti-HPV-16 and anti-HPV-18 neutralizing antbodies were presented in the review of study HPV-008.

Table 367-Study HPV-008: Seropositivity rates and GMTs for anti-HPV-16 titers using PBNA (ATP cohort for immunogenicity)

					≥ 40 ED50				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-16 PBNA	HPV	S-	PRE	46	0	0.0	0.0	7.7	20.0	20.0	20.0	<40.0	<40.0
			PIII(M7)	46	46	100	92.3	100	27364.8	19780.1	37857.9	1416.0	343855.0
			PIII(M12)	45	45	100	92.1	100	8385.9	5857.3	12006.0	881.0	129002.0
			PIII(M24)	46	46	100	92.3	100	3647.4	2586.5	5143.4	261.0	30246.0
	HAV	S-	PRE	44	0	0.0	0.0	8.0	20.0	20.0	20.0	<40.0	<40.0
			PIII(M7)	44	0	0.0	0.0	8.0	20.0	20.0	20.0	<40.0	<40.0
			PIII(M12)	43	0	0.0	0.0	8.2	20.0	20.0	20.0	<40.0	<40.0
			PIII(M24)	40	0	0.0	0.0	8.8	20.0	20.0	20.0	<40.0	<40.0

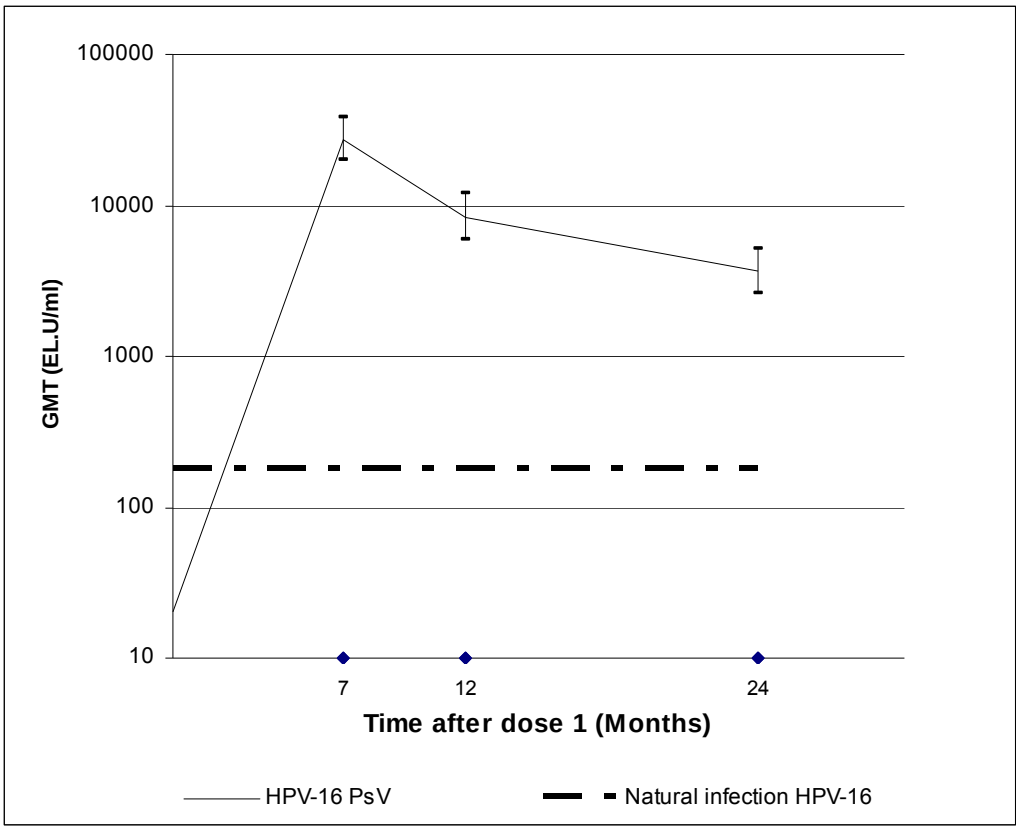
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
PBNA = pseudovirion based neutralizing assay
S- = seronegative subjects (antibody titre < 40 ED50) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination
PIII(M7) = Post Dose III (Month 7)
PIII(M12) = Post Dose III (Month 12)
PIII(M24) = Post Dose III (Month 24)
Source: STN 125259.48, CSR 008, Table 134, p. 464

Table 368-Study HPV-008: Seropositivity rates and GMTs for anti-HPV-18 titers using PBNA (ATP cohort for immunogenicity)

					≥ 40 ED50				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-18 PBNA	HPV	S-	PRE	48	0	0.0	0.0	7.4	20.0	20.0	20.0	<40.0	<40.0
			PIII(M7)	46	46	100	92.3	100	9052.7	6851.8	11960.5	1161.0	55863.0
			PIII(M12)	45	44	97.8	88.2	99.9	1889.9	1316.0	2714.1	<40.0	25047.0
			PIII(M24)	46	46	100	92.3	100	1695.6	1200.7	2394.4	67.0	20814.0
	HAV	S-	PRE	47	0	0.0	0.0	7.5	20.0	20.0	20.0	<40.0	<40.0
			PIII(M7)	44	0	0.0	0.0	8.0	20.0	20.0	20.0	<40.0	<40.0
			PIII(M12)	43	0	0.0	0.0	8.2	20.0	20.0	20.0	<40.0	<40.0
			PIII(M24)	40	0	0.0	0.0	8.8	20.0	20.0	20.0	<40.0	<40.0

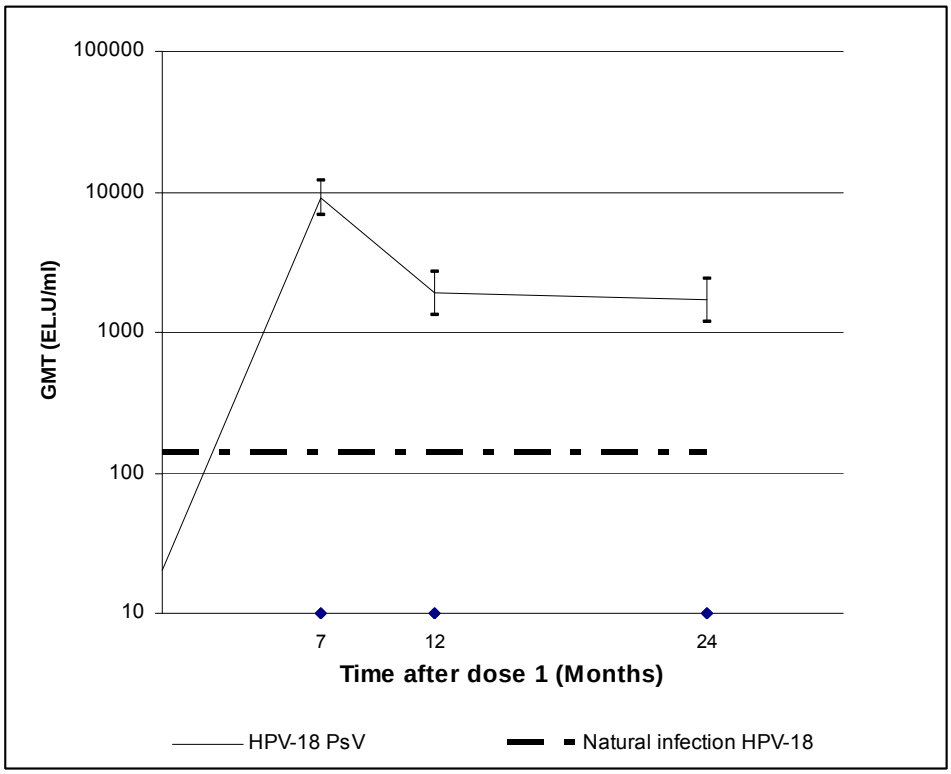
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
PBNA = pseudovirion based neutralizing assay
S- = seronegative subjects (antibody titre < 40 ED50) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination
PIII(M7) = Post Dose III (Month 7)
PIII(M12) = Post Dose III (Month 12)
PIII(M24) = Post Dose III (Month 24)
Source: STN 125259.48, CSR 008, Table 135, p. 465

Figure 38- Kinetics for anti-HPV-16 antibodies using PBNA in initially seronegative subjects with anti-HPV-16 PBNA results available at all timepoints (ATP cohort for immunogenicity – HPV group)



Source: STN 125259.48, CSR HPV-008

Figure 39- Kinetics for anti-HPV-18 antibodies using PBNA in initially seronegative subjects with anti-HPV-16 PBNA results available at all timepoints (ATP cohort for immunogenicity - HPV group)



Source: STN 125259.48, CSR HPV-008

Immunogenicity results were reported for study HPV 001/007 (Phase IIb study). Additional Phase III studies were conducted to assess consistency of lots prepared by different manufacturing processes and to compare immune responses in 15-25 year old women as compared to 10-14 year old females (Study HPV-012), and to assess lot consistency between different lots by final manufacturing processes (Study HPV-016). An additional study (HPV-014) was conducted to compare immune responses elicited by Cervarix in women 15-25 years of age as compared to women 26-55 years of age. Since the Phase III study to assess efficacy in women 26-55 years of age is ongoing (HPV-015), and the BLA does not provide data which is considered supportive of approval in this older age population, the immunogenicity results for women > 25 years of age are not included in this briefing document. The results for the consistency lot data are not repeated in this section, but all objectives were met for study HPV-012 and study HPV-016 as to ability of GSK to manufacture a consistent product.

In study HPV-001/007, anti-HPV-16 and anti-HPV-18 IgG responses by ELISA are presented out to Month 76. (Control recipients had very low seroresponse rates and GMTs as compared to Cervarix recipients, and these results are not reproduced below). See Tables 369 and 370.

Table 369-Study HPV-001/007: Seropositivity rates and GMTs for anti-HPV-16 IgG antibody (ATP cohort for immunogenicity)

			≥ 8 EL.U/mL				GMT			
					95% CI			95% CI			
Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Vaccine	PRE	301	18	6	3.6	9.3	4.3	4.2	4.4	<8.0	30
	PIII(M7)	301	301	100	98.8	100	4197.5	3766.1	4678.3	65	34561
	PIII(M12)	302	302	100	98.8	100	1241	1094.7	1406.8	70	25655
	PIII(M18)	300	299	99.7	98.2	100	737.8	651	836.2	<8.0	10228
	[M25-M32]	71	70	98.6	92.4	100	670.4	489.2	918.8	<8.0	9900
	[M33-M38]	172	171	99.4	96.8	100	454.7	381.7	541.6	<8.0	4974
	[M39-M44]	126	126	100	97.1	100	567.8	475.9	677.4	46	5264
	[M45-M50]	190	190	100	98.1	100	399.4	340.6	468.5	29	4562
	[M51-M56]	100	100	100	96.4	100	622.8	506.1	766.5	74	6137
	[M57-M62]	179	179	100	98	100	426.7	362	503	29	5479
	[M63-M68]	103	103	100	96.5	100	542.3	439.7	668.7	64	5659
	[M69-M74]	178	177	99.4	96.9	100	394.3	332	468.4	<8.0	4233
	[M75-M76]	52	52	100	93.2	100	463.6	360.8	595.5	89	4707

Vaccine = HPV-16/18; Placebo = Aluminum hydroxide
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
[M25-M32] = Post Dose III (25<=Month<=32); [M33-M38] = Post Dose III (33<=Month<=38)
[M39-M44] = Post Dose III (39<=Month<=44); [M45-M50] = Post Dose III (45<=Month<=50)
[M51-M56] = Post Dose III (51<=Month<=56); [M57-M62] = Post Dose III (57<=Month<=62)
[M63-M68] = Post Dose III (63<=Month<=68); [M69-M74] = Post Dose III (69<=Month<=74)
[M75-M76] = Post Dose III (75<=Month<=76)
Source: STN 125259.0048, CSR HPV-007, Month 36 report .

Table 370-Study HPV-001/007: Seropositivity rates and GMTs for anti-HPV-18 IgG antibodies (ATP cohort for immunogenicity)

			≥ 7 EL.U/mL	GMT		

					95% CI			95% CI			
Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Vaccine	PRE	301	30	10	6.8	13.9	3.9	3.8	4.1	<7.0	33
	PIII(M7)	300	300	100	98.8	100	3358	3041.8	3707	107	45888
	PIII(M12)	302	302	100	98.8	100	995.3	888.5	1115	91	30401
	PIII(M18)	300	299	99.7	98.2	100	591.9	524.7	667.8	<7.0	7518
	[M25-M32]	71	70	98.6	92.4	100	596.9	439.6	810.5	<7.0	12988
	[M33-M38]	172	171	99.4	96.8	100	378.6	320	447.9	<7.0	3711
	[M39-M44]	127	126	99.2	95.7	100	435.1	351.1	539	<7.0	11173
	[M45-M50]	190	190	100	98.1	100	297.5	254.4	348	22	5649
	[M51-M56]	100	100	100	96.4	100	454.9	370.8	558.1	23	8272
	[M57-M62]	179	179	100	98	100	322.5	274.9	378.4	23	4775
	[M63-M68]	103	103	100	96.5	100	359.9	295	439.2	24	6130
	[M69-M74]	178	177	99.4	96.9	100	305.3	258.1	361.1	<7.0	3415
	[M75-M76]	52	52	100	93.2	100	279.8	218	359.1	55	2408

Vaccine = HPV-16/18
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
[M25-M32] = Post Dose III (25<=Month<=32); [M33-M38] = Post Dose III (33<=Month<=38)
[M39-M44] = Post Dose III (39<=Month<=44); [M45-M50] = Post Dose III (45<=Month<=50)
[M51-M56] = Post Dose III (51<=Month<=56); [M57-M62] = Post Dose III (57<=Month<=62)
[M63-M68] = Post Dose III (63<=Month<=68); [M69-M74] = Post Dose III (69<=Month<=74)
[M75-M76] = Post Dose III (75<=Month<=76)
Source: STN 125259.0048, CSR 007, Month 36

No breakthrough cases of **persistent HPV-16/18 infection** (6-month and 12-month definition) were observed in the vaccine group during studies HPV-001 and HPV-007. However, three cases of breakthrough HPV-**16/18 incident infection** were reported in the vaccine group. The ELISA titers obtained for these subjects with breakthrough infection were provided. In two subjects, when compared to subjects in the ATP cohort for immunogenicity, the GMTs for anti-HPV 16 and 18 were lower throughout the study period as compared to subjects who did not develop an infection with either HPV 16 or HPV 18. The third subject's GMTs were somewhat lower for HPV 16 initially, but were higher than GMTs in the ATP cohort at the later time points, so there was no consistent pattern noted in these subjects with "breakthrough" cases. Because of the low number of subjects with breakthrough cases, and lack of consistent pattern in subjects with a breakthrough case, an immune correlate of protection was not possible to identify. It is difficult to state that the GMTs associated with natural infection is the protective level given the variability in these results.

Anti-HPV-16/18 neutralizing antibodies measured by pseudovirion neutralization assay: In study HPV-001/007, the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 pseudovirion neutralizing antibodies in a subset of subjects were presented. GMT levels for both HPV-16 and HPV-18 by assays for pseudovirion neutralizing antibodies showed a plateau that began approximately at Month 18 post vaccination and was sustained for up to 76 months of follow-up. Seropositivity rates for both HPV-16 and HPV-18 (≥ 98.0%) were similar to those observed with ELISA (≥ 98.6%).

Regarding immune responses to non-vaccine HPV types, although the anti-HPV 31 IgG seropositivity rates were > 80% and HPV-45 IgG seropositivity rates in vaccine recipients were >

83.7% at Month 24, the seropositivity rate for PSV neutralizing antibodies for HPV-31 reached a peak of 47.6% seropositivity rate at Month 7 and was 0% by Month 45-50. For HPV-45, the seropositivity rate for PSV neutralizing antibodies reached a peak of 9.5% at Month 7 and was 0% at Month 45-50 in a subset of subjects who were followed from study HPV-001 to study HPV-007. This observation may indicate that the immune response to non-vaccine HPV types HPV-31 and HPV-45 may be less robust and shorter in duration as compared to the immune response elicited for HPV 16 and HPV 18.

Immunogenicity Bridging to Females 10-14 years of age: Antibody responses in females 10-14 years of age were found to be more robust as compared to responses in women 15-25 years of age. Cervarix is a preventive vaccine, and is expected to have optimum impact on prevention of cervical dysplasias and cancers in females not yet exposed to the relevant vaccine HPV types. Younger females have generally not yet been exposed to HPV infection, but it was not possible to conduct genital HPV testing in these females prior to sexual exposure. Therefore, immunobridging was used to compare the vaccine immune response in women 15-25 years of age who received the vaccine (efficacy had been demonstrated in this older age group) to females 10-14 years of age (conducted in study HPV-012 and study HPV-013).

A secondary objective of study HPV-012 was to demonstrate that the 10-14 years age group was non-inferior to the 15-25 years age group in terms of immunogenicity when receiving the same industrial production lot. Two criteria for non-inferiority were assessed sequentially (if the first one was not demonstrated, the second one could not be tested): (1) 1 month after the third dose, the difference between the percentage of subjects who seroconverted in the older age group versus the younger age group was below 10%; (2) 1 month after the third dose of HPV vaccine, the GMT ratio between the older age group and younger age group was below 2. Anti-HPV 16 and anti-HPV 18 IgG antibodies elicited in females 10-14 years of age were non-inferior to the antibodies in females 15-25 years of age (<10% difference in seroconversion rates and upper limits of the 95% CI were < 2). The analyses are presented in Tables 371 and 372 below.

Table 371-Study HPV-012: Non-inferiority assessment between 10-14 year olds (group [10-14]) and 15-25 year olds (Lot 1 -b(4)- for anti-HPV 16 IgG and anti-HPV 18 IgG seroconversion rates at Month 7 (ATP cohort for immunogenicity). Calculation performed on subjects seronegative prior to Dose 1 to the respective antigen

Antibody	Group				Difference in seroconversion rate Lot 1 - [10-14]		
	Lot 1		[10-14]		%	95 % CI	
	N	%	N	%		LL	UL
HPV-16 IgG	118	100	143	100	0.00	-3.15	2.62
HPV-18 IgG	116	100	141	100	0.00	-3.21	2.65

Lot 1 = DHPVA004A b(4) (15≤Age≤25); [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
N = number of subjects with available results
% = percentage of subjects with HPV 16 IgG titre ≥8 EU/ML / HPV 18 IgG ≥7 EU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 012, Table 24, p.79

Table 372-Study HPV-012: Ratios of post-vaccination anti-HPV16 and anti-HPV18 GMT at Month 7 between 10-14 year olds (group [10-14]) and 15-25 year olds [Lot 1 (b(4))] with their 95% CIs (ATP cohort for immunogenicity).
Calculation performed on subjects seronegative prior to Dose 1 to the respective antigen

Anti body	Group				GMT ratio (Lot 1 / [10-14])		
	Lot 1		[10-14]		Value	95% CI	
	N	GMT	N	GMT		LL	UL
HPV 16 IgG	118	7438.9	143	17272.5	0.43	0.35	0.53
HPV 18 IgG	116	3070.1	141	6863.8	0.45	0.36	0.55

Lot 1 = DHPVA004A (b(4)) (15≤Age≤25); [10-14] = DHPVA004A (b(4)) (10≤Age≤14)
GMT = geometric mean antibody titre, expressed in EU/ml
N = Number of subjects with pre-vaccination results available
95% CI = 95% asymptotic confidence interval for the GMT ratio (ANOVA model); LL = lower limit, UL = upper limit
Source: STN 125259/0, CSR 012, Table 25, p.79

In addition to a pre-specified statistical comparison in study HPV-012, GSK also observationally compared the immune responses (anti-HPV-16 and anti-HPV-18 IgG by ELISA) in 10-14 year old females and 15-25 year old females who participated in the efficacy study HPV-001. The comparison was made for seropositivity rates and GMTs. The majority (84.9%) of the 383 subjects selected from the HPV-001 study (HPV-001 group) were seronegative for both HPV-16 and HPV-18 antigens before vaccination. In both groups, all initially seronegative subjects had seroconverted for both antigens after the third vaccine dose. The GMT values in the HPV-013 HPV vaccine group were higher for anti-HPV-16 antibodies and anti-HPV-18 antibodies as measured by ELISA as compared to study HPV-001: 19882.0 EU/mL versus 4415.9 EU/mL for anti-HPV-16 antibodies, and, 8262.0 EU/mL versus 3471.8 EU/mL for anti-HPV-18 antibodies. The reverse cumulative distribution curves for anti-HPV-16 and anti-HPV-18 antibodies show that all subjects in the two studies had seroconverted at Month 7 but with higher antibody titers achieved by subjects enrolled in the study HPV-013. The seroposivity rates and GMTs at Month 7 for anti-HPV 16 and HPV-18 are shown for each age group in Tables 373 and 374 below.

Table 373- HPV-013: Seropositivity rates and GMTs for HPV-16 IGG ELISA antibodies by pre-vaccination status (ATP cohort for immunogenicity)

		≥8 EU/mL	GMT	Min, Max
Group	**Timing**	**n/N**	**Value**	
HPV-013	**PRE**	40/670 (6.0%)	4.3	<8.0, 141.0
	PII(M2)	659/662 (99.5%)	4733.8	<8.0, 49477.0
	PIII)M7)	656/656 (100%)	20018.1	706.0, 244471.0
HPV-001	**PRE**	24/371 (6.5%)	4.3	<8.0, 30.0
	PIII)M7)	362/362 (100%)	4378.4	65.0, 110768.0

HPV-013 = HPV-16/18 L1/AS04 from study HPV-013; HPV-001 = HPV-16/18 L1/AS04 from study HPV-001
GMT = geometric mean antibody titre calculated on all subjects; N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range;
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR 013, Table 34, p. 86

Table 374 - HPV-013: Seropositivity rates and GMTs for HPV-18 IGG ELISA antibodies by pre-vaccination status (ATP cohort for immunogenicity)

		≥7 EU/mL	GMT	Min, Max
Group	**Timing**	**n/N**	**Value**	
HPV-013	**PRE**	29/668 (4.3%)	3.8	<7.0, 89.0
	PII(M2)	659/661 (99.7%)	3745.2	<7.0, 47111.0
	PIII)M7)	655/655 (100%)	8359.4	567.0, 2000687.0
HPV-001	**PRE**	37/371 (10.0%)	3.9	<7.0, 33.0
	PIII)M7)	362/362 (100%)	3459.8	107.0, 51346.0

HPV-013 = HPV-16/18 L1/AS04 from study HPV-013; HPV-001 = HPV-16/18 L1/AS04 from study HPV-001
GMT = geometric mean antibody titre calculated on all subjects; N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range;
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR 013, Table 35, p. 87

Based on the above data, precedent in immunobridging used in Gardasil licensure, and the vote of VRBPAC of 9/9/09, the immunobridge to females 10-14 years of age was assessed as appropriate to infer effectiveness in females 10-14 years of age based on comparison to females 15-25 years of age, some of whom had participated in an efficacy study.

Duration of Immune Response: The immune response to anti-HPV-16 and anti-HPV-18 as measured by anti-HPV-16 and anti-HPV-18 IgG by ELISA and neutralizing antibodies as measured by PBNA and was demonstrated to persist out to Month 76 as shown in Tables 369 and 370 above in study HPV-001/007.

Immune response in subjects with varied vaccination schedules (Total Vaccinated cohort): An additional analysis was performed to evaluate the immune response elicited by the vaccine in subjects vaccinated according to different schedules as follows:

- A flexible schedule for Dose 2 was evaluated based on subjects vaccinated according to a 0, 1, 6-month or a 0, 2, 6-month schedule.
- A flexible schedule for Dose 3 was evaluated based on subjects who received the three vaccine doses within a period of 5, 6, 7, 8 or 9 or more months.

An overview of the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies by schedule for subjects vaccinated according to the different schedules are presented in 375.

Table 375-Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies for different schedules –HPV group
(Total Vaccinated cohort – Subset of subjects who received three doses)

		Anti-HPV-16		Anti-HPV-18	
		≥8 EU/mL	GMT	≥7EU/mL	GMT
Group	Timing	n/N (%)	Value	n/N (%)	Value
0, 1, 6, months	PRE	1221/7499 (16.3%)	5.7	857/7513 (11.4%)	4.4
	PIII (M7)	1262/1267 (99.8%)	8113.4	1258/1263 (99.6%)	4390.0
	PIII (M12)	1205/1208 (99.8%)	3110.4	1204/1205 (99.9%)	1456.7
	PIII (M24)	1129/1130 (99.9%)	1558.2	1126/1127 (99.9%)	696.8
	PIII (M36)	1112/1112 (100%)	1257.5	1110/1110 (100%)	533.5
0, 2, 6 months	PRE	97/520 (18.7%)	5.8	67/519 (12.9%)	4.5
	PIII (M7)	78/78 (100%)	6757.1	76/77 (98.7%)	3861.5
	PIII (M12)	82/82 (100%)	2388.9	81/81 (100%)	1267.5
	PIII (M24)	71/71 (100%)	1230.6	70/70 (100%)	614.4
	PIII (M36)	69/69 (100%)	1000.8	69/69 (100%)	458.9
3 doses within 5 months	PRE	212/1041 (20.4%)	6.4	133/1049 (12.7%)	4.4
	PIII (M7)	270/271 (99.6%)	7326.0	273/274 (99.6%)	3969.4
	PIII (M12)	258/258 (100%)	2488.9	271/272 (99.6%)	1145.9
	PIII (M24)	235/235 (100%)	1195.4	159/159 (100%)	523.9
	PIII (M36)	243/243 (100%)	936.2	244/244 (100%)	402.2
3 doses within 6 months	PRE	900/5701 (15.8%)	5.7	641/5704	4.4
	PIII (M7)	943/947 (99.6%)	8089.8	938/942 (99.76%)	4351.0
	PIII (M12)	896/899 (99.7%)	3125.7	895/896 (99.9%)	1463.4
	PIII (M24)	93/93 (100%)	1587.7	859/860 (99.9%)	710.2
	PIII (M36)	90/90 (100%)	1311.8	840/840 (100%)	594.4
3 doses within 7 months	PRE	244/1448 (16.9%)	5.8	172/1449 (11.9%)	4.3
	PIII (M7)	150/150 (100%)	8808.8	148/148 (100%)	5081.7
	PIII (M12)	139/139 (100%)	3922.5	138/138 (100%)	2048.2
	PIII (M24)	116/116 (100%)	1968.0	115/115 (100%)	964.6
	PIII (M36)	110/110 (100%)	1412.7	109/109 (100%)	686.7
3 doses within 8 months	PRE	35/171 (20.5%)	6.1	23/170 (13.5%)	4.5
	PIII (M7)	38/38 (100%)	10064.8	37/37 (100%)	4757.8
	PIII (M12)	25/25 (100%)	4587.7	24/24 (100%)	1922.7
	PIII (M24)	30/30 (100%)	1452.4	29/29 (100%)	641.7
	PIII (M36)	28/28 (100%)	1204.7	27/27 (100%)	528.9
3 doses within 9+ months	PRE	14/100 (14.0%)	5.0	14/102 (13.7%)	4.4
	PIII (M7)	20/20 (100%)	5285.2	20/20 (100%)	1558.5
	PIII (M12)	14/14 (100%)	5568.8	14/14 (100%)	1819.2
	PIII (M24)	14/14 (100%)	1716.1	14/14 (100%)	580.4
	PIII (M36)	15/15 (100%)	1147.2	15/15 (100%)	380.1

HPV = HPV-16/18 vaccine (three lots)
3 Doses within 5M = Dose 1-Dose 3 interval equals 5 months (150 ± 15 Days)
3 Doses within 6M = Dose 1-Dose 3 interval equals 6 months (180 ± 15 Days)
3 Doses within 7M = Dose 1-Dose 3 interval equals 7 months (210 ± 15 Days)
3 Doses within 8M = Dose 1-Dose 3 interval equals 8 months (240 ± 15 Days)
3 Doses within 9M+ = Dose 1-Dose 3 interval equals 9 months and more (≥ 255 Days)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination; PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12)
PIII(M24) = Post Dose III (Month 24); PIII(M36) = Post Dose III (Month 36)
Source: STN 125259.0048, CSR 008, Supplements 410 and 411, p. 10938-10947

These analyses were exploratory. Values were similar across treatment schedules, but please note that small number of subjects in some analyses preclude definitive comparisons. Similar immune responses against HPV-16 and HPV-18 were elicited in subjects receiving the vaccine according to a 0, 1, 6-month schedule or a 0, 2, 6-month schedule. Also, similar immune responses against both antigens were observed for subjects receiving the three doses within a period of either 5, 6, 7, 8 or 9 or more months. Note that only a small number of subjects was available for the analysis of three doses within 9 or more months.

Immune correlates of protection: Due to this low number of cases at the time of final analysis, no correlate of protection could be identified.

10 Overview of Safety Across Trials

10.1. Safety Database-Number of Subjects, Types of Subjects, and Extent of Exposure

Common solicited and unsolicited adverse events were presented from the time of the original submission of the BLA in 3/07 because the time periods for these adverse events were 7- and 30-days after each vaccination. GSK prepared an update of safety through 8/31/08 for deaths, SAEs, pregnancy outcomes and abnormalities in children born to vaccinees, medically significant adverse events, study discontinuations due to adverse events, repeat meta-analysis of neuroinflammatory and musculoskeletal events, and updated pooled safety analysis of adverse events classified as NOCDs and NOADs. Additionally, post-marketing safety updates from foreign countries where Cervarix is licensed (including countries in Asia, Australia, Europe, and South America) were provided through 11/17/08, and more recently, through 4/09.

The number of subjects enrolled in Phase I studies (003, 004, and 005), Studies 001/007, 008, 012, 014 and 016 are shown Table 376 below. Please note that the studies included in the table below include subjects outside of the 10-25 year old age range (i.e, studies HPV-003, 004, and 005: 18-30 years of age; study HPV-014: 15-55 years.)

Table 376-Studies 003, 004, 005, 001/007, 013, 015, 016, and 018: Number of Subjects by Study (Cervarix Recipients and Control Recipients) – Safety Populations

	HPV 16/18 Vaccine	Aluminum hydroxide	Havrix 360	Havrix 720	Total Control
HPV-003 (18-*30*)	31	30			30
HPV-004 (18-*30*)	60				0
HPV-005 (18-*30*)	209				0
HPV-001/007 (15-25)	560 [7 were 26 years of age]	553 [3 were 26 years of age]			553
HPV-008 (15-25)	9319			9325*	9325*
HPV-012 (10-25)	770				0
HPV-013 (10-14)	1035		1032		1032
HPV-014 (15-55)	666 [229 were 15-25 years of age]				0
HPV-016 (15-25)	798				0

*10 subjects from study HPV-008 in the control group were > 25 years of age.

CBER was interested in assessing safety for the age group for which the vaccine is approved, as well as assess overall safety for serious adverse events and deaths.

Table 377-Number of Subjects per Treatment Group and Age

Age (years)	Group				Total
	HPV	HAV720	HAV360	Control	
10-14	1,194	-	1,032		2,226
15-25	11,591	9,315	-	581	21,487
Subtotal 10-25	12,785	9,315	1,032	581	23,713
>25	3,357	10*	-	2,873	6,240
Total all subjects	16,142	9,325	1,032	3,454	29,953

*10 subjects randomized to receive control vaccine in study HPV-008 over the age of 25 years were enrolled into study even though age specified was 15-25 years.
Source: GSK VRBPAC Briefing Document, Table 25, p. 93

From these studies, the safety of Cervarix was evaluated by pooling data from controlled and uncontrolled clinical trials involving 23,713 females 10 through 25 years of age in the pre-licensure clinical development program, of which 12,785 females (10 through 25 years of age) received at least one dose of Cervarix and 10,928 females received at least one dose of a control vaccine (Hepatitis A Vaccine 720 EL.U. for females 15 through 25 years of age, Hepatitis A Vaccine 360 EL.U. for females 10 through 14 years of age or control [$Al(OH)_3$] for females 15 through 25 years of age). The individual studies have been reviewed and safety reported in this review.

Solicited local adverse reaction and solicited general adverse events: The solicited local reaction, solicited adverse events, and unsolicited adverse events were tabulated based on the 10-25 year age group who filled out a diary safety card. These included subjects in the Safety Diary Card subset in study HPV-008, subjects from study HPV-012, subjects from Study HPV-014, Study HPV-016, subjects in study HPV-013, and subjects in Study HPV-001.

A composite table of solicited local adverse reactions and solicited general adverse events was prepared by GSK. Detailed comparisons were presented earlier for each study in this review, and solicited adverse events were as noted in each study. A higher proportion of subjects in the Cervarix group reported a local adverse reaction in the 7 days after vaccination as compared to subjects who received either the active control Havrix (dose depended on age group) or aluminum hydroxide. In general, except for pyrexia, 10-14 year old subjects had a lower frequency of either local adverse reactions and general solicited adverse events as compared to subjects 15-25 years of age. The proportions of subjects with general adverse events in the Cervarix group were comparable to subjects in the Havrix control group and generally comparable to the aluminum hydroxide control (although a higher proportion in the aluminum hydroxide group experienced a headache as compared to the Cervarix group).

Table 378-Solicited Local Adverse Reactions and General Adverse Events in Females 10 Through 25 Years of Age Within 7 Days of Vaccination (Total Vaccinated Cohort)

Adverse Reaction/Event	CERVARIX %	HAV 720 %	HAV 360 %	$Al(OH)_3$ Control %
Local Adverse Reaction	**N = 6,431**	**N = 3,079**	**N = 1,027**	**N = 549**
Pain	91.8	78.0	64.2	87.2
Redness	48.0	27.6	25.2	24.4
Swelling	44.1	19.8	17.3	21.3
General Adverse Event	**N = 6,432**	**N = 3,079**	**N = 1,027**	**N = 549**
Fatigue	55.0	53.7	42.3	53.6
Headache	53.4	51.3	45.2	61.4
GI[a]	27.8	27.3	24.6	32.8
Fever (≥99.5°F)	12.8	10.9	16.0	13.5
Rash	9.6	8.4	6.7	10.0
	N = 5,881	**N = 3,079**	**N = 1,027**	—
Myalgia	49.1	44.9	33.1	—
Arthralgia	20.8	1739	19.9	—
Urticaria	7.4	7.9	5.4	—

Source: Table compiled by GSK ; Studies HPV-001, HPV-008, HPV-013, HPV-012, HPV-014, and HPV-016.

Local adverse reactions were also presented by solicited reaction per dose. A higher proportion of subjects in the Cervarix group had pain in the 7 days after vaccination as compared to the subjects in either Havrix group or aluminum hydroxide group. The proportion of subjects with pain was lower after dose 2 for all groups. Grade 3 pain was more frequently reported in the Cervarix group as compared to subjects in the Havrix group although subjects in the Aluminum hydroxide group had higher proportions of grade 3 pain than either group. A higher proportion of

Cervarix recipients experienced redness and swelling as compared to either Havrix group. There was an increase in the proportions of subjects in the Cervarix group who reported redness and swelling after subsequent doses. This trend was not noted in the Havrix group, although there was a higher proportion of subjects with redness after dose 3 aluminum hydroxide (15.6%) as compared to after doses 1 or 2 (11.5%). In each individual study report, although there was a higher proportion of subjects with local adverse reactions in the Cervarix group, there was no apparent impact on the compliance with completion of vaccination series.

Table 379- Solicited Local Adverse Reactions in Females 10 Through 25 Years of Age by Dose Within 7 Days of Vaccination (Total Vaccinated Cohort)

Adverse Events	CERVARIX %			HAV 720 %			HAV 360 %			$Al(OH)_3$ Control %		
	Post-Dose			Post-Dose			Post-Dose			Post-Dose		
	1 (N=6,415)	2 (N=6,197)	3 (N=5,936)	1 (N=3,070)	2 (N=2,919)	3 (N=2,758)	1 1,027	2 1,021	3 1,011	1 546	2 521	3 500
Pain	86.9	76.2	78.7	65.6	54.4	56.1	48.5	38.5	36.9	79.1	66.8	72.4
Pain, Grade 3	7.5	5.7	7.7	2.0	1.4	2.0	0.8	0.2	1.6	9.0	6.0	8.6
Redness	27.8	29.6	35.6	16.6	15.2	16.1	15.6	13.3	12.1	11.5	11.5	15.6
Redness, >50mm	0.2	0.5	1.0	0.1	0.1	0.0	0.1	0.2	0.1	0.2	0.0	0.0
Swelling	22.7	25.2	32.7	10.5	9.4	10.5	9.4	8.6	7.6	10.3	10.4	12.0
Swelling, >50mm	1.2	1.0	1.3	0.2	0.2	0.2	0.4	0.3	0.0	0.0	0.0	0.0

Source: Data compiled by GSK ; Studies HPV-001, HPV-008, HPV-013, HPV-012, HPV-014, and HPV-016

Table 380- Unsolicited Adverse Events in Females 10 Through 25 Years of Age Within 30 Days of Vaccination (Total Vaccinated Cohort)
[≥ 1% for Cervarix and Greater than HAV 720, HAV 360, and $Al(OH)_3$ control subjects]

Adverse Event	CERVARIX % (N=6,654)	HAV 720[c] % (N=3,186)	HAV 360[d] % (N=1,032)	$Al(OH)_3$ Control[e] % (N=581)
Headache	5.3	7.6	3.3	9.3
Nasopharyngitis	3.6	3.4	5.9	3.3
Influenza	3.2	5.6	1.3	1.9
Pharyngolaryngeal pain	2.9	2.7	2.2	2.2
Dizziness	2.2	2.6	1.5	3.1
Upper respiratory infection	2.0	1.3	6.7	1.5
Chlamydia infection	2.0	4.4	0.0	0.0
Dysmenorrhea	2.0	2.3	1.9	4.0
Pharyngitis	1.5	1.8	2.2	0.5
Injection site bruising	1.4	1.8	0.7	1.5
Vaginal infection	1.4	2.2	0.1	0.9
Injection site pruritus	1.3	0.5	0.6	0.2
Back pain	1.1	1.3	0.7	3.1
Urinary tract infection	1.0	1.4	0.3	1.2

The proportions of subjects with unsolicited adverse events in the 30 days after vaccination across all groups were presented. The most frequently reported unsolicited adverse events were as noted in Table 380 above. There were some differences based on the age of the subjects. For example, 10-14 year old subjects had higher rates of upper respiratory infections as compared to subjects 15-25 years of age. Subjects 15-25 year old subjects had higher rates of Chlamydia infection as compared to 10-14 year old subjects.

Deaths in Entire Safety Database: GSK provided a breakdown of deaths in each treatment group in JMP datasets. The total number of subjects comes from all studies in which Cervarix has been studied in all age groups (some studies ongoing). From the tables provided, there were 17 subjects in the control group and 20 subjects in the HPV group who died during all studies (including some studies not yet completed). The number and proportion of Cervarix recipients who died (20/33623 or 0.06%) was similar to the number of control recipients (18/23700 or 0.08%). Trauma was the most common cause of death for both the Cervarix and control groups. A summary table is shown below. One subject in the HPV group who died of complications related to infection due to immunosuppression for SLE was found to have markers for SLE in blood samples obtained prior to vaccination. Individual and mean times to first event after any dose in months are included in parentheses. One subject in the Cervarix group was considered to have died from pyoderma gangrenosum at 18 months after dose 2, although she was diagnosed with inflammatory bowel disease at 44 days after dose 2. These numbers are small, but overall, the proportions are similar in the treatment groups.

Table 381-Deaths Overall in All Cervarix Studies

Cause of Death	Cervarix N=33623	Control N=23700
Trauma	7	6
Suicide	2	5
Neoplasms	3	2
Infections	4	1
Cardiac disorders	1	0
Gastrintestinal disorders	2	0
Death not specified	0	2
Endocrine disorders	0	1
PE with lung mass (CA or TB)	1	0
Total	20 (0.06%)	17 (0.08%)

Additional details of the deaths are provided in Table 382 and Table 383 below.

Table 382-Deaths reported in all clinical studies Cervarix recipients (Number of subjects = 20)

	Cervarix N=33623	Time postdose
	PID (Study)/Age in yrs	Time postdose
DVT, Pulmonary mass	17678 (008)/28	2 yrs postdose 3
Cardiac disorders Acute myocardial infarction	817 (1048290)/31	16 months postdose 3
Neoplasms Cervix cancer Gestational trophoblastic tumor with lung mets Ovarian cancer	5322 (104820)/46 76286 (008)/22 362607 (009)/23	7 months postdose 3 5 months postdose 2 3 years postdose 3
Gastrointestinal disease Crohn's diseases, benign teratoma Inflammatory bowel disease, diarrhea, anaphylactic shock, Osteomyeltitis, Stevens-Johnson syndrome, Skin disorder, Henoch-Schonlein purpura, Pyoderma gangrenosum	 389954 (009)/25-26 71903 (008)/26-27	 Crohn's dis @ 44 days postdose 2 Benign teratoma @ 108 days postdose 2 Inflammatory bowel disease @ 2months postdose 3 Diarrhea @ 5 months postdose 3 Anaphylactic shock @ 6 months postdose 3 Osteomyeltitis @ 16 months postdose 3 Stevens Johnson syndrome @ 6 months postdose 3 Skin disorder @ 8 months postdose 3 Henoch-schonlein purpurs@11 months postdose 3 Pyoderma gangrenosum @ 18 months postdose 3
Infections and Infestations AIDS Candida sepsis and stypical pneumomonia in subject with SLE Pneumococcal sepsis with cardiopulmonary failure Sepsis	 237484 (009)/23 369716 (009)/24-26 89479 (008)/27 20945 (008)/21	 8 months postdose 1 SLE @ 6 months postdose 1 Atypical pneumonia @ 19 months postdose 1 Candida sepsis @ 20 months postdose 1 2 years postdose 3 2 years postdose 3
Psychiatric disorders Suicide attempt and completed suicide Gunshot wound	 9446 (104820)/28 18105 (008)/21	 Suicide attempt @ 102 days postdose 3 Completed suicide @ 5 months postdose 3 22 months postdose 3
Trauma Head injury, splenic rupture Homicide Homicide with drowning Road traffic accident Road traffic accident Road traffic accident Subarachnoid hemorrhage	 3106 (104902)/13 45183 (009)/21 8746 (008)/23 274 (105881)/55 317629 (009)/19 76544 (008)/22 22586 (008)/22	 13 months postdose 3 2 years postdose 3 7 months postdose 3 3 years postdose 3 6 months postdose 1 3 years postdose 1 18 months postdose 3

Table 383-Deaths reported in all clinical studies in Control recipients (HAV or Aluminum Hydroxide) (Number of subjects = 17)

	Control N=23700	Time postdose
	PID (Study)/Age in yrs-Control	Time postdose
Death (not specified)	16201 (008)/19-HAV 6594 (104820)/38-HAV	3 years postdose 3 67 days postdose 3
Endocrine disorders Diabetic ketoacidosis (IDDM)	18876 (008)/25-HAV	6 months postdose 1
Neoplasms Bone sarcoma Colon cancer	6726 (008)/18-ALU 196354 (009)/25-HAV	6 months postdose 3 112 days postdose 2
Infections and Infestations Lower respiratory tract infection with sepsis	5238 (104820)/55-ALU	22 months postdose 3
Psychiatric disorders Completed suicide Completed suicide Completed suicide Suicide attempt Suicide attempt	312860 (009)/24-HAV 14290 (008)/20-HAV 141567 (009)/23-HAV 393049 (009)/20-HAV 130431 (009)/20-HAV	5 months postdose 2 2 years postdose 3 5 months postdose 3 49 days postdose 3 23 months postdose 2
Trauma Homicide Road traffic accident Road traffic accident Road traffic accident Road traffic accident Road traffic accident	70443 (008)/25-HAV 6054 (008)/18-HAV 302780 (009)/23-HAV 211712 (009)/20-HAV 1899 (008)/20-HAV 16505 (008)/20-HAV	3 years postdose 3 10 months postdose 3 2 years postdose 3 6 months postdose 3 30 days postdose 3 101 days postdose 2

***Serious Adverse Events*:** In studies which were included in the BLA, including all ages, the following proportions of subjects with SAEs were reported during the vaccination period and during the entire observation period. In general, the proportions of subjects with SAEs across these studies are comparable in incidence both during the vaccination phase of the study and throughout the entire study period, and proportions of SAEs when categorized by System Organ Class in each of these time periods are comparable.

Table 384-Percentage of subjects reporting the occurrence of at least one serious adverse event in the update of the pooled safety analysis in the BLA submission (Total vaccinated cohort)

Follow-up period	**HPV N=16142**	**Alu N=3454**	**HAV 360 N=1032**	**HAV 720 N=9325**	**Pooled control N=13811**
Vaccination period (Month 0-Month 7)	**206 (1.3%)**	**35 (1.0%)**	**14 (1.4%)**	**131 (1.4%)**	**180 (1.3%)**
Entire observation period	**851 (5.3%)**	**84 (2.4%)**	**26 (2.5%)**	**699 (7.5%)**	**809 (5.9%)**

Studies HPV-001, HPV-003, HPV-004, and HPV-005, HPV-007 [final analysis], HPV-008 [final analysis], HPV-012, HPV-013, HPV-013 Ext [Month 18 analysis], HPV-014, HPV-014, Ext [Month 18 analysis], HPV-015 [Month 7 safety interim analysis] and HPV-016
Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, supplemental safety update, Table 19, p. 72

In general, the proportions of subjects with SAEs across these studies are comparable in incidence both during the vaccination phase of the study and throughout the entire study period, and proportions of SAEs when categorized by System Organ Class in each of these time periods are comparable.

Table 385- Pooled safety analysis: percentage of subjects reporting SAEs classified by MedDRA Primary System Organ Class, during the vaccination period (Month 0 - Month 7) (Total vaccinated cohort)

Primary System Organ Class	HPV N=16142	Control N=13811
At least one symptom	206 (1.3%)	180 (1.3%)
Blood and lymphatic system disorders	0 (0.0%)	3 (0.02%)
Cardiac disorders	4 (0.02%)	0 (0.0%)
Congenital, familial and genetic disorders	1 (0.006%)	2 (0.01%)
Ear and labyrinth disorders	0 (0.0%)	2 (0.01%)
Endocrine disorders	1 (0.006%)	1 (0.007%)
Eye disorders	1 (0.006%)	0 (0.0%)
Gastrointestinal disorders	23 (0.1%)	10 (0.1%)
General disorders and administration site conditions	2 (0.001%)	2 (0.01%)
Hepatobiliary disorders	5 (0.03%)	6 (0.04%)
Immune system disorders	1 (0.006%)	5 (0.04%)
Infections and infestations	62 (0.4%)	61 (0.4%)
Injury, poisoning, and procedural complications	21 (0.1%)	19 (0.1%)
Investigations	0 (0.0%)	2 (0.01%)
Metabolism and nutrition disorders	4 (0.02%)	3 (0.02%)
Musculoskeletal and connective tissue disorders	3 (0.02%)	2 (0.02%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (0.05%)	7 (0.1%)
Nervous system disorders	11 (0.1%)	5 (0.04%)
Pregnancy, puerperium and perinatal conditions	27 (0.2%)	20 (0.1%)
Psychiatric disorders	11 (0.1%)	17 (0.1%)
Renal and urinary disorders	2 (0.001%)	1 (0.007%)
Reproductive system and breast disorders	10 (0.1%)	12 (0.1%)
Respiratory, thoracic and mediastinal disorders	4 (0.02%)	7 (0.1%)
Skin and subcutaneous tissue disorders	2 (0.001%)	2 (0.01%)
Surgical and medical procedures	2 (0.001%)	3 (0.02%)
Vascular disorders	4 (0.02%)	1 (0.01%)

Studies HPV-001, HPV-003, HPV-004, and HPV-005, HPV-007 [final analysis], HPV-008 [final analysis], HPV-012, HPV-013, HPV-013 Ext [Month 18 analysis], HPV-014, HPV-014 Ext [Month 18 analysis], HPV-015 [Month 7 safety interim analysis] and HPV-016

Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]

Pooled control = ALU+HAV360+HAV720

Table 386- Pooled safety analysis: percentage of subjects reporting SAEs classified by MedDRA Primary System Organ Class, during the entire follow-up period* (Total Vaccinated Cohort)

Primary System Organ Class	HPV N=16142	Control N=13811
At least one symptom	851 (5.3%)	809 (5.9%)
Blood and lymphatic system disorders	6 (0.04%)	7 (0.05%)
Cardiac disorders	11 (0.1%)	4 (0.03%)
Congenital, familial and genetic disorders	2 (0.01%)	3 (0.02%)
Ear and labyrinth disorders	2 (0.01%)	5 (0.03%)
Endocrine disorders	4 (0.02%)	3 (0.02%)
Eye disorders	3 (0.02%)	1 (0.007%)
Gastrointestinal disorders	61 (0.4%)	54 (0.4%)
General disorders and administration site conditions	5 (0.03%)	5 (0.03%)
Hepatobiliary disorders	26 (0.2%)	22 (0.2%)
Immune system disorders	6 (0.04%)	10 (0.1%)
Infections and infestations	247 (1.5%)	236 (1.7%)
Injury, poisoning, and procedural complications	99 (0.6%)	97 (0.7%)
Investigations	0 (0.0%)	2 (0.01%)
Metabolism and nutrition disorders	9 (0.1%)	7 (0.05%)
Musculoskeletal and connective tissue disorders	22 (0.1%)	12 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (0.1%)	21 (0.2%)
Nervous system disorders	44 (0.3%)	23 (0.2%)
Pregnancy, puerperium and perinatal conditions	246 (1.5%)	232 (1.7%)
Psychiatric disorders	46 (0.3%)	49 (0.4%)
Renal and urinary disorders	8 (0.05%)	7 (0.05%)
Reproductive system and breast disorders	44 (0.3%)	45 (0.3%)
Respiratory, thoracic and mediastinal disorders	18 (0.1%)	19 (0.1%)
Skin and subcutaneous tissue disorders	5 (0.03%)	5 (0.03%)
Surgical and medical procedures	9 (0.1%)	9 (0.1%)
Vascular disorders	9 (0.1%)	9 (0.1%)

*Entire study period = up to 7.4 years
Studies HPV-001, HPV-003, HPV-004, and HPV-005, HPV-007 [final analysis], HPV-008 [final analysis], HPV-012, HPV-013, HPV-013 Ext [Month 18 analysis], HPV-014, HPV-014 Ext [Month 18 analysis], HPV-015 [Month 7 safety interim analysis] and HPV-016
Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]
Pooled control = ALU+HAV360+HAV720

In women 10-25 years of age, the percentages of subjects with Serious Adverse Events were similar in Cervarix (6.4%) and control groups (7.2%) for the entire study period (up to 7.4 years of follow-up). The breakdown by treatment group is shown in Table 387.

Table 387-Pooled safety analysis: percentage of subjects reporting the occurrence of SAEs throughout the follow-up period (up to 7.4 years) (Total vaccinated cohort, 10-25 year old females)

Follow-up period	HPV [10-25] N=12784	HAV-720 [15-25] N=9315	HAV 360 [10-14] N=1032	Aluminum hydroxide [15-25] N=581	Pooled control [10-25] N=10928
	n/%	n/%	n/%	n/%	n/%
Entire observation period	**819/6.41%**	**698/7.49%**	**31/3.00%**	**58/9.98%**	**787/7.20%**

Adverse Events/Serious Adverse Events leading to discontinuation from studies: In studies submitted to the BLA, from a total of 29,953 subjects included in the pooled safety analysis, 72 subjects were withdrawn due to an AE or SAE (43 subjects received Cervarix [0.27%] and 29 subjects received control [0.21%]). A total of 31 subjects withdrew due to an SAE (14 subjects received Cervarix [0.09%] and 17 subjects received control vaccine [0.12%]). Of these, sixteen events were fatal events and the other 15 subjects withdrew due to other SAEs, none of which were considered as causally related to vaccination by the study investigator. The 15 non-fatal SAEs include the following:

- 7 subjects received Cervarix: the withdrawals were due to multiple sclerosis, a prolapsed vertebral disc, moderate dermatological infection, invasive ductal carcinoma stage I (left breast), cervical adenocarcinoma, and spontaneous abortion (2 subjects);
- 8 subject received Havrix (360 EL.U. HAV antigen and 250µg Al(OH)3 per 0.5 mL dose): enteritis, abdominal pain, renal abscess, anorexia nervosa, cervical carcinoma stage 0, malignant neoplasm, uterine prolapse, and multiple trauma following an automobile crash.

There were in total 41 other subjects who experienced non-serious adverse events that led to study withdrawal, of which 29 subjects received Cervarix (0.18%) and 12 subjects received control vaccine or placebo (0.09%).

- The non-serious adverse events reported by Cervarix recipients included: lymphadenopathy, nausea, fatigue, injection site pain, malaise, bronchopneumonia, erisypelis, herpes zoster, influenza, arthralgia, arthritis reactive, breast neoplasm, thyroid neoplasm, headache, syncope, abortion threatened, depression, emotional disorder, ovarian cyst, vaginal discharge, asthma, acne, pruritus, rash and urticaria. Some subjects reported more than one event.
- The control subjects reported the following events as reasons for discontinuation: dyspepsia, facial pain, fatigue, injection site pain, malaise, gastroenteritis, arthralgia, joint swelling, muscle spasms, dizziness, headache, migraine, mental disorder, uterine hemorrhage, and vaginal hemorrhage. (Some subjects reported more than one event).

Tables 2B and 3B lists subjects who discontinued from studies due to adverse events (by treatment group) and are located in Appendix B.

New Onset of Chronic Diseases and New Onset of Autoimmune Diseases: GSK provided an update of the reporting of adverse events classified as new onset of chronic diseases (NOCDs) in studies included in the pooled analysis of NOCDs in the initial BLA submission (March 2007), i.e., HPV-007 [final analysis], HPV-008 [final analysis], HPV-012, HPV-013, HPV-013 Ext [Month 18 analysis], HPV-014, HPV-014 Ext [Month 18 analysis], HPV-015 [Month 7 safety interim analysis] and HPV-016. NOCDs were not collected as a separate category in Studies HPV-001, HPV-003, HPV-004, and HPV-005. This updated analysis of NOCDs is based on the case attribution "GSK assessment" and considered two different reporting periods post-vaccination: vaccination period (Month 0 to Month 7) and throughout the entire reporting period. The analysis included all subjects that received at least one dose of *Cervarix* or control in the studies considered. The data are presented in terms of the percentage of subjects reporting at least one MsAEs classified by MedDRA Primary System Organ Class (SOC) and Preferred Term (PT).

The overall incidence of reported NOCDs over the vaccination period (Month 0 to Month 7) and throughout the entire reporting period for all subjects that received at least one dose of HPV-16/18 vaccine or control, up to the data lock-point of August 31, 2008, is presented. For the vaccination period (Month 0 to Month 7), the overall reporting rates of NOCDs in subjects that received HPV-16/18 vaccine was similar to that observed in subjects who received control: 1.2% (95% CI: 1.0; 1.4) in the HPV group and 1.0% (95% CI: 0.9; 1.3) in the pooled control group. For the entire reporting period (4.3 years of follow-up, mean 3.0 years), the percentage of subjects with reports of NOCDs were 2.4% (95% CI: 2.2; 2.7) in the HPV group and 2.6% (95% CI: 2.4; 2.9) in the pooled control group. There was a higher percentage of subjects reporting NOCDs in the HAV360 group than the other groups including the HPV groups. The HAV360 group exclusively has subjects of 10-14 years of age from Study HPV-013 and its extension study.

The most commonly reported NOCDs were asthma, hypersensitivity and urticaria. The percentage of subjects reporting these events was low and similar among the treatment groups.

The percentage of subjects reporting the occurrence of NOCD, stratified by reporting period and age is also presented. During the vaccination period (Month 0 to Month 7), there was a higher percentage of subjects reporting NOCDs in the [10-14] age group, compared to the [15-25] and [25+] age groups. However, there were no differences between the HPV group and the control groups in reporting of NOCDs when considering subjects of each age group.

The most commonly reported NOCD were asthma, urticaria and hypersensitivity, which were each reported at similar frequencies in the HPV-16/18 vaccine and control groups. There were no apparent differences in the rates of NOCDS among the age groups, when compared to their corresponding control groups. The actual percentages are presented in Table 388 below.

Table 388-Percentage of Subjects Reporting the Occurrence of New Onset Chronic Diseases (Asthma, Hypersensitivity and Urticaria) (Total Vaccinated Cohort)

MedDRA PT	Follow-up period	HPV N/n(%)	Alu N/n(%)	HAV 360 N/n(%)	HAV 720 N/n(%)	Pooled control N/n(%)
Asthma	**Vaccination period (Month 0-Month 7)**	13591/15 (0.1%)	984/0 (0.0%)	1032/3 (0.3%)	9325/5 (0.1%)	11341/8 (0.1%)
	Entire observation period	13984/45 (0.3%)	1367/1 (0.1%)	1032/4 (0.4%)	9325/37 (0.4%)	11724/42 (0.4%)
Hypersensitivity	**Vaccination period (Month 0-Month 7)**	13591/25 (0.2%)	984/1 (0.1%)	1032/3 (0.3%)	9325/18 (0.2%)	11341/22 (0.2%)
	Entire observation period	13984/34 (0.2%)	1367/1 (0.1%)	1032/3 (0.3%)	9325/28 (0.3%)	11724/32 (0.3%)
Urticaria	**Vaccination period (Month 0-Month 7)**	13591/28 (0.2%)	984/3 (0.3%)	1032/1 (0.1%)	9325/13 (0.1%)	11341/17 (0.1%)
	Entire observation period	13984/40 (0.3%)	1367/3 (0.2%)	1032/1 (0.1%)	9325/22 (0.2%)	11724/26 (0.2%)

HPV = HPV-16/18 vaccine (Studies HPV-007, HPV-008, HPV-012, HPV-012 EXT, HPV-013, HPV-013 EXT HPV-014, HPV-014 EXT, HPV-015, HPV-016)
ALU = Al(OH)3 control [Study HPV-015];
HAV360 = Hepatitis A vaccine containing 360 EL.U. hepatitis A antigen per dose [Studies HPV-013 and HPV-013 EXT];
HAV720 = Hepatitis A vaccine containing 720 EL.U. hepatitis A antigen per dose [Study HPV-008]
Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]
Pooled control group = ALU+HAV360+HAV720 groups
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259.48, Supplemental safety update, Table 26, p. 94

Table 389-Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (at least one symptom) by reporting period and age (Total Vaccinated Cohort)

Follow-up period	HPV	HAV 360	HPV	HAV 720	HPV	ALU
	10-14	**10-14**	**15-25**	**15-25**	**25+**	**25+**
Vaccination period (M0-M7)	28/1194 (2.3%)	22 /1032 (2.1%)	124/10946 (1.1%)	8/9315 (0.9%)	11/1451 (0.8%)	10/984 (1/0%)
Entire Observation period	36 /1194 (3.0%)	25 /1032 (2.4%)	292/11339 (2.6%)	268/9315 (2.9%)	14/1451 (1.0%)	10/984 (1.0%)

HPV = HPV-16/18 vaccine (Studies HPV-007, HPV-008, HPV-012, HPV-012 EXT, HPV-013, HPV-013 EXT HPV-014, HPV-014 EXT, HPV-015, HPV-016)
[10-14] = 10-14 years Studies HPV-012, HPV-012 EXT, HPV-013, HPV-013 EXT
[15-25] = 15-25 years Studies HPV-008, HPV-012, HPV-012 EXT, HPV-014, HPV-014 EXT
[25+] = Above 25 years Studies HPV-014, HPV-014 EXT, HPV-015
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259.48, Supplemental safety update, Table 27 and 28, p. 95

To evaluate the incidence of new onset of autoimmune diseases (NOADs), a list of potential autoimmune events, which excluded allergy related events or isolated signs and symptoms and

events not considered as strictly of autoimmune origin, was approved by the IDMC supervising the Studies HPV-008, HPV-013 and HPV-015. Based on this list, a GSK Biologicals physician reviewed the adverse events that were considered NOCDs for the classification of events considered as new onset of autoimmune disease. The percentage of subjects reporting the occurrence of new onset of potential autoimmune diseases during the vaccination period (Month 0 to Month 7) and throughout the entire follow-up period is reported in Table 390 below. There were no differences in the overall incidences of potential autoimmune diseases with new onset reported in the HPV group compared to the control groups or the pooled control group for either reporting period.

Table 390-Percentage of subjects reporting the occurrence of New Onset Autoimmune Diseases (GSK asessment) (at least one symptom) by reporting period (Total vaccinated cohort)

Follow-up period	HPV N/n(%)	Alu N/n(%)	HAV 360 N/n(%)	HAV 720 N/n(%)	Pooled control N/n(%)
Vaccination period (Month 0-Month 7)	**13591/25 (0.2%)**	**984/2 (0.2%)**	**1032/3 (0.3%)**	**9325/14 (0.2%)**	**11341/19 (0.2%)**
Entire observation period	**13984/96 (0.7%)**	**1367/6 (0.4%)**	**1032/5 (0.5%)**	**9325/77 (0.8%)**	**11724/88 (0.8%)**

HPV = HPV-16/18 vaccine (Studies HPV-007, HPV-008, HPV-012, HPV-012 EXT, HPV-013, HPV-013 EXT HPV-014, HPV-014 EXT, HPV-015, HPV-016)
ALU = Al(OH)3 control [Study HPV-015];
HAV360 = Hepatitis A vaccine containing 360 EL.U. hepatitis A antigen per dose [Studies HPV-013 and HPV-013 EXT];
HAV720 = Hepatitis A vaccine containing 720 EL.U. hepatitis A antigen per dose [Study HPV-008]
Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]
Pooled control group = ALU+HAV360+HAV720 groups
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
Source: STN 125259.48, Supplemental safety update, Table 29, p. 96

During the vaccination period (Month 0 to Month 7), there were no differences in the reporting of at least one NOADs between the HPV age groups and the corresponding control age groups:

- [10-14] age group: 1 subject in the HPV group (0.1%) versus 3 subjects in the HAV360 group (0.3%),
- [15-25] age group: 21 subjects in the HPV group (0.2%) versus 14 subjects in the HAV720 group (0.2%),
- [25+] age group: 3 subjects in the HPV group (0.2%) versus 2 subjects in the ALU group (0.2%).

During the vaccination period, the two most frequently reported NOADs were hypothyroidism, with three subjects in the HPV/[15-25] age group (< 0.1%) versus one subject in the HAV720/[15-25] age group (< 0.1%), and goiter with one subject in the HPV/[15-25] age group (< 0.1%) versus three subjects in the HAV720/[15-25] age group (< 0.1%).

For the **entire follow-up period (up to 7.4 years, mean 3.0 years),** the reporting of at least one NOAD was higher than that observed for the vaccination period but similar in the HPV age groups and the corresponding control age groups:

- [10-14] age group: 4 subjects in the HPV group (0.3%) versus 5 subjects in the HAV360 group (0.5%),
- [15-25] age group: 89 subjects in the HPV group (0.8%) versus 4 subjects in the ALU group (1.0%) and 77 subjects in the HAV720 group (0.8%),
- [25+] age group: 3 subjects in the HPV group (0.2%) versus 2 subjects in the ALU group (0.2%).

During the follow-up period, the most frequently reported potential autoimmune disease with new onset was hypothyroidism with 22 subjects in the HPV/[15-25] age group (0.2%) versus 20 subjects in the HAV720/[15-25] age group (0.2%), three subjects in the ALU/[15-25] age group (0.8%) and one subject in the HPV/[25+] age group.

GSK has tabulated New Onset Autoimmune Diseases in subjects 10-25 years. These are shown in Table 391 below.

Table 391- Incidence of Conditions Potentially Indicative of New Onset Autoimmune Disease Throughout the Follow-up Period Regardless of Causality in Females 10 Through 25 Years of Age (Total Vaccinated Cohort)

Medical Condition	CERVARIX n (%) (N=12,533)	Pooled Control Group n (%) (N=10,730)
	95 (0.8)	87 (0.8)
Arthritis	9 (0.0)	4 (0.0)
Celiac disease	2 (0.0)	5 (0.0)
Dermatomyositis	0 (0.0)	1 (0.0)
Diabetes mellitus insulin-dependent (Type 1 or unspecified)	5 (0.0)	5 (0.0)
Erythema nodosum	3 (0.0)	0 (0.0)
Hyperthyroidism	14 (0.1)	15 (0.1)
Hypothyroidism	30 (0.2)	28 (0.3)
Inflammatory bowel disease	8 (0.1)	4 (0.0)
Multiple sclerosis	4 (0.0)	1 (0.0)
Myelitis transverse	1 (0.0)	0 (0.0)
Optic neuritis/Optic neuritis retrobulbar	3 (0.0)	1 (0.0)
Psoriasis	8 (0.1)	11 (0.1)
Raynaud's phenomenon	0 (0.0)	1 (0.0)
Rheumatoid arthritis	4 (0.0)	3 (0.0)
Systemic lupus erythematosus	2 (0.0)	3 (0.0)
Thrombocytopenia	1 (0.0)	1 (0.0)
Vasculitis	1 (0.0)	3 (0.0)
Vitiligo	2 (0.0)	2 (0.0)

Arthritis = reactive arthritis and arthritis; hyperthyroidism = Basedow's, goiter, and hyperthyroidism; hypothyroidism = autoimmune thyroiditis, thyroiditis, and hypothyrodism; Inflammatory bowel disease = Ulcerative colitis, ulcerative proctitis, Crohn's disease, and inflammatory bowel disease; Psoriasis=psoriatic arthropathy, nail psoriasis, guttate psoriasis, and psoriasis; SLE=cutaneous lupus erythematosis and SLE; thrombocytopenia = ITP and thromboncytopenia; and vasculitis = leukocytoclastic vasculitis and vasculitis.

Neuroinflammatory events and musculoskeletal events: In the original BLA submission, CBER had noted a numerical imbalance in the number of events of potential neuroinflammatory etiology (i.e., combined cases myelitis, optic neuritis, multiple sclerosis) when comparing the HPV-AS04 group (6 events) and control group (3 events). In addition, CBER also requested a further accounting of muscuoskeletal events such as arthritis. Because the vaccine uses an adjuvant with MPL, CBER requested that GSK provide a meta-analysis to compare the rates of such events. In addition, CBER requested a consultation from an expert in the neurology field. A list of terms was agreed upon with which to conduct the meta-analysis. This is included in Table 4b inAppendix B, Overview of Safety, along with a more detailed description of the different level of analyses conducted (Levels 1-4).

- Based on a search for these events, GSK provided a meta-analyses for adverse events related to neuroinflammatory events and musculoskeletal events in HPV-AS04 vaccines in IND-b(4)-. GSK also provided additional analyses for other products which contained AS04 adjuvant (Level 2 analyses); analyses for products with any MPL-containing adjuvants (Level 3); and

analyses of all products in preventive and therapeutic programs which have used MPL. The most pertinent analyses are the Level 1 analyses since they involve HPV-AS04 adjuvanted products, although these analyses also include females > 25 years of age.

At the time of the final BLA submission, two reporting periods were considered for the start date of a reported neuroinflammatory or musculoskeletal event:

- throughout the entire follow-up up to the data lock-point of August 31, 2008 (except Study HPV-009: data lock-point of July 1, 2008) for levels 1 to 4,
- a 12 month follow-up period following first vaccination for levels 1 and 2 (a "theoretical risk" period covering the 6 month period of active vaccination during which the three doses of Cervarix are administered and the 6 month period following the end of the vaccination course, during which the active immune response to vaccination is expected to be high and autoimmune diseases that could potentially be causally associated with vaccination might be expected to start).

Rates of events were compared between treatment groups (MPL and non-MPL groups) with an adjustment for study effect to assess whether there was an increased risk for any of the events evaluated. The common relative risk across studies and its 95% CI was estimated on the exact conditional likelihood approach adjusted for the study effect. No relative risk was calculated for uncontrolled studies since this calculation requires a reference group.

Neuroinflammatory events: In the original BLA, 9 subjects who participated in GSK trials involving HPV vaccines adjuvanted with AS04 were diagnosed with a neuroinflammatory event of interest. At the time of the final BLA review, 4 additional subjects had been added to the HPV-AS04 list (new total 10 HPV-AS04 and 3 control group) but the new cases occurred > 2 years after dose 3. Based on length of time between vaccination and event, there was no apparent temporal relationship established for these 4 additional events. (There was one additional event reported as optic neuritis retrobulbar, but in review of the case history, the complaint was pain behind the eyes and not optic neuritis. This subject went onto receive additional doses of vaccine without reported problem). See Table 392 for all neuroinflammatory events.

Table 392-Overview of Neuroinflammatory Events

Event	HPV-AS04 N=27515	Control N=27742
Demyelinating disease	1 *129 days after dose 2 [CIS] [U]	0
Multiple sclerosis	3 *25 days after dose 2 [CIS] [U] 2 other cases > 2 years after dose 3	1 *60 days after dose 1
Myelitis	2 *47 days after dose 2 [insufficient dx] 22 months after dose 3 [TM]	0
Optic neuritis	3 *9 days after dose 1 [CIS] [U] *15 months after dose 3 [ON] 1 other case > 2 years after dose 3	2 *134 days after dose 3 [CIS] *23 months after dose 3 [CIS]
Optic neuritis/multiple sclerosis	1 *17 months after dose 3 [CIS]	0

*Events were reviewed at time of original review; CIS=clinically isolated syndrome; TM=transverse myelitis; ON=optic neuritis; [U] = uncontrolled studies; cases highlighted in blue occurred within 12 weeks of vaccination.

GSK also convened an expert panel of neurologists who assessed the cases. The cases assessed by the experts did not include one subject in the non-MPL group with MS diagnosed 60 days

after dose 1 and included another case of transverse myelitis which occurred 22 months after dose 3.

GSK performed an overall assessment of all neuroinflammatory events which occurred in clinical studies with GSK's MPL–containing products, up to the new data lockpoint of August 31, 2008 (except for Study HPV-009 for which the data lock-point is July 1, 2008). In the expanded analysis (Levels 1-3) from the data lock-point for the response to the CR Letter (December 31, 2007; December 14, 2007 for Study HPV-009) up to the data lockpoint of August 31, 2008 (for all studies except Study HPV-009: July 1, 2008) there were six new events reported: four events in level 1 controlled studies, one event in level 1 uncontrolled studies and one event in level 2 controlled studies) and one event (optic neuritis) in level 1 controlled studies was changed by the investigator to multiple sclerosis in a follow-up report. In all new cases, the neuroinflammatory diseases occurred approximately 2 to 6 years after third study vaccination, which argues against a causal association between the vaccine administration and the events. In three of these cases, supportive and confirmatory paraclinical examinations were not described to corroborate diagnosis or exclude other possible diagnoses and therefore it was not possible to estimate diagnostic certainty. As noted above, four additional cases were dx'd in the HPV group (1 additional case not ON as initially coded). 2 of these subjects developed MS, 1 ON, and 1 myelitis. Because of the interval from vaccination to event (2-6 yrs), these were not thought to be temporally related to vaccination

In GSK's meta-analysis for HPV-AS04 products in controlled studies (Level 1 analysis), the overall relative risk was increased at 2.33, but not statistically significant (95% CI: 0.53, 13.97). (MS RR = 1.50 [0.17, 17.97]; ON RR = 3.00 [0.24, 157.50]) In uncontrolled studies, the proportions were calculated [5/6951]= (0.07%) throughout the study period. These included: 1 demyelinating disease [CIS] or 0.01% (0.00, 0.08%); 1 MS at 0.01% (0.00, 0.08); 1 Myelitis at 0.01% (0.00, 0.08%); and 2 Optic neuritis at 0.03% (0.00, 0.10%). GSK's expert panel concluded that there was not an increased risk of developing neuroinflammatory disorders following vaccination with MPL-containing vaccines.

Considering all events, GSK calculated the overall relative risk for neuroinflammatory events in level 1 was calculated at 2.33 (95% CI: 0.53; 13.97).
Reviewer's Comment: Again, this meta-analysis includes controlled trials. Uncontrolled studies are included in Table 393.

Table 393: Percentage of subjects reporting the occurrence of neuroinflammatory events throughout the entire follow-up period, classified by CBER Verbatim Terms with estimated relative risks and homogeneity test
(Level 1 [controlled HPV studies] Total vaccinated cohort)

CBER Verbatim Term	MPL group N = 27515				Non-MPL group N = 27742				Relative Risk (groups MPL over Non-MPL)			P-value homogeneity
			95% CI				95% CI			95% CI*		
	N	%	LL	UL	n	%	LL	UL	RR	LL	UL	
At least one symptom	7	0.0	0.0	0.1	3	0.0	0.0	0.0	2.33	0.53	13.97	0.2403
Multiple sclerosis	3	0.0	0.0	0.0	2	0.0	0.0	0.0	1.50	0.17	17.97	0.1708
Myelitis	1	0.0	0.0	0.0	0	0.0	0.0	0.0	INF	0.03	INF	NA
Myelitis transverse	1	0.0	0.0	0.0	0	0.0	0.0	0.0	INF	0.03	INF	NA
Optic neuritis	3	0.0	0.0	0.0	1	0.0	0.0	0.0	3.00	0.24	157.59	NA

At least one symptom = at least one symptom experienced [e.g., weakness, numbness, decrease visual acuity] regardless of the CBER Verbatim Term;
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)
INF=infinity, no cases are reported in the Non-MPL group
NA = Not applicable (p-value for homogeneity test is calculated when there is at least 1 case in each group and when the cases are reported in more than one study)
Table 65, p. 186

For the level 1 analysis of uncontrolled HPV studies throughout the entire follow-up period, there was one additional event which was reported as optic neuritis which occurred at 3 days after dose 1 of an HPV vaccine formulated with a higher dose of each antigen (40 mcg) as compared to cervarix. However, from the history provided, the subject complained of retrobulbar pain and not optic neuritis, so the diagnosis was coded incorrectly. The subject went onto receive the 2nd and 3rd doses of the vaccine without problem. Therefore, there were a total of five neuroinflammatory events: one case of multiple sclerosis, two cases of optic neuritis, one case of myelitis and one case of demyelination disease.

Table 394-Percentage of subjects reporting the occurrence of neuroinflammatory events throughout the entire follow-up period, classified by CBER Verbatim Terms (Level 1 [uncontrolled HPV studies] Total vaccinated cohort)

CBER Verbatim Term	MPL group N = 6951			
			95% CI	
	n	%	LL	UL
At least one symptom	5	0.07	0.02	0.17
Demyelination disease	1	0.01	0.00	0.08
Multiple sclerosis	1	0.01	0.00	0.08
Myelitis	1	0.01	0.00	0.08
Optic neuritis	2	0.03	0.00	0.10

At least one symptom = at least one symptom experienced (regardless of the CBER Verbatim Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
STN 125259.48, Supplemental safety update, Table 68, p. 188

An assessment of neuroinflammatory events was performed with the input of an **expert panel** consisting of three external and independent experts in the field of neurology. The expert panel

reviewed the reports of potential neuroinflammatory disorders, the results of the meta-analysis of MPL-containing vaccines with a data lock point of December 31, 2007 and the results of the additional analyses agreed with the experts. For each neuroinflammatory event, the panel of experts was provided with the case narratives, safety reports and source documents in a blinded fashion. They reviewed each event, taking into consideration the diagnostic level of certainty for each case, the role of study vaccination, the presence of any common features among the events or any unusual aspects, and whether the event report contained sufficient/insufficient information to assess the reported diagnosis (if not, the experts could suggest additional information to collect that could be of value). They also assessed clustering of events with respect to time to onset following vaccination, considered pre-existing symptoms or morbidity, and made comparison between observed and expected incidence rates.

The panel reviewed the 17 events reported up to the data lock-point of December 31, 2007 and reached a confirmed diagnosis for 12 events. No temporal clustering of events was observed. Six events were reclassified as "clinically isolated syndrome" (three each in MPL and non-MPL groups). The rate of clinically isolated syndrome in controlled studies was similar in each treatment group (8.0/100,000 person-years) and within the range of background rates of multiple sclerosis (3.1-15.9/100,000 person-years), for which published rates are available in the literature (Persons with clinically isolated syndrome may or may not go on to develop multiple sclerosis).

The panel concluded based on their review of data up to the data lock-point of December 31, 2007 that there was not an increased risk of neuroinflammatory disorders following vaccination with MPL-containing vaccines.

At the time of the original BLA submission (6 cases in HPV-AS04 and 3 cases in the HPV-non-MPL control group), CBER requested that a neurologist with expertise in multiple sclerosis and neuroimmunology and nervous system infections conduct an analysis of the neuroinflammatory cases. CBER sent source documents for the subjects reported at the time of the original assessment (one subject's records not available at time of request for consultation in 12/07.) In general, events that occurred within 3 months of vaccination were considered to occur within a time frame which was biologically plausible if a relationship was being considered. The expert did not feel that the data was sufficient to establish a link, although it was sufficient to raise concern. Continued tracking of such events was recommended in the post-marketing period, with attention to use of steroids as well.

Reviewer's Comment: As of May 2009 (in the Post-marketing safety update report submitted by GSK) very few cases of optic neuritis or multiple sclerosis had been reported by passive surveillance in other countries in which Cervarix is already licensed, and the rate has not exceeded the estimated background rate (estimated dose distribution was approximately$_{b(4)}$ million doses of vaccine). In a post-marketing study to be conducted in a large managed care origanization, CBER has requested that events of potential autoimmune nature, including neuroinflammtory events, be followed and reported. Given the totality of data, although no definitive relationship of neuroinflammatory events to receipt of Cervarix was ascertained, monitoring of such events will be continued in the post-marketing period as noted.

Grave's disease: In review of the original BLA, the CBER statistician notes that the results of the statistical test for homogeneity of the common relative risks of Grave's disease tended to be statistically significant in both Levels 2 and 3 analyses. This evidence of lack of homogeneity of relative risks across studies suggested that the overall summary analysis results may be subject to bias. The CBER statitiscian advised review of the data CBER suggested repeating analysis of

Grave's disease to make sure there was no statistical difference in rates between non-MPL material recipients and MPL-containing study material.

GSK provided this update, and there were no imbalances statistically when comparing the occurrence rates of Graves disease between the MPL group and non-MPL group for all three levels analysed. For level 2, there were 6 events in the MPL group and 4 events in the Non-MPL group. In the additional studies included for level 3, there were no reports of Graves disease, therefore, there was no difference in the number of events reported for levels 2 and 3 (6 events in the MPL group and 4 events in the Non-MPL group). There were no reports of Graves disease in level 4.

There was no significant heterogeneity (p-value less than 0.05) for any of the levels with level 1 having a p-value of 0.2793 but there was a trend towards significance for levels 2 and 3 (p-values of 0.0755 and 0.0631). Of note, the similarity of the values for levels 2 and 3 are clearly due to the fact that the same events are reported for Graves disease in both levels (i.e. there were no additional reports of Graves disease from level 2 to level 3).

Since the homogeneity of the relative risks across studies with respect to Graves disease was called into question, the Company calculated, as requested, the percentage of subjects reporting the occurrence of Graves disease and the estimated relative risks per study, for level 2.

- For Study HPV-008, five cases were reported: four in the MPL group and one in the non-MPL group, with an estimated relative risk of 4.00 (95% CI: 0.40; 197.11).
- For Study HPV-009, one case was reported in the MPL group. No estimated relative risk could be calculated.
- For Study HPV-015, one case was reported in the non-MPL group, with an estimated relative risk of 0.00 (95% CI: 0.00; 38.86).
- For Study -b(4)------, two cases were reported in the non-MPL group, with an estimated relative risk of 0.00 (95% CI: 0.00; 2.76).
- For Study --b(4)------, 1 case was reported in the MPL group. No relative risk could be calculated.

Overall, in three HPV-AS04 controlled studies (Level 1), there were 5 cases in the HPV-AS04 group and 2 in the non-MPL group (one aluminum hydroxide, one in the Havrix group). The overall relative risk was 2.24 (95% CI: 0.41, 15.15). The sponsor postulated that the obtained p-value for the homogeneity testing was probably due to the small number of events observed and the distribution of these events across studies. In Level 2 analyses (includes HBV and HSV vaccines), the relative risk of reporting Grave's disease was 1.27 (95% CI: 0.31, 5.56).
Reviewer's Comment: In review of updated datasets with numbers of potential autoimmune diseases, the proportions of subjects 10-25 years of age with hyperthyroidism and hypothyroidism were similar in the Cervarix group (0.1% and 0.2%, respectively) and control group (0.1% and 0.3%, respectively). In the updated safety dataset for HPV-008 (submitted 3/09), the wunsol dataset was searched for the Preferred Terms Basedow's disease, autoimmune thyroiditis, or thyroiditis. In this dataset, there were 5 Havrix recipients and 8 HPV vaccine recipients with these diagnoses. As to the timing of these events, one Basedow's disease event occurred on the day of dose 2 in the Cervarix group and another Basedow's disease event event occurred 22 days after dose 2 Havrix control. All other events occurred ≥ 115 days after the last vaccination. In wumsol datasets for study 013 and 001, these diagnoses were not identified. It is noted that study 009 is ongoing at this time. Events of autoimmune nature will be followed in the post-marketing study in the managed care organization.

Musculoskeletal events: In the original BLA, one comment pertained to events of potential musculoskeletal nature, given a possible numerical imbalance in the the number of cases noted in the datasets. CBER requested additional information to assess this issue, and also requested a meta-analysis of these events. The terms included in Table 4b in Appendix B-Overview of Safety were utilized in this meta-analysis.

In response, GSK performed an overall assessment of all musculoskeletal events which occurred in clinical studies with GSK's MPL–containing products, up to the new data lock-point of August 31, 2008 (except for Study HPV-009 for which the data lock-point is July 1, 2008).

Level 1 analysis: For the level 1 analysis of controlled HPV studies, throughout the entire follow-up period, there were overall 68 subjects reporting at least one musculoskeletal event.

With 39 subjects in the MPL group and 29 subjects in the non-MPL group, the overall relative risk was 1.31 (95% CI 0.79; 2.20). The most frequently reported musculoskeletal events were:

- arthritis with 9 events in the MPL group and 11 events in the non-MPL group (RR =0.82, 95% CI 0.30; 2.17),
- fibromyalgia with 10 events in the MPL group and 6 events in the non-MPL group (RR = 1.66, 95% CI 0.55; 5.57),
- rheumatoid arthritis with 10 events in the MPL group and 8 events in the non-MPL group (RR = 1.25, 95% CI 0.44; 3.65),
- systemic lupus erythematosus with 4 events in the MPL group and 2 in the non-MPL group (RR = 2.00, 95% CI 0.29; 22.14).
- For juvenile rheumatoid arthritis, reactive arthritis and scleroderma, there were one, four and one events respectively in the MPL group.
- Arthropathy was reported infrequently with one event in the MPL group versus two events in the non-MPL group (RR = 0.50, 95% CI 0.01; 9.55).

Table 395-Percentage of subjects reporting the occurrence of musculoskeletal events throughout the entire follow-up period, classified by CBER Verbatim Terms with estimated relative risks and homogeneity test
(Level 1 [controlled HPV studies] Total vaccinated cohort)

CBER Verbatim Term	MPL group N = 27515				Non-MPL group N = 27742				Relative Risk (groups MPL over Non-MPL)			P-value homogeneity
			95% CI				95% CI			95% CI*		
	n	%	LL	UL	n	%	LL	UL	RR	LL	UL	
At least one symptom	39	0.1	0.1	0.2	29	0.1	0.1	0.2	1.31	0.79	2.20	0.2678
Arthritis	9	0.0	0.0	0.1	11	0.0	0.0	0.1	0.82	0.30	2.17	0.5051
Arthropathy	1	0.0	0.0	0.0	2	0.0	0.0	0.0	0.50	0.01	9.55	0.2227
Fibromyalgia	10	0.0	0.0	0.1	6	0.0	0.0	0.0	1.66	0.55	5.57	0.1707
Juvenile rheumatoid arthritis	1	0.0	0.0	0.0	0	0.0	0.0	0.0	INF	0.03	INF	NA
Reactive arthritis	4	0.0	0.0	0.0	0	0.0	0.0	0.0	INF	0.66	INF	NA
Rheumatoid arthritis	10	0.0	0.0	0.1	8	0.0	0.0	0.1	1.25	0.44	3.65	0.5701
Scleroderma	1	0.0	0.0	0.0	0	0.0	0.0	0.0	INF	0.03	INF	NA
Systemic lupus erythematosus	4	0.0	0.0	0.0	2	0.0	0.0	0.0	2.00	0.29	22.14	0.2204

At least one symptom = at least one symptom experienced (e.g., joint pain, swelling, etc.) regardless of the CBER Verbatim Term; N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)
INF=infinity, no cases are reported in the Non-MPL group
NA = Not applicable (p-value for homogeneity test is calculated when there is at least 1 case in each group and when the cases are reported in more than one study); Source: STN 125259.48, Supplemental safety update, Table 77, p. 199

For the level 1 analysis of controlled HPV studies, during the 12 month follow-up period following dose 1, there were overall 31 subjects reporting at least one musculoskeletal event with 19 events in the MPL and 12 events in the non-MPL group (RR = 1.58, 95% CI 0.73; 3.57).

For this reporting period, the most frequently reported musculoskeletal events were arthritis, fibromyalgia and rheumatoid arthritis with similar number of events for arthritis, and fibromyalgia in the MPL and non-MPL groups but a higher number of rheumatoid arthritis events were reported in the MPL group than in the non-MPL group, although the lower limit of the confidence interval remained below 1:

- arthritis with seven events in the MPL group and six events in the non-MPL group (RR = 1.16, 95% CI 0.33; 4.19),
- fibromyalgia with five events in the MPL group and four events in the non-MPL group (RR = 1.25, 95% CI 0.27; 6.29),
- rheumatoid arthritis with six events in the MPL group and one event in the non-MPL group (RR = 6.02, 95% CI 0.73; 276.71),
- For reactive arthritis, there were two events in the MPL group and for arthropathy, there was one event reported in the non-MPL group.

For the level 1 analysis of uncontrolled HPV studies, throughout the entire follow-up period, there were a total of 14 subjects for which a musculoskeletal event was reported.

Table 396-Percentage of subjects reporting the occurrence of musculoskeletal events throughout the entire follow-up period, classified by CBER Verbatim Terms (Level 1 [uncontrolled HPV studies] Total vaccinated cohort)

CBER Verbatim Term	MPL group N = 6951			
			95% CI	
	n	%	LL	UL
At least one symptom	14	0.20	0.11	0.34
Arthritis	8	0.12	0.05	0.23
Arthropathy	3	0.04	0.01	0.13
Reactive arthritis	3	0.04	0.01	0.13
Rheumatoid arthritis	2	0.03	0.00	0.10

At least one symptom = at least one symptom experienced (regardless of the CBER Verbatim Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
STN 125259.48, Supplemental safety update, Table 79, p. 200

For the level 1 analysis of uncontrolled HPV studies, during the 12 month follow-up period following dose 1, there were a total of 12 subjects for which a musculoskeletal event was reported, similar to the reporting of events throughout the entire follow-up period except for the exclusion of the two reports of rheumatoid arthritis.

GSK convened a panel of experts to review of musculoskeletal events of potentially autoimmune etiology.

The experts reviewed the clinical information as well as source documents, blinded to treatment allocation, provided by study sites to GSK Biologicals on the musculoskeletal events identified in the meta-analysis of musculoskeletal events with data lock-point of December 31, 2007. Consultations with the experts, based on blinded data, were held to determine whether the available information supported an immune-mediated inflammatory rheumatologic nature of the event and to consider the diagnostic level of certainty for each event. When individual expert assessment of the diagnosis of the immune-mediated inflammatory rheumatologic nature of the event or the diagnostic certainty were not in agreement for a specific event, meetings with the panel of experts were held to reach a consensus and final diagnosis.

Following the review of the individual events, GSK performed a comparative analysis of reporting rates by treatment allocation in immune-mediated rheumatologic events for which a confirmed consensus diagnosis was reached and events for which the consensus diagnosis was uncertain. This analysis was presented in response to CBER request at the June 24 meeting with GSK for an analysis of treatment allocation for the group of events determined to have an uncertain diagnosis by the expert panel.

The experts also made recommendations in the methodology for the meta-analysis of musculoskeletal events, principally, reviewing and revising the list of terms used to search the database for musculoskeletal events with the addition of new terms also considered to be potentially autoimmune musculoskeletal events, taken from the other CBER Categories of disease.

Summary of consensus diagnosis assessment by the external expert panel for musculoskeletal events: In total, the external expert panel reviewed 146 musculoskeletal events that were reported in 142 subjects up to the data lock-point of December 31, 2007 (except for Study HPV- 009: data lock-point of December 14, 2007) for all studies (controlled and uncontrolled) in levels 1 to 4 of analysis. Sixty-seven events reported in 65 subjects were not considered to be immunemediated rheumatologic events and were mainly with degenerative or traumatic disorders or fibromyalgia (not considered as immune-mediated event by the external expert panel). Of the remaining 79 events reported in 77 subjects, the classification as an immunemediated rheumatologic event was uncertain for 43 events reported in 42 subjects because the case documentation was insufficient to permit adequate assessment to confirm or exclude an immune-mediated rheumatologic event. In the remaining 36 events, reported in 35 subjects, the case documentation was adequate to permit a classification as a confirmed immune-mediated rheumatologic event.

Table 397-Summary of consensus diagnosis assessment by the external expert panel for musculoskeletal events

Expert consensus diagnosis	Confirmed IMRE	Uncertain IMRE	Not IMRE	Total
Arthritis	7	21	0	28
Arthropathy	1	0	0	1
Fibromyalgia	0	0	13	13
Reactive arthritis	2	1	0	3
Rheumatoid arthritis	10	7	0	17
Scleroderma	2	0	0	2
Systemic lupus erythematosus	6	1	0	7
Other*	8	13	54	75
Total	36	43	67	146

IMRE: immune-mediated rheumatologic event
Events reclassified by experts with an alternative diagnosis (term not in CBER category of musculoskeletal events)
STN 125259.48, Supplemental safety update, Table 89, p. 208

Analysis of potentially immune-mediated rheumatologic events with a confirmed or uncertain consensus diagnosis by the external expert panel

A comparative analysis of terms in the CBER category of musculoskeletal events was performed using the events adjudicated in a blinded manner by the external experts to be potential immune-mediated rheumatologic events with a confirmed consensus diagnosis and an uncertain consensus diagnosis for levels 1 and 2. Data were presented according to diagnostic certainty, i.e. an analysis of:

- confirmed immune-mediated rheumatologic events,
- immune-mediated rheumatologic events of uncertain diagnosis,
- confirmed and uncertain immune-mediated rheumatologic events combined.

The events included in the level 1 analysis (HPV-AS04) are presented in tabular form by treatment group and age. Tables 398 and 399 include the subjects in whom events were assessed as immune-mediated by the GSK experts.

Table 398-Listing Of Confirmed Immune-Mediated Rheumatologic Events by External Expert Panel-HPV Vaccine and Control [15-25 years of age]

Case number, Study, Age	Event	Time to Event	Outcome
HPV			
85619, 008, 17y	Arthritis reactive	244 days after dose 3	Recovered
123422, 009, 18y	Juvenile arthritis*	61 days after dose 1	Not recovered
6336, 001, 19y	Juvenile arthritis*	82 days after dose 3	Not recovered
216829, 009, 19y	RA	76 days after dose 2	Not recovered
11150, 008, 22y	RA	194 days after dose 3	Recovered with sequelae
8416, 008, 24y	RA	269 days after dose 3	Recovered
12833, 008, 17y	RA	372 days after dose 3	Not recovered
13415, 008, 17y	RA	505 days after dose 3	Not recovered
1546, 012, 16y	Celiac disease	497 after dose 3	Not recovered
391654, 009, 19y	Scelroderma	287 days after dose 3	Not stated
369716, 009, 24y	SLE*	186 days afterdose 1	Fatal (included in deaths)
2241, 008, 24y	SLE (questionably pre-existing*)	195 days after dose 3	Recovered
19518, 008, 21y	SLE	222 days after dose 3	Recovered
CONTROL			
8050, 008. 22y	Arthritis	267 days after dose 3	Recovered
11954, 008, 16y	Arthritis	815 days after dose 3	Recovered
88202, 008, 19y	Arthritis	380 days after dose 3	Recovered
229946, 009, 23y	RA	56 days after dose 3	Nor recovered
15673, 008, 16y	RA	310 days after dose 3	Not recovered
4140, 008, 18y	RA	616 days after dose 3	Not recovered
7669, 001, 20y	RA	1145 days after dose 3	Not recovered
22297, 008. 22y	SLE	622 days after dose 3	Recovered

*Pre-exsiting conditions

Table 399-Listing Of Confirmed Immune-Mediated Rheumatologic Events by External Expert Panel-HPV Vaccine [>25 years of age]

Case number, Study, Age	Event	Time to Event	Outcome
HPV			
2779, 015, 35y	Arthritis*	29 days after dose 3	Recovered
2371, 015 44y	Arthritis reactive	4 days after dose 1	Recovered
85, 014, 50y	RA	470 & 548 days after dose 3	Not recovered

*Pre-existing conditions

Brief narratives were provided for subjects who received Cervarix and control and had illnesses of confirmed immune-mediated etiology. These narratives are located in Appendix B-Overview of Safety (p. 11-14).

There were events which were considered to be of uncertain diagnoses as well. The cases which occurred in the HPV-AS04 group and control groups (Level 1) are provided in Tables 400 and 401 below (15-25 years in Table 400 and >25 years in Table 401).

Table 400-Listing of Immune-mediated Rheumatologic Events with Uncertain Diagnosis by External Expert Panel-HPV Vaccine [15-25 years of age]

Case number, Study, Age	Event	Time to Event	Outcome
HPV-AS04			
1063, 012, 12y	Arthritis [knee, possible mechanical]	1 day after dose 2	Recovered
3022, TETRA-050, 20y	Arthritis [hand, insufficient data]	3 days after dose 1	Recovered
7706, 008, 19y	Arthritis [knee, + gyn discharge]	7 days after dose 3	Recovered
5018, 016, 24y	Arthritis [knee, ligament rupture]	7 days after dose 1	Not recovered
14118, 008, 16y	Arthritis [reactive, HLAB27+, Chlamydia+strep infection pre-event]	112 days after dose 2	Recovering
160, 016, 21y	Arthritis reactive [polyarticular]	63 days after dose 2	Not recovered
1623, 048, 25y	Degenerative/mechanical/undefined disorder [shoulder]	25 days after dose 1	Recovered
11747, 008, 16y	Spondylarthropathy [HLAB27+]	802 days after dose 3	Recovering
1031, 042, 15y	Synovitis [hip]	0&29 days after dose 3	Recovering
21505, 008, 21y	Temporomandibular joint syndrome	2 days after dose 2	Recovered
CONTROL			
**230320, 009, 25y [HAV]*	*Arthritis [ankle pain +swelling]*	*417 days after dose 1*	*Not stated*
105646, 009, 24y [HAV]	RA [ankylosing spondylitis]	254 days after dose 3	Not stated
6595, 001, 18y [alum]	Temporomandibular joint syndrome	Day 0 of dose 2	Recovered

**Subject 230320-Re-coded as ankylosing spondylitis*

Table 401-Listing of Immune-mediated Rheumatologic Events with Uncertain Diagnosis by External Expert Panel-HPV Vaccine [>25 years of age]

Case number, Study, Age	Event	Time to Event	Outcome
HPV			
4101, 015, 43 y	Arthritis [knee, ankle, hx OA]	15 days after dose 2	Recovering
CONTROL			
1441, 015, 44y [alum]	Arthritis [knee]	8 days after dose 2	Recovered

The cases not considered to be of immune etiology are presented in Tables 402 and 403 below.

Table 402-Listing of Events Not Considered to be Immune-mediated by External Expert Panel-HPV Vaccine [15-25 years of age]

Case number, Study, Age	Event	Time to Event	Outcome
HPV-AS04			
4023, TETRA-051, 24y	Degenerative mechanical undefined disorder	1 day after dose 3	Recovered
86676, 008, 16y	Degenerative mechanical undefined disorder	66 days after dose 2	Recovered
13140, 008, 17y	Fibromyalgia	Day of dose 3	Recovering
482958, 009, 22y	Fibromyalgia	35 days after dose 1	Not stated
294498, 009, 21y	Fibromyalgia	78 days after dose 2	Not stated
14935, 008, 16y	Fibromyalgia	476 days after dose 3	Not recovered
15004, 008, 17y	Fibromyalgia	794 days after dose 3	Not recovered
2018, TETRA 050, 19y	Temporomandibular joint syndrome	41 days after dose 1	Recovered
86618, 008, 16y	Traumatic disorder	371 days after dose 3	Not recovered
57, 016, 24y	Viral syndrome	106 days after dose 2	Recovered
CONTROL			
17064, 008, 23y	Traumatic disorder	572 days after dose 3	Not recovered
7621, 001, 18y	Traumatic disorder	1875 days after dose 3	Recovering

Table 403-Listing of Events Not Considered to be Immune-mediated by External Expert Panel-HPV Vaccine [>25 years of age]

Case number, Study, Age	Event	Time to Event	Outcome
HPV-AS04			
9906, 015, 54y	Degenerative mechanical undefined disorder	Day of dose 2	Not recovered
731, 014, 45y	Degenerative mechanical undefined disorder	100 days after dose 2	Recovered
*103, 015, 44y**	*Degenerative mechanical undefined disorder*	*120 days after dose 3*	*Not recovered*
237, 014, 34y	Degenerative mechanical undefined disorder	126 days after dose 2	Recovered
4593, 015, 36y	Fibromyalgia	100 days after dose 3	Not recovered
**9162, 015, 26y*	*Fibromyalgia*	*88 days after dose 3*	*Recovered*
60, 035, 30y	Traumatic disorder	Day of dose 1	Recovered
CONTROL			
10610, 015, 42y	Degenerative mechanical undefined disorder	128 days after dose 3	Not recovered
4609, 015, 59y	Degenerative mechanical undefined disorder	5 days after dose 2	Recovering
5471, 015, 45y	Degenerative mechanical undefined disorder	12 days after dose 2	Recovered
5288, 015, 33y	Fibromyalgia	118 days after dose 2	Recovered
9916, 015, 38y	Fibromyalgia	19 days after dise 1	Not recovered
2508, 010, 45y	Fibromyalgia [non-MPL, Gardasil]	33 days after dose 2	Not recovered
2423, 010, 44y	Fibromyalgia [non-MPL, Gardasil]	95 days after dose 3	Not recovered
3613, 015, 29y	Fibromyalgia	348 days after dose 3	Not recovered
**19, 015, 64y*	*Traumatic disorder*	*7 days after dose 1*	*Recovered*

**Subject 9162-AE deleted by investigator*

***Subject 103-removed (initial AE corrected to exacerbation of back disorder)*

**Subject 19-removed (re-classified as hand fracture)*

Additional events were reported in various clinical trials and were also included in the meta-analyses conducted by GSK. Most of the additional events occurred at longer time periods after the last dose of vaccine (although a few were within a shorter period of time). The majority of these events were non-serious. Please see Table 5b in Appendix B-Overview of Safety.

The meta-analysis was also conducted using the diagnoses by the expert panel. For the level 1 analysis of confirmed immune-mediated rheumatologic events, throughout the entire follow-up period, there were overall 21 subjects reporting at least one event with 13 subjects in the MPL group and 8 subjects in the non-MPL group; the overall relative risk was 1.63 (95% CI 0.65; 4.14). The most frequently reported events were:

- arthritis with one event in the MPL group and four events in the non-MPL group (RR = 0.25, 95% CI 0.01; 2.53),
- rheumatoid arthritis with five events in the MPL group and three events in the non- MPL group (RR = 1.81, 95% CI 0.37; 9.66),
- systemic lupus erythematosus with three events in the MPL group and one event in the non-MPL group (RR = 2.39, 95% CI 0.25; 30.86).
- For juvenile arthritis and reactive arthritis, there were two events in the MPL group.

Table 404-Percentage of subjects reporting the occurrence of immune-mediated rheumatologic events (confirmed diagnosis by external experts) throughout the entire follow-up period, classified by CBER Verbatim Terms with estimated relative risks (Level 1 [controlled HPV studies] Total vaccinated cohort)

Preferred Term (CODE)	MPL N = 25580				Non-MPL N = 25438				Relative Risk (MPL over Non-MPL)		
			95% CI				95% CI			95% CI*	
	n	%	LL	UL	n	%	LL	UL	RR	LL	UL
At least one symptom	13	0.05	0.03	0.09	8	0.03	0.01	0.06	1.63	0.65	4.14
Arthritis (10003246)	1	0.00	0.00	0.02	4	0.02	0.00	0.04	0.25	0.01	2.53
Arthritis reactive (10003267)	2	0.01	0.00	0.03	0	0.00	0.00	0.01	INF	0.19	INF
Juvenile arthritis (10059177)	2	0.01	0.00	0.03	0	0.00	0.00	0.01	INF	0.21	INF
Rheumatoid arthritis (10039073)	5	0.02	0.01	0.05	3	0.01	0.00	0.03	1.81	0.37	9.66
Systemic lupus erythematosus (10042945)	3	0.01	0.00	0.03	1	0.00	0.00	0.02	2.39	0.25	30.86

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)
INF=infinity, no cases are reported in the Non-MPL group
Source: STN 125259.48, Supplemental safety summary, Table 90, p.210

For the level 1 analysis of uncertain immune-mediated rheumatologic events, throughout the entire follow-up period, there were overall 5 subjects reporting at least one event with 3 subjects in the MPL group and 2 subjects in the non-MPL group; the overall relative risk was 1.88 (95% CI 0.21; 23.88). The most frequently reported events was:

- arthritis with three events in the MPL group and one event in the non-MPL group (RR = 3.00, 95% CI 0.24; 157.27).
- For rheumatoid arthritis, there was one event in the non-MPL group.

Table 405-Percentage of subjects reporting the occurrence of immune-mediated rheumatologic events (uncertain diagnosis by external experts) throughout the entire follow-up period, classified by CBER Verbatim Terms with estimated relative risks (Level 1 [controlled HPV studies] Total vaccinated cohort)

Preferred Term (CODE)	MPL N = 25580				Non-MPL N = 25438				Relative Risk (MPL over Non-MPL)		
			95% CI				95% CI			95% CI*	
	n	%	LL	UL	n	%	LL	UL	RR	LL	UL
At least one symptom	3	0.01	0.00	0.03	2	0.01	0.00	0.03	1.88	0.21	23.88
Arthritis (10003246)	3	0.01	0.00	0.03	1	0.00	0.00	0.02	3.00	0.24	157.27
Rheumatoid arthritis (10039073)	0	0.00	0.00	0.01	1	0.00	0.00	0.02	0.00	0.00	117.00

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)
STN 125259.48, Supplemental safety update, Table 91, p. 211

For the level 1 analysis of confirmed and uncertain immune-mediated rheumatologic events combined, throughout the entire follow-up period, there were overall 26 subjects reporting at least one event with 16 subjects in the MPL group and 10 subjects in the non-MPL group; the overall relative risk was 1.67 (95% CI 0.73; 3.87). The most frequently reported events were:

- arthritis with four events in the MPL group and five events in the non-MPL group (RR = 0.80, 95% CI 0.16; 3.71)
- rheumatoid arthritis with five events in the MPL group and four events in the non-MPL group (RR = 1.54, 95% CI 0.34; 7.08),
- systemic lupus erythematosus with three events in the MPL group and one event in the non-MPL group (RR = 2.39, 95% CI 0.25; 30.86),
- For juvenile arthritis and reactive arthritis, there were two events in the MPL group.

Table 406-Percentage of subjects reporting the occurrence of immune-mediated rheumatologic events (confirmed and uncertain diagnosis combined) throughout the entire follow-up period, classified by CBER Verbatim Terms with estimated relative risks (Level 1 [controlled HPV studies] Total vaccinated cohort)

Preferred Term (CODE)	MPL N = 25580				Non-MPL N = 25438				Relative Risk (MPL over Non-MPL)		
			95% CI				95% CI			95% CI*	
	n	%	LL	UL	n	%	LL	UL	RR	LL	UL
At least one symptom	16	0.06	0.04	0.10	10	0.04	0.02	0.07	1.67	0.73	3.87
Arthritis (10003246)	4	0.02	0.00	0.04	5	0.02	0.01	0.05	0.80	0.16	3.71
Arthritis reactive (10003267)	2	0.01	0.00	0.03	0	0.00	0.00	0.01	INF	0.19	INF
Juvenile arthritis (10059177)	2	0.01	0.00	0.03	0	0.00	0.00	0.01	INF	0.21	INF
Rheumatoid arthritis (10039073)	5	0.02	0.01	0.05	4	0.02	0.00	0.04	1.54	0.34	7.08
Systemic lupus erythematosus (10042945)	3	0.01	0.00	0.03	1	0.00	0.00	0.02	2.39	0.25	30.86

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk; STN 125259.48, Supplemental safety update, Table 92, p. 212

Extended musculoskeletal analysis based on preferred terms considered of interest by the external expert panel: On the advice of the panel of experts in rheumatologic and musculoskeletal disorders consulted by GSK, a second analysis was performed based on a search of MedDRA Preferred Terms in the CBER category of musculoskeletal events which was extended to other terms from other CBER categories of diseases as the experts considered these additional terms as relevant for an analysis of musculoskeletal disorders (extended musculoskeletal analysis); the additional terms used for this analysis are listed. Similar to the analysis of musculoskeletal events, all events reported in clinical studies with GSK's MPL–containing products, up to the new data lock-point of August 31, 2008 (except for Study HPV-009 for which the data lock-point was July 1, 2008) were considered for the analysis. Please see Table 6b in Appendix B-Overview of Safety for the additional terms used.

In this extended analysis of Level I controlled HPV studies over the entire study period, 2 additional cases were added to the MPL group and 9 events were added to the non-MPL group. In this extended analysis, there were overall 79 subjects reporting at least one event with 41 subjects in the MPL group and 38 subjects in the non-MPL group; the overall relative risk was 1.08 (95% CI 0.68; 1.72). The most frequently reported events were the same events as noted prior to use of additional searh terms (arthritis, fibromyalgia, RA and SLE (no additional cases) and relative risks were unchanged from analysis without the extended search terms. Vasculitis events were added to both treatment groups (RR= 0.67, 95% CI: 0.06, 5.82). Cutaneous lupus, dermatomyositis, psoriatic arthropathy, and Raynaud's phenomenon were reported in the non-MPL group only.

For the level 1 analysis of controlled HPV studies, for events reported between dose 1 and 6 months after dose 3, there were overall 37 subjects reporting at least one event with 21 events in the MPL and 16 events in the non-MPL group (RR = 1.31, 95% CI: 0.65, 2.69). Two events were added to the MPL group and 4 events were added to the non-MPL group. For this reporting period, the most frequently reported events were again arthritis, fibromyalgia and rheumatoid arthritis as noted in the analysis without extension of terms. There were cases of vasculitis added to both treatement groups (RR=2.0, 95% CI: 0.10, 117.93), and cases of arthropathy, cutaneous lupus, and Raynaud's phenomenon added to the non-MPL group.

For the level 1 analysis of uncontrolled HPV studies, there was no difference throughout the entire follow-up period. For the level 1 analysis of uncontrolled HPV studies, during the 12 month follow-up period following dose 1, there were a total of 12 subjects for which an event was reported, (similar to the reporting of events throughout the entire follow-up period except for the exclusion of the two reports of rheumatoid arthritis.)

GSK also submitted in 8/09 a **Time to Onset analysis** which included the assessment of one additional blinded expert . In this assessment, further calculations of relative risks of immune-mediated rheumatologic events with a confirmed diagnosis adjudicated by the expert panel for subjects reporting at least one event (Levels 1 controlled studies, Total vaccinated cohort): During time at risk (Time at risk 1 to 6 months after last vaccination), 4 events occurred (3 HPV-MPL, 1 control) with a RR = 3.00 (95% CI: 0.24, 157.41). The 3 events in the HPV group were 2 reactive arthritis and 1 RA and for the HPV group, and there was 1 case of RA in the control group. In the two subjects with reactive arthritis in the HPV group, one subject had a concurrent Chlamydia infection, and the other subject had concurrent gastroenteritis. In the time to risk analysis, the relative risks for individual events were as follows: arthritis reactive (2/0, RR=INF [95% CI: 0.19, INF]; RA (1/1, RR=1.00 [95% CI: 0.01, 78.52]). For the anytime at risk period, there were 14 events, 7 in each group, RR = 1.00, (95% CI: 0.30, 3.34). For individual events,

Arthritis (0/3, RR = 0 [95% CI: 0, 2.42]; Reactive arthritis 2:0, RR=INF [95% CI: 0.19, INF]; RA 4:3, RR=1.33 [95% CI: 0.23, 9.09]; SLE 1/1, RR=1 [95% CI: 0, 78.54]).

Table 407: Relative Risks of immune-mediated rheumatologic events with a confirmed diagnosis adjudicated by the expert panel for subjects reporting at least one event (Level 1, controlled studies, Total Vaccinated Cohort)

Level of analysis	TTO classification	Number of subjects with IMRE confirmed	Relative Risk	95% CI
Level 1 (HPV vaccines)	Time-at-risk	4	3.00	0.24, 157.41
	Anytime at risk	14	1.00	0.30, 3.34

IMRE=Immune mediated rheumatologic events

Reviewer's Comment: The time to onset analysis was reviewed and narratives reviewed. One subject with SLE after HPV vaccine was noted by the new expert to have had symptoms of arthralgia in 1997 and 2002 after the birth of her children. The additional expert postulated that this subject's symptoms started in 1997, not after vaccination. Another subject was assessed to have pre-existing JRA.

As noted in the definitions of Levels 1-4 of analyses (see Appendix B), Level 2 analyses include a broader group of AS04-adjuvanted vaccines (HPV, HSV and HBV), and Level 3 includes an even wider range of products. In addition, different vaccines may be indicated for different subject populations. For example. The HBV-AS04 vaccine ----------b(4)----------and may be more difficult to generalize the results from these analyses as they pertain to females 10-25 years of age. It is also noted that the Level 1 analsysis includes females who are > 25 years of age. Different age populations may have different background rates of such autoimmune events which may impact on the analyses. Nonetheless, this was considered a way in which to assess if a specific safety concern could be identified with use an MPL containing product. The overall results of levels 1, 2, and 3 are shown in Table 408. The relative risks were generally similar across levels of analysis, and none of these reached statistical significance.

Table 408: Relative risks of neuroinflammatory and musculoskeletal events for subjects reporting at least one event (Levels 1 to 3, controlled studies, Total vaccinated cohort)

Level of Analysis	Reporting period	Neuroinflammatory Events	Musculoskeletal events (CBER terms)	Musculoskeletal events (extended term analysis)
		RR (95% CI)	RR (95% CI)	RR (95% CI)
1	Month 0-12	0.00 (0.00, 5.33)	1.58 (0.73, 3.57)	1.31 (0.65, 2.69)
	Entire follow-up period	2.33 (0.53, 13.97)	1.31 (0.79, 2.20)	1.08 (0.68, 1.72)
2	Month 0-12	0.39 (0.01, 7.82)	0.99 (0.63, 1.54)	0.95 (0.63, 1.44)
	Entire follow-up period	1.74 (0.54, 6.54)	1.14 (0.80, 1.63)	1.02 (0.73, 1.43)
3	Entire follow-up period	1.49 (0.48, 5.03)	1.19 (0.84, 1.70)	1.05 (0.76, 1.47)

It is noted that Siegrist et al (2007) published the incidence rates of diseases of potential autoimmune etiology in a large Health Maintenance Organization (HMO) in young women prior to the introduction of an HPV vaccine into the recommended immunization schedule. In this cohort study in 2005, immune-mediated conditions were a frequent cause (10.3%) of emergency room consultation by adolescent girls. That these events occurred relatively frequently in this population adds to the difficulty in ascribing attribution of the event to the receipt of an HPV vaccine.

As noted in the bioepidemiology review, although no statistically significant different relative risks for development of a disease of autoimmune etiology was identified in pre-licensure, detection of these adverse events is limited in clinical trials to identify such events. In addition, as also noted in the bioepidemiology review, the post-marketing safety update report (includes safety reports from oer 90 countries in which Cervarix is licensed) did not identify a clear safety signal related to the neuroinflammatory and musculoskeletal events of potential autoimmune etiology. (There is a stated limitation to data collected in the post-marketing period because it is based on passive surveillance, which has limitations including reporting biases, incomplete data or medical review, and lack of sensitivity for adverse events with lomg latency periods.) Events of this nature will be specifically collected during the planned US Managed Care Organization Safety Study. (The exact study design and protocol are being discussed and the final protocol is pending).

Pregnancies and pregnancy outcomes: GSK updated the analysis of pregnancy outcomes as presented in the BLA with a more recent data lock point (DLP) of August 31, 2008. Studies included in this extended pooled safety analysis are: studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023.

The database includes 19,871 subjects that received at least one dose of Cervarix and 17,548 subjects that received at least one dose of control, depending on their age at enrolment.

Overview of number of subjects with pregnancies reported: Of the 7,276 subjects with pregnancies reported, 761 subjects (10.46%) became pregnant around the time of vaccination (i.e. LMP occurred from 30 days before up to 45 days after vaccination). Overall, the age of subjects included in this analysis ranged from 13 to 50 years.

Table 409-Number of subjects who became pregnant during the entire study period and around vaccination per age group in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023
(Total vaccinated cohort, data lock-point of August 31, 2008)

Characteristics	HPV	HAV 360	Total	HPV	HAV 720	ALU	Total	HPV	ALU	Total
	10-14 N=29	10-14 N=10	10-14 N=39	15-25 N=3457	15-25 N=3185	15-25 N=196	15-25 N=6838	25+ N=210	25+ N=184	25+ N=394
Entire study period	29	10	39	3457	3185	196	6838	210	184	394
Around vaccination	1	1	2 (5.13%)	374	319	12	705 (10.31%)	21	31	52 (13.2%)

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023)
ALU = Al(OH)3 control group (Studies HPV-001, 003, 007, 015, 023)
HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)
HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)
[10-14] = 10-14 years
[15-25] = 15-25 years
[25+] = Above 25 years
N = number of pregnancies
Pregnancies around-vaccinations: Pregnancy in subjects for which last menstrual period occurred between 30 days before and 45 days after vaccination (pregnancies with missing
date of last menstrual period are not included)
Source: STN 125259.48, Supplemental safety update, Table 36, p. 109

Analysis of pregnancy outcomes overall

Table 410- Pregnancy outcomes overall for the total number of pregnancies in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lock-point of August 31, 2008)

Pregnancy outcomes	HPV N=3696	HAV 720 N=3190	Alu N=380	HAV 360 N=10	Pooled control N=3580	Total N=7276
Normal infant	2300 (62.23%)	2012 (63.07%)	221 (58.16%)	7 (70.0%)	2240 (62.57%)	4540 (62.40%)
Premature birth	73 (1.98%)	51 (1.60%)	9 (2.37%)	2 (20.0%)	62 (1.73%)	135 (1.86%)
Abnormal infant other than congenital anomaly	105 (2.84%)	106 (3.32%)	8 (2.11%)	0 (0.0%)	114 (3.18%)	219 (3.01%)
Elective termination	216 (5.84%)	194 (6.08%)	22 (5.79%)	1 (10.0%)	217 (6.06%)	433 (5.95%)
Therapeutic sbortion	4 (0.11%)	1 (0.03%)	3 (0.79%)	0 (0.0%)	4 (0.11%)	8 (0.11%)
Ectopic pregnancy	22 (0.60%)	15 (0.47%)	6 (1.58%)	0 (0.0%)	21 (0.59%)	43 (0.59%)
Spontaneous abortion	408 (11.04%)	323 (10.13%)	65 (17.11%)	0 (0.0%)	388 (10.84%)	796 (10.94%)
Stillbirth	20 (0.54%)	17 (0.53%)	2 (0.53%)	0 (0.0%)	19 (0.53%)	39 (0.54%)
Congenital anomaly	30 (0.81%)	22 (0.69%)	6 (1.58%)	0 (0.0%)	28 (0.78%)	58 (0.80%)
Lost to follow-up	24 (0.65%)	24 (0.75%)	1 (0.26%)	0 (0.0%)	25 (0.70%)	49 (0.67%)
Not applicable	4 (0.11%)	3 (0.09%)	0 (0.0%)	0 (0.0%)	3 (0.09%)	7 (010%)
Pregnancy ongoing	490 (13.26%)	422 (13.23%)	37 (9.74%)	0 (0.0%)	459 (12.82%)	949 (13.04%)

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023); ALU = Al(OH)3 control group (Studies HPV-001, 003, 007, 015, 023)
HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)
HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)
Pooled Control = ALU, HAV360 and HAV720 groups
Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]
N = number of pregnancies with LMP during the entire study period; n = number of pregnancies in a given category
Value = value of the considered parameter
% = n / N x 100
Twin pregnancies counted as one pregnancy
Spontaneous abortion includes missed abortion
Not applicable: e.g. mole, trophoblastic tumor
Source: STN 125259.48, Supplemental safety update, Table 37, p. 111

Reviewer's Comment: Pregnancy outcomes are also presented by age and treatment group overall. In Table 411 below, the rates of spontaneous abortion are similar across treatment groups for each age (although for females > 25 years of age, the rates are higher than for females 15-25 years of age). A similar pattern is noted when considering only pregnancies for which an outcome is known.

Table 411-Pregnancy outcomes overall for the total number of pregnancies per age group in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lockpoint of August 31, 2008)

Pregnancy outcomes	HPV	HAV 360	Total	HPV	HAV 720	ALU	Total	HPV	ALU	Total
	10-14 N=29	10-14 N=10	10-14 N=39	15-25 N=3457	15-25 N=3185	15-25 N=196	15-25 N=6838	25+ N=210	25+ N=184	25+ N=394
Normal infant	22 (75.86%)	7 (70%)	29 (74.36%)	2173 (62.86%)	2008 (63.05%)	145 (73.98%)	4326 (63.26%)	105 (50.0%)	76 (41.30%)	181 (45.94%)
Premature birth	0	2 (20%)	2 (5.13%)	68 (1.97%)	51 (1.60%)	6 (3.06%)	125 (1.83%)	5 (2.38%)	3 (1.63%)	8 (2.03%)
Abnormal infant other than congenital anomaly	0	0	0	105 (3.04%)	106 (3.33%)	5 (2.56%)	216 (3.16%)	0	3 (1.63%)	3 (0.76%)
Elective termination	1 (3.45%)	1 (10%)	2 (5.13%)	200 (5.79%)	193 (6.06%)	7 (3.57%)	400 (5.85%)	15 (7.14%)	15 (7.14%)	30 (7.61%)
Therapeutic sbortion	0	0	0	4 (0.12%)	1 (0.03%)	2 (1.02%)	7 (0.10%)	0	1 (0.54%)	1 (0.25%)
Ectopic pregnancy	0	0	0	19 (0.55%)	15 (0.47%)	1 (0.51%)	35 (0.51%)	3 (1.43%)	5 (2.72%)	8 (2.03%)
Spontaneous abortion	1 (3.45%)	0	1 (2.56%)	367 (10.62%)	323 (10.14%)	21 (10.71%)	711 (10.40%)	40 (19.05%)	44 (23.91%)	84 (21.32%)
Stillbirth	0	0	0	20 (0.58%)	17 (0.53%)	1 (0.51%)	38 (0.56%)	0	1 (0.54%)	1 (0.25%)
Congenital anomaly	0	0	0	29 (0.84%)	22 (0.69%)	3 (1.43%)	54 (0.79%)	1 (0.48%)	3 (1.53%)	4 (1.02%)
Lost to follow-up	0	0	0	23 (0.67%)	24 (0.75%)	1 (0.51%)	48 (0.70%)	1 (0.48%)	0	1 (0.25%)
Not applicable	0	0	0	4 (0.12%)	3 (0.09%)	0	7 (0.10%)	0	0	0
Pregnancy ongoing	5 (17.24%)	0	5 (12.82%)	445 (12.87%)	422 (13.25%)	4 (2.04%)	871 (12.74%)	40 (19.05%)	33 (17.93%)	73 (18.53%)

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023)
ALU = Al(OH)3 control group (Studies HPV-001, 003, 007, 015, 023)
HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)
HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)
[10-14] = 10-14 years; [15-25] = 15-25 years; [25+] = Above 25 years
N = number of pregnancies with LMP during the entire study period
n = number of pregnancies in a given category
Value = value of the considered parameter
% = n / N x 100
Twin pregnancies counted as one pregnancy
Spontaneous abortion includes missed abortion
Not applicable: e.g. mole, trophoblastic tumor
Source: STN 125259.48, Supplemental safety update, Table 38, p. 112

Known outcomes of pregnancies are also presented.

Table 412-Pregnancy outcomes overall for the pregnancies with known outcomes in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lock-point of August 31, 2008)

Pregnancy outcomes	HPV N=3178	HAV 720 N=2741	Alu N=342	HAV 360 N=10	Pooled control N=3093	Total N=6271
Normal infant	2300 (72.37%)	2012 (73.40%)	221 (64.62%)	7 (70%)	2240 (72.42%)	4540 (72.40%)
Premature birth	73 (2.30%)	51 (1.86%)	9 (2.63%)	2 (20%)	62 (2.0%)	135 (2.15%)
Abnormal infant other than congenital anomaly	105 (3.30%)	106 (3.87%)	8 (2.34%)	0	114(3.69%)	219 (3.49%)
Elective termination	216 (6.80%)	194 (7.08%)	22 (6.43%)	1 (10%)	217 (7.02%)	433 (6.90%)
Therapeutic sbortion	4 (0.13%)	1 90.04%)	3 (0.88%)	0	4 (0.13%)	8 (0.13%)
Ectopic pregnancy	22 (0.69%)	15 (0.55%)	6 (1.75%)	0	21 (0.68%)	43 (0.69%)
Spontaneous abortion	408 (12.84%)	323 (11.78%)	65 (19.01%)	0	388 (12.54%)	796 (12.69%)
Stillbirth	20 (0.63%)	17 (0.62%)	2 (0.58%)	0	19 90.61%)	39 (0.62%)
Congenital anomaly	30(0.94%)	22 (0.80%)	6 (1.75%)	0	28 (0.91%)	58 (0.92%)

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023)
ALU = Al(OH)3 control group (Studies HPV-001, 003, 007, 015, 023)
HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)
HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)
Pooled Control = ALU, HAV360 and HAV720 groups
Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]
N = number of completed pregnancies with LMP during the entire study period
n = number of pregnancies in a given category
Value = value of the considered parameter
% = n / N x 100
Twin pregnancies counted as one pregnancy
Spontaneous abortion includes missed abortion
Completed pregnancies: number of pregnancies with a known outcome (i.e. excluding ongoing pregnancies, lost to follow-up and pregnancies categorized as “not applicable”)
Source: STN 125259.48, Supplemental safety update, Table 39, p. 113

Table 413-Pregnancy outcomes overall for the pregnancies with known outcomes, per age group in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lock-point of August 31, 2008)

Pregnancy outcomes	HPV	HAV 360	Total	HPV	HAV 720	ALU	Total	HPV	ALU	Total
	10-14 N=24	10-14 N=10	10-14 N=34	15-25 N=2985	15-25 N=2736	15-25 N=191	15-25 N=5912	25+ N=169	25+ N=151	25+ N=320
Normal infant	22 (91.67%)	7 (70%)	29 (85.29%)	2173 (72.80%)	2008 (73.39%)	145 (75.92%)	4326 (73.17%)	105 (62.13%)	76 (50.33%)	181 (56.56%)
Premature birth	0	2 (20%)	2 (5.88%)	68 (2.28%)	51 (1.86%)	6 (3.14%)	125 (2.11%)	5 (2.96%)	3 (1.99%)	8 (2.50%)
Abnormal infant other than congenital anomaly	0	0	0	105 (3.52%)	106 (3.87%)	5 (2.62%)	216 (3.65%)	0	3 (1.99%)	3 (0.94%)
Elective termination	1	1 (10%)	2 (5.88%)	200 (6.70%)	193 (7.05%)	7 (3.66%)	400 (6.77%)	15 (8.88%)	15 (9.93%)	30 (9.38%)
Therapeutic sbortion	0	0	0	4 (0.13%)	1 (0.04%)	2 (1.05%)	7 (0.12%)	0	1 (0.66%)	1 (0.31%)
Ectopic pregnancy	0	0	0	19 (0.64%)	15 (0.55%)	1 (0.52%)	35 (0.59%)	3 (1.78%)	5 (3.31%)	8 (2.50%)
Spontaneous abortion	1 (4.17%)	0	1 (2.94%)	367 (12.29%)	323 (11.81%)	21 (10.99%)	711 (12.03%)	40 (23.67%)	44 (29.14%)	84 (26.25%)
Stillbirth	0	0	0	20 (0.67%)	17 (0.62%)	1 (0.52%)	38 (0.64%)	0	1 (0.66%)	1 (0.31%)
Congenital anomaly	0	0	0	29 (0.97%)	22 (0.80%)	3 (1.57%)	54 (0.91%)	1 (0.59%)	3 (1.99%)	4 (1.25%)

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023)
ALU = Al(OH)3 control group (Studies HPV-001, 003, 007, 015, 023)
HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)
HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)
[10-14] = 10-14 years
[15-25] = 15-25 years
[25+] = Above 25 years
N = number of completed pregnancies with LMP during the entire study period
Twin pregnancies counted as one pregnancy
Spontaneous abortion includes missed abortion
Completed pregnancies: number of pregnancies with a known outcome (i.e. excluding ongoing pregnancies, lost to follow-up and pregnancies categorized as "not applicable")
Source: STN 125259.48, Supplemental safety update, Table 40, p. 114

Analysis of pregnancies around vaccination (-30 to + 45 days around LMP): There were a total of 761 pregnant subjects who had their LMP around vaccination (defined as LMP from 30 days before until 45 days after vaccination). Consistent to what has been observed in the analyses of pregnancies around vaccination made for the initial BLA submission (March 2007) and the CR letter responses (April-May 2008), the rate of spontaneous abortion in this subgroup analysis shows a similar numerical imbalance between the groups.

Reviewer's Comment: An imbalance in the proportions of subjects with spontaneous abortions pregnancies are noted when the estimated date of conception is within -30 to +45 days of vaccination. When all age groups are assessed together, the aluminum hydroxide group has the highest proportion of pregnancy losses > HPV vaccine > HAV vaccine. When assessed by age, there is a higher proportion of spontaneous pregnancy lossed in the HPV>HAV>ALU in subjects 15-25 years of age.

Table 414-Pregnancy outcomes around vaccination for the total number of pregnancies per age group in Studies HPV-001, 003, 004, 005, 008, 009, 012, 013, 014, 015, 016 (Total vaccinated cohort, data lock-point of August 31, 2008)

Pregnancy outcomes	HPV	HAV 360	Total	HPV	HAV 720	ALU	Total	HPV	ALU	Total
	10-14 N=1	10-14 N=1	10-14 N=2	15-25 N=374	15-25 N=319	15-25 N=12	15-25 N=705	25+ N=21	25+ N=31	25+ N=52
Normal infant	1 (100%)	0	1 (50%)	241 (64.44%)	230 (72.10%)	10 (83.33%)	481 (68.23%)	16 (76.19%)	12 (38.71%)	28 (53.85%)
Premature birth	0	1 (100%)	1 (50%)	10 (2.67%)	6 (1.88%)	1 (8.33%)	17 (2.41%)	0	1 (3.23%)	1 (1.92%)
Abnormal infant other than congenital anomaly	0	0	0	20 (5.35%)	16 (5.02%)	0	36 (5.11%)	0	1 (3.23%)	1 (1.92%)
Elective termination	0	0	0	38 (10.16%)	26 (8.15%)	0	64 (9.08%)	1 (4.76%)	8 (25.81%)	9 (17.31%)
Therapeutic sbortion	0	0	0	1 (0.27%)	1 (0.31%)	0	2 (0.28%)	0	0	0
Ectopic pregnancy	0	0	0	2 (0.53%)	1 (0.31%)	0	3 (0.43%)	0	0	0
Spontaneous abortion	0	0	0	50 (13.37%)	28 (8.78%)	1 (8.33%)	79 (11.21%)	4 (19.05%)	6 (19.35%)	10 (19.23%)
Stillbirth	0	0	0	1 (0.27%)	2 (0.63%)	0	3 90.43%)	0	1 (3.23%)	1 (1.92%)
Congenital anomaly	0	0	0	7 (1.87%)	4 (1.25%)	0	11 (1.56%)	0	1 (3.23%)	1 (1.92%)
Lost to follow-up	0	0	0	4 (1.07%)	5 (1.57%)	0	9 (1.28%)	0	0	0
Not applicable	0	0	0	0	0	0	0	0	0	0
Pregnancy ongoing	0	0	0	0	0	0	0	0	1 (3.23%)	1 (1.92%)

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 008, 009, 012, 013, 014, 015, 016)
ALU = Al(OH)3 control group (Studies HPV-001, 003, 015)
HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013)
HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)
[10-14] = 10-14 years; [15-25] = 15-25 years; [25+] = Above 25 years
N = number of pregnancies with LMP around vaccination period
Pregnancies around-vaccinations: Pregnancy in subjects for which last menstrual period occurred between 30 days before and 45 days after vaccination (pregnancies with missing date of last menstrual
period are not included)
Twin pregnancies counted as one pregnancy
Spontaneous abortion includes missed abortion
Not applicable: e.g. mole, trophoblastic tumor
Source: STN 125259.48, Supplemental safety update, Table 42, p. 117

Pregnancies with known outcomes with LMP around vaccination: From the 761 pregnant subjects who had their LMP around vaccination, 751 had a known outcome (i.e. completed pregnancies). These observations are very similar to those made in the analysis for all pregnancies in subjects who had their LMP around vaccination.

The overall rates of spontaneous abortion (8.96% overall rate) from the updated analysis were similar between the HPV group (8.97%) and the HAV720 control group (8.66%) and lower than that reported for ALU control group alone (12.18%). No cases were reported in the HAV360 control group. As mentioned above, this difference across groups might be explained by the age distribution in the studies using either ALU placebo control (including subjects of 26 years old and above from Study HPV-015) or HAV360 control (including subjects of 10-14 years old), and the well known higher risk of miscarriage with increasing maternal age.

Analysis of spontaneous abortions: In the clinical trial program, information collected on pregnancies takes into account the date of the last menstruation period (LMP) and not the

estimated date of conception, as the latter is considered to be less reliable. The date of conception is usually not known and ovulation varies in timing from onset of menstruation among different women and from cycle to cycle. Therefore, the estimated date of conception was calculated as the LMP + 14 days assuming that ovulation/conception occurs on cycle day 14 in the average 28-day menstrual cycle. In this pooled analysis, the HPV group is based on data from all studies, while the HAV720 group is only based on Studies HPV-008 and HPV-009.

Table 415-Percentage of spontaneous abortions in pregnancies with known outcomes in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lock-point of August 31, 2008)

	HPV	HAV 720	Alu	HAV 360	Pooled control	Total
Overall pregnancy outcomes	12.84%	11.78%	19.01%	0%	12.54%	12.69%
Pregnancy outcomes around vaccination	13.78%	8.86%	16.67%	0%	9.75%	11.85%

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023)
ALU = Al(OH)3 control group (Studies HPV-001, 003, 007, 015)
HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)
HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)
N = number of completed pregnancies with LMP around vaccination period
Source: STN 125259.48, Supplemental safety update, Table 47, p. 124

Table 416-Reporting rate of spontaneous abortions with LMP around vaccination period by analysis (Total vaccinated cohort)

	HPV	HAV 720	Alu	HAV 360
BLA submission March 2007*	23/210 (11.0%)	10/175 (5.7%)	4/29 (13.8%)	0/1 (0%)
Updated pooled analysis DLP 8/31/08†	54/396 (13.6%)	28/321 (8.72%)	7/43 (16.3%)	0/1 (0%)

*Studies HPV-001, HPV-003, HPV-004, HPV-005, HPV-008 (interim analysis), HPV-012, HPV-013, HPV-014, HPV-015 (interim Month 7 safety analysis), HPV-016.
†Studies HPV-001, HPV-003, HPV-004, HPV-005, HPV-008, HPV-009, HPV-012, HPV-013, HPV-014, HPV-015, HPV-016.
N= number of total pregnancies with LMP around vaccination period
n= number of spontaneous abortion with LMP around vaccination period
Note: all reporting rates based on 'total' number of pregnancies around vaccination
Source: STN 125259.48, Supplemental safety update, Table 48, p. 124

Analysis performed by the NCI on a combined pregnancy dataset from Studies HPV-008 and HPV-009: At the request of the HPV-009 Data Safety Monitoring Board (DSMB), an analysis of spontaneous abortion rates in the pooled pregnancy datasets of studies HPV-008 and HPV-009 was performed because HPV-008 and HPV-009 are two of the largest trials in the HPV development program, including over 25,000 women. The two trials are similarly designed, using double blind, randomized methodology and the same control vaccine (Hepatitis A vaccine).

The analysis was performed by an unblinded trial statistician (Sholom Wacholder, NCI) in consultation with two experts in the epidemiology of reproductive health (Drs. George Macones [Washington University] and Alan Wilcox [NIH]) and according to a prespecified statistical plan developed by NCI, reviewed by GSK and approved by the DSMB overseeing the HPV-009 trial. The analysis plan was designed specifically to address the issues of timing of vaccine administration relative to pregnancy onset and its possible role in risk for spontaneous abortion, with careful control of Type I errors (false positive rate). A manuscript presenting the results of this pooled analysis has been submitted for publication.

Prior to conducting this analysis, a number of issues were addressed:

- The time of pregnancy onset used in this analysis was defined as the expected date of conception (14 days following date of onset of last menstrual period).
- The date of pregnancy onset was expressed relative to the date of vaccination (either first vaccination, most recent vaccination or vaccination closest to pregnancy onset).
- The rates of spontaneous abortion in the HPV and HAV arms of the trials were calculated for pregnancies with onset during specified intervals with respect to vaccination.
- The rate of spontaneous abortion was defined as the ratio of pregnancy loss before 20 weeks gestational age to all intra-uterine pregnancies with known outcome, with a correction for ongoing pregnancies and induced abortions. Ectopic and molar pregnancies were excluded from the numerator and denominator.

Because the mechanisms by which the vaccine could potentially affect pregnancies are unknown, the specific window of time between conception and vaccination for pregnancies that might be at risk is unknown as well. As explained in the report, a permutation test was used maintaining Type 1 error with only small loss of power regardless of the true window of increased risk. The choice of permutation test was based on the fact that the external scientific experts could not agree on a specific time window in which an excess risk of spontaneous abortions could be expected due to vaccination, since the expert consultants stated that it is impossible to identify a gestation age interval *a priori* before and during early pregnancy during which any effect on spontaneous abortion risk is most likely to occur.

The 1-sided p-value for the pre-specified primary analysis by permutation testing of the combined data was 0.16, well above the standard value of 0.025 for a 1-sided test. Overall there was no significant increase in the rate of spontaneous abortions in women vaccinated with Cervarix compared to control (HAV720) when the onset of pregnancy, defined as the estimated date of conception (14 days following date of onset of last menstrual period), occurred anytime from 0 to 2 years following vaccination.

A secondary descriptive analysis was performed evaluating the rates of spontaneous abortions for different time intervals (day of pregnancy onset after nearest vaccination). When restricting to pregnancies that began in the first 3 months after vaccination (i.e., with onset between 0 and 89 days from nearest vaccination), there was a higher rate of spontaneous abortion in the HPV-16/18 vaccine arm (15.4%) compared to the control arm (9.6%). For pregnancies that began beyond 90 days after vaccination, there was no apparent difference between groups (11.3% vs. 11.1%). This secondary analysis was considerd exploratory. It is also noted that the pregnancies reported in the Studies HPV-008 and HPV-009 account for 87.9% of pregnancies reported in the HPV program.

Based on the available data, the NCI concluded the following:

- The primary test of the effect of vaccination with HPV-16/18 vaccine on risk of spontaneous abortion was not significant.
- The spontaneous abortion rate was higher (15.4% vs. 9.6%) in the HPV-16/18 vaccine arm than the control arm for pregnancies with onset within the 90 days following vaccination.
- Most (58.3%) of the miscarriages occurred between 7 and 12 weeks of gestation, consistent with published literature.
- There was no decrease in the incidence of total pregnancies or live births in the HPV-16/18 vaccine arm overall [including the period of 3 months after vaccination].
- These data do not establish a relationship between HPV vaccination and spontaneous abortion risk but are insufficient to rule out a small effect in pregnancies conceived in the 3 months immediately after vaccination.

GSK reported that the NCI presented this analysis to the IDMC of the HPV-008 study. The IDMC provided the following statement:
"Following further consideration of the spontaneous abortion analysis and new information presented today, the IDMC concludes:

1. Overall, the IDMC finds no evidence for a causal association between HPV vaccine and spontaneous abortion.
2. However, given the uncertainty of the data, particularly with respect to the diagnosis of pregnancy, we cannot exclude a possible association between HPV vaccine and spontaneous abortion in the first 90 days following vaccination and onset of pregnancy.
3. The IDMC is reassured that the two planned Phase IV studies in Scotland and Finland can potentially provide data to illuminate the uncertainty at 0-90 days. Non-randomized post-marketing surveillance programs are less likely to be informative."

The dataset which included all spontaneous abortions was reviewed by CBER, and searched for events which occurred in the time window from vaccination to EDC within -30 to +45 days. In this subset, the distribution of time of spontaneous abortions was similar in the treatment groups, It was noted that the times at which the spontaneous abortions occurred were similar (mean app. 10 weeks gestation). CBER notes that the proportions of spontaneous abortions which occurred were within the reported background rates which are reported for such events in the general population, although the estimates can range from 9-44% in the literature. When compared to the spontaneous abortion rates in the Gardasil database, the rates in each group are actually lower than those reported for subjects participating in the Gardasil studies (either in the Gardasil group or the control group), although no imbalance was noted between the treatment groups in the time period -30 to +30 days from time to vaccination to EDC, nor in the overall rates. Neither development program studied pregnancy in a controlled manner, however, and populations were not identical. Although there is no definitive indication that there is an enhanced risk of spontaneous abortions with use of Cervarix, and overall rates of spontaneous abortion are low in the study, a post-marketing pregnancy registry will be conducted to study this issue.

Limitations of analysis of spontaneous abortion: CBER acknowledges that there are limitations to assessing spontaneous abortion rates in this situation. These include the following:

- Spontaneous abortion was not a pre-specified outcome.
- The clinical trials were not designed to study spontaneous abortion.
- There was post-hoc selection of a time window.
- The rates of spontaneous abortions vary widely in the literature (9%-44%) the expected background rates range from app. 9%-21%. The proportions in each treatment group are within the expected background rate reported in the general population.
- In pregnancies which occurred around the time of vaccination, there was no difference in the mean time to spontaneous abortion in each group.
- Pre-clinical reproductive toxicology studies were without such a signal.

Stillbirths: Stillbirths were defined as any intrauterine death occurring after week 20 (generally fetus weighs more than 500g). The number of subjects who became became pregnant and in which the child was stillborn was approximately the same in each group across studies as noted in tables above, There were 19 such events in the pooled control group and 20 such events in the HPV 16/18 group. In the HPV group, the time from last vaccination to estimated date of conception ranged from 60-996 days after, and there was one subject who was vaccinated 9 days before estimated date of conception. The one event considered possibly related to vaccination was in one subject in study HPV-009 who was vaccinated 60 days prior to estimated date of conception. In the control group, the time from last vaccination to estimated date of conception

ranged from 4-1577 days after, and there was one subject who was vaccinated 22 days before estimated date of conception. One event in which the time from last vaccination to estimated date of conception was 4 days was considered possibly related to vaccination, and one event in which the time to vaccination and estimated date of conception was 116 days was considered related to vaccination.
Reviewer's Comment: The number and percentage of these events were comparable across pregnancies.

Analysis of Child cases (serious adverse events) and abnormal infant outcomes: A total of 92 child case reports including abnormal infant outcomes (other than congenital anomalies) were reported from 87 study subjects (including 5 twin pregnancies) in GSK sponsored studies up to the data lock point of August 31, 2008. These reports were from 37 subjects in the HPV-16/18 vaccine group, 12 subjects in the aluminium hydroxide (control) group and 38 subjects in the Hepatitis A vaccine (HAV 720 control) group; one subject did not receive any study vaccination. The most commonly reported events were associated with prematurity: 46 study subjects delivered 50 premature infants (including 4 twin pregnancies).

The most commonly reported events were as follows:
- Respiratory disorders related to hypoxia perinatal: foetal or neonatal respiratory distress syndrome or asphyxia (56 infants), neonatal aspiration (10 infants) and respiratory failure (12 infants).
- Prematurity reported in 44 infants (6 twins) from 38 study subjects, and
- Jaundice, reported in 39 infants (1 twin).

Fatalities in offspring: Twenty three fatalities were reported in 22 neonates (6 twins) and 1 fetus. There were 7 neonatal fatalities (including 2 twins) in the Cervarix group and 15 neonatal fatalities (4 twins) in the control group as well as one fetal death. Summary information of the deaths are listed and described in Appendix B- Overview of Safety (Tables 7b and 8b, and narratives).

Fatal neonatal and infant cases in study HPV-009: Study HPV-009 is ongoing, but reports of abnormal infant outcomes were requested in the Complete Response letter of 12/14/07. The following fatalities were reported in 9 neonates (5 in the control group and 4 in the HPV group). The most frequent cause of death was prematurity (5 case fatalities). Descriptions are located in Appendix B-Overview of Safety (Tables 9b and 10b and narratives).

Congenital anomalies:
Ventricular Septal Defects: Regarding pregnancies with abnormal infant outcomes, CBER noted in the Complete Response letter of 12/14/09 that there was a neonate with a ventricular septal defect (VSD) whose mother participated in Study HPV-009 and received dose 2 of Cervarix approximately 5 weeks prior to her last menstrual period (LMP). A second neonate whose mother received aluminum hydroxide also developed a ventricular septal defect, but the time interval between vaccination and estimated date of conception was 714 days, and temporal association in this second case is not apparent.

As noted by the sponsor, VSDs are the most common cardiac congenital anomalies from the group of birth defects, affecting around 6–8 per 1000 live births. From the clinical studies included in the BLA up to the data lock point of September 30, 2006, two cases of VSD from the 1,244 live births were reported to GSK (frequency of reporting of 1.6 cases per 1000 live births). From the overall clinical program with the HPV vaccine (completed and ongoing trials with the bivalent and tetravalent formulations), including HPV-009, up to the data lock point of September

30, 2007, no new cases of VSD have been reported from the 3,642 reported pregnancies which resulted in live births (frequency of reporting of 0.5 cases per 1000 live births). This number represents a lower incidence compared to the reported background rates of VSD in the general population (6–8 per 1000 live births). From these two cases, one neonate's mother was reported to have suffered from Diabetes Mellitus which is associated with a five-fold increase risk of cardiovascular malformations in offspring (1.7–4.0% risk of malformation.) It appears that since the sensitive period for the main organ-formation is reported to last from the 29th day (or on the 15th post conception day) to the 70th day of gestation, and the mothers were exposed to the blinded vaccine before conception (52 days and 730 days, respectively), the two cases of VSD observed in these two neonates were likely not associated with the vaccination.

From the full results provided to the BLA for VSDs and congenital anomalies, the events appear unrelated to HPV vaccine. In addition, the reports of congenital anomalies presented in the BLA did not reveal any specific pattern of birth defects.

Overall Congenital Anomalies: Up to the data lock-point of August 31, 2008, a total of 60 reports of congenital anomalies in offspring of 59 study subjects (1 twin pregnancy) were reported: 30 reports in subjects that received HPV-16/18 vaccine (30/3696 pregnancies), 28 reports in subjects that received a control (28/3580 pregnancies) and one subject did not receive any study vaccination (PID 243111 in Study HPV-009 was enrolled in the study but did not receive study vaccine due to her pregnancy).

Among the 60 cases, no specific pattern or cluster of type of defects was identified. The three categories of defects most frequently reported were related to isolated cardiovascular defects (10 cases), central nervous system defects (9 cases) and limb defects (9 cases). This is consistent with the distribution from the literature, in which congenital cardiovascular abnormalities are the most common birth defects followed by central nervous system (CNS) anomalies.

A total of 7,276 subjects were reported as pregnant (i.e. had a pregnancy form completed) during the entire study period in this updated pooled analysis of pregnancy outcomes (data lock-point of August 31, 2008). Of these 7,276 pregnancies, a total of 6,271 completed pregnancies (which include live births, stillborn and terminated pregnancies) were reported during the entire study period for studies included in the updated pooled analysis of pregnancy outcomes (data lockpoint of August 31, 2008).

No major difference in reporting frequency of congenital anomalies in 100 completed pregnancies by country were identified. The sponsor notes that approximately half of the congenital anomalies were reported in Study HPV-009 in Costa Rica. When considering the reporting frequency of congenital anomalies in 100 completed pregnancies, by study, the majority of reports are derived from subjects participating in the large phase III clinical Studies HPV-008, HPV-009 and HPV-015.

Timing of exposure: The sensitive period for embryo-organ development was considered to be during pregnancy, and the main organ-forming period was reported by the sponsor to last from the 29th day (or on the 15th post-conception day) to the 70th day of gestation. From the 60 congenital anomalies reported, the mother's last menstrual period (LMP) was unknown in 7 cases, but the onset dates were greater than 12 months after the last vaccine dose in 6 cases and in one case the mother did not receive the vaccine. Of the 53 cases with reported Last Menstrual Period (LMP), the estimated date of conception (EDC) was calculated as the LMP + 14 days. This is based on the assumption that ovulation/conception occurs on cycle day 14 in the average 28 day menstrual cycle. Among these 53 cases, there were 6 reports of congenital anomalies in

offspring of 5 study subjects (1 twin pregnancy) where exposure to study vaccine occurred within 15 days after the estimated date of conception. It is reported that exposures during the first 2 weeks after conception are not known to cause congenital anomalies in human embryos. For the remaining 47 reports, the study subjects were exposed to the study vaccine before the estimated date of conception, as follows:

- Within 30 days before the EDC: 2 reports
- Within 30 to 60 days before the EDC: 5 reports
- >61 days before the EDC: 40 reports

GSK has also provided a summary of 6 reports of congenital anomalies in offspring of 5 study subjects (1 twin pregnancy) where exposure to study vaccine occurred after the estimated date of conception. There were 4 reports in control recipients (2 aluminum hydroxide and 2 hepatitis A vaccine) and 2 reports in children of HPV recipients. These are provided in 10b in Appendix B-Overview of Safety. The congenital anomalies reported in offspring of women who received Cervarix or control are presented in Tables 12b and 13b in Appedix B-Overview of Safety.

In the Cervarix group, two babies born to mothers who were conceived within 30 days of vaccination had congenital anomaly: one child had hip dysplasia and one child had talipes. In the control group**,** the mother of one child with gastroschisis received HAVRIX control vaccine within 30 days of vaccination.

GSK convened a panel of three experts to review the congenital anomalies. A blinded presentation of the events was conducted, allowing for discussion and a consensus to be reached by the three experts. An event listing of the complete set of reports of congenital anomalies was reviewed by the panel according to System Organ Class and with emphasis on embryology.

The panel of experts was provided with a summary report for each event, summary tabulations and background data of the HPV Program (Investigator Brochure, and pre-clinical data). The three experts agreed to review each event, considering but not limited to the following criteria:

- For individual cases -Diagnostic certainty (e.g., definite, probable, unlikely, or unassessable cases); Characteristic features that indicate a possible cause (including those other than maternal vaccination)
- For groups of related defects - Background rates; Embryological considerations such as: sensitive period of organogenesis and patterns or constellations of defects.

An assessment report was prepared and submitted for the 41 case reports (in 40 study subjects, 1 twin pregnancy) that were considered previously in the CBER's complete response (DLP: December, 31, 2007).

The 20 new case reports of congenital anomalies in offspring reported since the datalock-point considered previously for the CBER's complete response (December 31, 2007) up to the data lock-point of August 31, 2008, as well as any update of the cases submitted previously were reviewed and discussed by the external panel of expert in a meeting that was held on 1/27/09. The external experts concluded that there is no evidence that the risk of birth defects in children of women who were immunized with Cervarix prior to pregnancy is measurably increased or that any particular birth defect occurs in excess among these children. However, the experts further expressed the opinion that the data available to assess the potential reproductive toxicity of Cervarix are limited.

Overall Pregnancy Outcomes: With respect to the analysis of overall pregnancies, the most frequently reported outcomes ranked as follows: normal infant, spontaneous abortion and elective termination. Overall, the proportion of subjects who experienced specific outcomes (normal infant, abnormal infant, stillbirth, premature birth, elective or spontaneous abortion) was similar between treatment groups. The overall frequencies of spontaneous abortion in this updated analysis were similar between treatment groups. No difference was seen between treatment groups with respect to the rate of abnormal infant outcomes, including congenital anomalies. The expert panel concluded that the currently available data do not indicate an increased risk of congenital anomalies in subjects vaccinated with HPV-16/18 vaccine candidate.

10.3.8 Human Carcinogenicity: No testing conducted.

10.3.9 Withdrawal Phenomena/Abuse Potential: Not applicable

10.3.10 uman Reproduction and Pregnancy Data:

Please see discussions under Safety regarding pregnancy data. Also, preclinical toxicology studies and reproductive toxicology studies were conducted with Cervarix. These studies were reviewed in detail by Dr. Steve Kunder, Dr. David Green, Dr. Ching-long Sun, and Dr. Marion Gruber, respectively. Please see their reviews for full assessment.

10.3.11 Assessment of Effect on Growth: No testing was conducted.

10.3.12 Overdose Experience: No overdose experience in clinical studies.

10.3.13 Person-to-Person Transmission, Shedding: This product is not a live viral product, so there is no issue of vaccine shedding or person-to-person transmission.

10.3.14 Post-Marketing Experience: Cervarix was licensed for use in Australia in 5/07 and many other countries in the EU, South America and Asia after that date. GSK has provided a post-marketing safety report which covers the period 5/18/07 to 5/18/09. 1706 reports of AEs were tabulated in that time period (CBER analysis). Of the 1706 reports (CBER tally), 793 (64%) were non-serious and 450 (26%) were serious. Two deaths have been reported in the post-marketing period to date: a 12 year old female who died from Group A strep septicemia which occurred 3 weeks after dose 2; and a 14-year old female who died shortly after receiving a dose of Cervarix. In a preliminary communication from GSK, the girl was reported to have a large tumor. (Official details are pending on this second case). It is noted that these post-marketing safety reports represent passive reports submitted to the sponsor, and are often limited in information provided (and in turn may limit assessment of such events).

Table 417-Frequency of 10 Most Reported Adverse Events per 100,000 Doses Distributed [May 2007 through May 2009]

Event Preferred Term	Number of Events	Reported Frequency per 100,000 Doses Distributed
Headache	249	3.65
Injection site pain	246	3.61
Pyreaxia	223	3.27
Dizziness	188	2.76
Nausea	163	2.39
Pain in extremity*	162	2.38
Malaise	119	1.75
Rash	115	1.69
Product quality issue	110	1.61
Syncope	101	1.48

Source: STN 125259, PSUR update 5/09

The most frequently reported spontaneous adverse events reported through May 2009 include the events in the table above (doses distributed). Syncope was the most

frequently reported serious adverse event and 4% of syncopal events were associated with tonic-clonic movements some of which have been classified as seizures.

Other events of interest included the following: Lymhadenopathy -25 (3.7/1million doses); Thrombocytopenia -5; hyperthyroidism-1; hypoacusis-2 (somatization); transient blindness – vasovagal syncope; diplopia; Guillain-Barre syndrome; angioedema/allergic reactions ; facial palsy; ulcerative colitis 1 case; chronic fatigue; anaphylaxis – 1 per million doses; allergic reaction; diabetes mellitus; juvenile rheumatoid arthritis; systemic lupus erythematosis; brachial neuritis/radiculopathy; convulsion; complex regional pain syndrome;multiple sclerosis; optic neuritis; erythema multiforme and Stevens Johnson syndrome (7 cases). These events continue to be monitored in post-marketing studies. Two events have been added to the label by GSK based on post-marketing reports: allergic reactions (including anaphylactic and anaphylactoid reactions), angioedems, and syncope or vasovagal responses to injection (sometimes accompanied by tonic-clonic movements). CBER also advised inclusion of erythema multiforme due to seriousness of event. None of the other events reported were considered to exceed expected incidence, but data are still being collected. GSK has estimated that there have been$_{b(4)}$million doses of Cervarix distributed since the time of original licensure in Australia. The Post-Marketing Safety Update Report was reviewed by the Office of Biostatistics and Epidemiology. Please see separate review.

10.3.15 Safety Conclusions

In females 10-25 years of age, Cervarix, when administered in a 3 dose regimen at 0, 1, and 6 months appeared to produce generally comparable adverse event profiles in those who received either Havrix formulation (active control, specific formulation for 10-14 year old females and 15-25 year old females) or aluminum hydroxide control (500 mcg dose). The following differences were noted:

- A higher proportion of Cervarix recipients as compared to either Havrix or aluminum hydroxide control recipients reported an injection site adverse event in the 7 days after any vaccination. A higher proportion of Cervarix recipients reported Grade 3 pain as compared to control recipients. A higher proportion of Cervarix recipients experienced redness and swelling as compared to either Havrix group or aluminum hydroxide group. The rates of subjects reporting redness and swelling increased in frequency with subsequent doses of Cervarix. Pain was the most commonly reported local adverse reaction, followed by erythema and swelling.
- The proportions of subjects with general adverse events in the Cervarix group were comparable to subjects in the Havrix control group and generally comparable to the aluminum hydroxide control (although a higher proportion in the aluminum hydroxide group experienced a headache as compared to the Cervarix group). The most common systemic adverse events included headache, pyrexia, and nausea.
- For unsolicited adverse events reported within 30 days after vaccination, there were some differences in incidence rates based on the age of the subjects. For example, 10-14 year old subjects had higher rates of upper respiratory infections as compared to subjects 15-25 years of age. Subjects 15-25 year old subjects had higher rates of Chlamydia infection as compared to 10-14 year old subjects. The rates of unsolicited adverse events were generally comparable in the Cervarix and control groups.
- There were comparable rates of deaths and SAEs in both treatment groups. All deaths which were reported during studies which involved administration of Cervarix were presented by GSK. The most frequent cause of death in both groups was trauma and suicide.

- There were few discontinuations in either group due to an adverse event.
- The most commonly reported new onset chronic diseases were asthma, hypersensitivity and urticaria. The percentage of subjects reporting these events was low and similar among the treatment groups. There were no differences between the HPV group and the control groups in reporting of new onset chronic diseases when considering subjects of each age group.
- There were no differences in the overall incidences of new onset autoimmune diseases (NOAD) with new onset reported in the HPV group compared to the control groups or the pooled control group for either the vaccination period or the full observation reporting period. When considering NOADs alone: 0.7% subjects in the HPV group and 0.8% in the pooled control group were diagnosed with a NOAD over the entire study period. The most common NOAD across the study was hypothyroidism (23 or 0.2% in the HPV group and 24 or 0.2% in the control group. Events reported in the 10-25 year old were separated out as well (N-C=12533; pooled control-10,730). There was an imbalance in the number of cases with reactive arthritis (5 to 0) but these events may be associated with other etiologies. There was also an imbalance in the number of subjects with EN (3 to 0) – at least one of these events was associated with use of antibiotics.
- In response to request from CBER in the Complete Response letter, GSK provided comparison of events related to musculoskeletal system (e.g., arthritis, fibromyalgia) in subjects (meta-analysis for MPL containing products). Cases reviewed in blinded manner by panel of expert rheumatologists (GSK). The overall relative risk for HPV-AS04 containing products in controlled studies over entire study period was 1.31 (95% CI: 0.79, 2.20). The most frequently reported musculoskeletal events were arthritis, fibromyalgia, rheumatoid arthritis, systemic lupus erythematosus and arthropathy. In extended analysis recommended by expert panel using additional MedDRA terms, RR for entire study period for HPV-AS04 vaccines in controlled trials was 1.08 (95% CI: 0.68, 1.72). Expert panel assessed some events as uncertain etiology, and when diagnoses combined (confirmed and uncertain), RR = 1.67 (95% CI: 0.73, 3.87) for HPV-MPL vaccines in controlled trials. GSK submitted Time to Onset analysis with one additional blinded expert in 8/09. In that assessment, further calculations of relative risks of immune-mediated rheumatologic events with a confirmed diagnosis adjudicated by the expert panel for subjects reporting at least one event (Levels 1 controlled studies, Total vaccinated cohort): During time at risk (Time at risk 1 to 6 months after last vaccination), 4 events occurred (3 HPV-MPL, 1 control) with a RR = 3.00 (95% CI: 0.24, 157.41). The 3 events in the HPV group were 2 reactive arthritis and 1 RA and for the HPV group, and there was 1 case of RA in the control group. For the anytime at risk period, there were 14 events, 7 in each group, RR = 1.00, (95% CI: 0.30, 3.34). For individual events, Arthritis (0/3, RR = 0 [0, 2.42]; Reactive arthritis 2:0, RR=INF [0.19, INF]; RA 4:3, RR=1.33 [0.23, 9.09]; SLE 1/1, RR=1 [0, 78.54]).
- At the time of the original BLA submission, a nominal imbalance in events of of potential neuroinflammatory etiology was noted in the HPV-AS04 studies. The 6 events in the HPV group: optic neuritis [clinically isolated syndrome (CIS)] 9 days postdose 1; multiple sclerosis [CIS] 25 days postdose 2; Myelitis (? diagnosis) 47 days days postdose 2; demyelinating disease [CIS] (129 days postdose 2; optic neuritis [CIS] 15 months postdose 3; optic neuritis and multiple sclerosis [CIS] 17 months postdose 3. The 3 events in the pooled control group was multiple sclerosis 60 days postdose 1 (not new case); optic neuritis [CIS] 134 days postdose 3; optic neuritis [CIS] 23 months postdose 3. The assessment of the adverse events were similar among the different neuorology experts. In additional follow-up provided in 3/09, 4 additional cases were

dx'd in the HPV group (1 additional case not optic neuritis as initially coded). 2 of these subjects developed multiple sclerosis, 1 optic neuritis, and 1 myelitis. Because of the interval from vaccination to event (2-6 yrs), these were not thought to be temporally related to vaccination. In GSK's meta-analysis for HPV-AS04 products in controlled studies, the overall relative risk was increased at 2.33, but not statistically significant (95% CI: 0.53, 13.97). (MS RR = 1.50 [0.17, 17.97]; ON RR = 3.00 [0.24, 157.50]). In uncontrolled studies, the proportions were calculated [5/6951]= (0.07%) throughout the study period. These included: 1 demyelinating disease [CIS] or 0.01% (0.00, 0.08%); 1 MS at 0.01% (0.00, 0.08); 1 Myelitis at 0.01% (0.00, 0.08%); and 2 Optic neuritis at 0.03% (0.00, 0.10%). GSK's expert panel concluded that there was not an increased risk of developing neuroinflammatory disorders following vaccination with MPL-containing vaccines. CBER's requested expert opinion from an outside neurologist concluded that the data were insufficient to establish a link, although sufficient to raise concern, and further monitoring recommended (post-marketing reports).

- Outcomes of completed pregnancies (pregnancies for which pregnancy outcome is known) are presented. When comparing rates of events for specific outcomes, the proportions in each of the treatment groups are very similar. Listings of congenital anomalies, stillbirths and infants with a serious outcome were reviewed. There was no apparent nominal or qualitative imbalance noted in the two treatment groups. GSK also provided a report by a panel of teratology experts and no apparent signal was identified, although the small number of cases limited definitive assessments.
  - CBER was interested in the rates of spontaneous abortions which occurred in the treatment groups because of a nominal imbalance in pregnancies around the time of vaccination in the HPV group as compared to the HAV group in study 008 at the time of the interim analysis. The proportions of pregnancy with known outcomes in which the estimated date of conception was within -30 to +45 days around vaccination were also presented. For pregnancies which occurred within -30 to +45 days. The majority of proportions of events were similar in the treatment groups. A nominally higher proportion of spontaneous abortions in the Cervarix group as compared to HAV group, (although a nominally higher rate is also noted for the aluminum hydroxide group as compared to either vaccine). The events were also assessed by age. Of all completed pregnancies in the 15-25 year old age group, the proportions of subjects who experienced a spontaneous abortion were similar among the treatment groups: 12.29% in the HPV group, 11.81% in the HAV group, and 10.99% of the aluminum hydroxide group. In women 25+ years of age, 23.67% in the HPV group and 29.14% of the aluminum hydroxide group experienced a spontaneous abortion. Of pregnancies around the time of vaccination, there was a nominally higher rate of spontaneous abortions noted in Cervarix recipients 15-25 years of age as compared to either Havrix control or alum recipients in that age group. In the 25+ year old age group, in which fewer pregnancies occurred as compared to the 15-25 year old age group, there is no nominal imbalance noted in the treatment groups (approximately 19% for both groups).
  - Limitations to assessing spontaneous abortion rates were noted in this situation. These include the following: spontaneous abortion was not a pre-specified outcome; clinical trials were not designed to study spontaneous abortion; post-hoc selection of a time window; rates of spontaneous abortions vary widely in the literature (9%-44%) the expected background rates range from app. 9%-21%; proportions in each treatment group are within the expected background rate reported in the general population. In pregnancies which occurred around the time of vaccination, there was no difference in the mean time to spontaneous abortion in each group. Further, pre-clinical reproductive toxicology studies were without such a signal.

- In an NCI analysis of spontaneous abortions which occurred in study HPV-008 and study HPV-009, the 1-sided p-value for the primary analysis by permutation testing of the combined data was 0.16, using the nearest vaccination as the reference date. Onset of pregnancy was defined as the estimated date of conception (14 days following date of onset of last menstrual period), occurred anytime from 0 to 2 years following vaccination. Among pregnancies with estimated date of conception data between day 0 and 89 from the nearest vaccination, the miscarriage rate was 15.4% (58) in the treatment arm and 9.6% (34) around the control arm (1 sided p-value of 0.036 did not meet the standard threshold for significance.) For pregnancies that began beyond 90 days after vaccination, there was no apparent difference between groups (11.3% vs. 11.1%). The secondary analysis could neither deny nor confirm an increased discrepancy in spontaneous abortion rates among vaccine recipients. The IDMC found no evidence for causal association between HPV and spontaneous abortion, but could not exclude a possible association between HPV vaccine and spontaneous abortions in the first 90 days after vaccination and onset of pregnancy.
- This issue of spontaneous abortions was discussed at VRBPAC meeting of 9/9/09. There were several obstetricians/gynecologists who noted that the rates of spontaneous abortions were well within the expected background rate. An epidemiologist noted that the issue was identified in controlled studies, and even if below the expected background rate, the finding needs to be followed. A post-marketing study to assess this issue is being required of GSK (as specified by CBER Office of Bioepidemiology).

11. **Additional Clinical Issues:**

Complete Response Comments and Resolution: GSK provided responses to comments in the the complete response letter (12/14/07) and responses were considered to have been adequate and complete as of the final submission of 3/27/09**.** The responses to CBER clinical comments contained in the letter of 12/14/07 are included within the overview of efficacy and safety.

11.1 Directions for Use

Cervarix is supplied as a single dose vial or as a prefilled syringe. The vaccine should be used as supplied. No dilution or reconstitution is necessary. The vaccine should be thoroughly agitated prior to administration.

11.2 Dose Regimens and Administration: Cervarix should be administered intramuscularly as a 0.5-mL dose by intramuscular injection according to the following schedule: 0, 1, and 6 months. The preferred site of administration is the deltoid region of the upper arm.

11.3 Special Populations: The product has not been tested in subjects with immunosuppresssion or HIV infection.

11.4 Pediatrics: Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

CBER is deferring submission of the pediatric study, for 9 years of age, until June 30, 2010, because this product is ready for approval for use in girls and women ages 10 through 25 years of age and this pediatric study has not been completed.

GSK's deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. Deferred pediatric study under PREA for the evaluation of the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV vaccine when administered in healthy females aged 9 to 25 years using an alternative schedule and an alternative dosing as compared to the standard schedule and dosing.
   Final Report Submission: June 30, 2010 (to be submitted to the BA).

CBER is waiving the pediatric study requirement for ages 0 to 8 years of age because the necessary studies are impossible or highly impractical because there are too few children with the disease/condition to study.

CBER notes that GSK has fulfilled the pediatric study requirement for ages 10 through 17 years of age for this application.

12. **Conclusions – Overall**

Available data appear adequate to support the safety and efficacy of Cervarix in females 10-25 years of age who are naïve to the specific vaccine HPV type. The conclusion regarding efficacy in prevention of vaccine HPV- related CIN2/3 or AIS or cervical cancer in females 15-25 years of age is based on one pivotal efficacy trial which utilized histopathololgical endpoints which included identification of the vaccine HPV type within the same specimen, Supportive efficacy results are provided by study HPV-001/007. Efficacy was inferred in the 10-14 year old female group because of immune responses that were non-inferior to those seen in the 15-25 year old female population. Females who are naïve to vaccine HPV types are expected to derive the most benefit from the vaccine in prevention of vaccine related HPV disease. Other females who are PCR positive and/or seropositive for one of the vaccine HPV types may still benefit in prevention of disease due to the HPV type for which they are not already PCR positive and/or seropositive. The vaccine did not show therapeutic efficacy against existing infection with HPV-16 or 18. Evidence of efficacy against non-vaccine oncogenic HPV types, especially HPV type 31, was suggestive.

Due to the presence of a new adjuvant extensive safety data analyses were undertaken for new onset chronic diseases, neuroinflammatory events and potentially autoimmune musculoskeletal events. In those women who were inadvertently vaccinated during pregnancy the overall pregnancy outcomes, including congenital anomalies, were similar between the treatment groups. There was an imbalance in the rate of spontaneous abortions between the Cervarix and the Havrix group among vaccine recipients with pregnancies around the time of vaccination. Safety issues have been discussed in the Safety conclusions above, and other clinical issues also discussed within the overall sections on efficacy and immunogenicity.

13. Recommendations

13.1 Approval Recommendations

The clinical data provided support approval of Cervarix in females 10-25 years of age.

13.2 Recommendations on Postmarketing Actions

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Post-marketing Requirement: FDA has determined that GSK is required to conduct a postmarketing study pursuant to section 505(o)(3)(B)(iii) of the Act based upon a sub analysis of clinical trial data suggesting a numerical imbalance in spontaneous abortions among Cervarix recipients whose pregnancies occurred around the time of vaccination (defined as the last menstrual period occurring 30 days before until 45 days after vaccination), compared to control subjects. The findings were strengthened by exploratory analyses conducted by the National Cancer Institute (NCI) which identified higher rates of spontaneous abortion among those 15 to 25 years of age who received Cervarix around the time of conception (–30 days to +90 days after the estimated date of conception), and identified a possible increased risk of spontaneous abortion in women within 90 days after vaccination. Bsed on appropriate scientific data, GSK is required to conduct the following study:

Analytic Epidemiologic Study to Assess the Risk of Spontaneous Abortion Following Cervarix Administration: GSK has committed to a post-licensure analytic epidemiologic study to assess the risk of spontaneous abortion following Cervarix vaccination. The primary study population will be comprised of women whose estimated date of conception lies between –30 days and +90 days from nearest Cervarix vaccination, relative to a comparison group. The study will include karyotype analysis in a subset of women in order to address the issue of background spontaneous abortions due to chromosomal abnormalities. While the study design is still under discussion, all aspects of the final study protocol are subject to FDA review and ultimate approval pursuant to Section 505(o)(3) of FDAAA. You have committed to providing the draft protocol within two months after vaccine licensure followed by the final study protocol within 6 months after vaccine licensure. Study initiation will preferably occur within six months but no later than 12 months after protocol finalization.

CBER acknowledges the timetable GSK submitted on September 21, 2009, which states that GSK will conduct this trial according to the following schedule:

- Final Protocol Submission: April 2010
- Study Start Date: April 2011
- Final Report Submission: 6 months after study completion

GSK is required to report periodically to FDA on the status of this study pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 601.70. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or trial otherwise undertaken to investigate a safety issue associated with Cervarix.

Post-marketing commitments include the following:

1. GSK has committed to a US-based Phase IV, observational, cohort study in a managed care organization. The primary objective is to evaluate the incidence of autoimmune disease within 12 months of the first dose of Cervarix vaccine, compared to an unexposed cohort. A composite endpoint consisting of a predefined list of autoimmune diseases will be used. The study will comprise a total of 50,000 females age 10 through 25 years of age who received Cervarix, compared to 50,000 control subjects of the same age who were not exposed to Cervarix, but who potentially received other age-appropriate vaccines. Propensity score matching methods would be used to address unequal distribution of risk factors. Each subject would be followed for 12 months after the first vaccination.

2. GSK has committed to provide the final clinical study report of study HPV-008 (A Phase II, double-blind, randomized, controlled, multi-center study to evaluate the efficacy of GlaxoSmithKline Biologicals' HPV-16/18 VLP/AS04 vaccine compared to hepatitis A vaccine as control in prevention of persistent HPV-16 or HPV-18 cervical infection and cervical neoplasia, administered intramuscularly according to a 0, 1, 6 month schedule in healthy females 15-25 years of age). The estimated date of study completion is 10/30/09, and the projected submission of this clinical report will be December 2010.

3. GSK has committed to provide the final clinical study report for HPV-009 (A double blind, controlled, randomized, phase III study of the efficacy of an HPV16/18 VLP vaccine in the prevention of advanced cervical intraepithelial neoplasia (CIN2, CIN3, adenocarcinoma *in situ* [AIS] and invasive cervical cancer) associated with HPV16 or HPV18 cervical infection in healthy young adult women in Costa Rica (study under supervision of National Cancer Institute). The estimated dates of completion and projected date of submission of final clinical study reports are pending confirmation from the National Cancer Institute.

4. GSK has committed to provide the final clinical study report for HPV-015 (A phase III, double-blind, randomized, controlled study to evaluate the safety, immunogenicity and efficacy of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a three-dose schedule (0, 1, 6 month) in healthy adult female subjects aged 26 years and above.) The estimated date of study completion is 10/30/10, and the projected submission date of the final clinical study report is 12/11.

5. GSK has committed to provide the final clinical study report for HPV-023 (A blinded long-term follow-up study of the efficacy of candidate HPV-16/18 L1 VLP AS04 vaccine in young adult women in Brazil vaccinated in the phase IIb, double-blind, multi-center primary study HPV-001 and having participated in the follow-up study HPV-007). The estimated date of study completion is 9/30/10 and the projected date of final clinical study report is 9/11.

6. GSK has committed to provide the final clinical study report for HPV-024 (An open, phase II, multicenter study to assess the safety and immune response to a HPV-16/18 L1 VLP AS04 vaccine fourth dose in healthy, young, adult women in North America previously vaccinated with 3 doses of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine). The study was completed 12/22/08 and the projected date of the final clinical study report is 9/09.

7. GSK has committed to provide the final clinical study report for HPV-040 (A phase III/IV, community-randomized, controlled study to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule in healthy female -b(4)- study participants aged 12 – 15 years.) The

estomated date of study completion is 6/30/14, and the projected date of submission of the final clinical study report is 12/15.

The sponsor has also committed to conduct the following Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70:

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13.3 **Labeling**

The package insert submitted by the applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. There were multiple communications with the sponsor to work on the label in order to achieve consistency with CBER's current guidance on the intent and format of package inserts.

14. **Comments and questions for the applicant**

The sponsor provided responses to all reviewer questions during the course of the BLA review. The comments and responses pertinent to clinical issues are noted within the Overview of efficacy and safety of this review. GSK provided to the comments in the complete response letter (12/14/09) and the responses were considered complete with the submission of 3/27/09.

APPENDIX A-PHASE I/IIA STUDIES

STUDY HPV-002

Duration: 56 days for subjects who received 2 doses of HPV 18 VLP and HPV 16/18 VLP vaccines; 140 days for subjects who received 3 doses of HPV 16 VLP vaccine. When twenty-four subjects had been entered in the HPV-16 and HPV-18 groups combined, all had received one dose of study vaccine, and safety at Day 7 was assessed by a safety monitor as acceptable in at least 16 subjects in the HPV-16 and HPV-18 groups, further enrollment could proceed with the HPV 16/18 group.

Reason for dose selected: The dose of 20 mcg VLPs used in this study was based on previous data in animals with HPV-11, -16, and -18 as well as previous human experience with HPV-11 VLP vaccine in humans. Doses similar to 20 mcg have yielded maximal antibody responses in animal systems, including non-human primates, with HPV-16/18 VLPs formulated with AS04 and with HPV-11 VLPs in humans. A 20 mcg dose was expected to be safe since limiting toxicities were not seen in a human trial with doses as high as 100 pg HPV-11 VLPs.

Population: Healthy female adults (18-30 years) who, within 3 weeks of study entry, were seronegative for HPV-16 and HPV-18 antibodies, had a normal Pap smear, had a pelvic examination showing no evidence of anogenita1 HPV 1esions or other gynecologic pathogens, and had a cervica1 specimen negative for HPV. Women were excluded for acute illness, pregnancy, history of cancer or other specified illnesses (e.g., Hepatitis C, Hepatitis B, HIV), prior receipt of specified immunosuppressive therapy, prior receipt of study material including monophosphoryl lipid A or prior receipt of a vaccine for HPV.

Vaccination Schedule: Subjects received one of the vaccine formulations at Days 0 and 28 by intramuscular injection. Eight subjects who received HPV-16 L1 VLP vaccine received a 3rd dose at Day 112.

Safety was assessed on Study Days 0, 7, 28, 35 and 56 by clinical exam for adverse events and by laboratory parameters, as well as site of injection examination on Study Days 7 and 35. Specific solicited 1ocal injection site (pain, redness, swelling) and general adverse event (fever, headache, GI symptoms, fatigue, rash, pruritus) data were collected on diary cards provided at each injection visit and recorded daily by the volunteer for 7 days. In addition, other adverse events could be reported. Each adverse event was graded and assessment as to relationship to vaccination was provided. Vital signs were assessed prior to and at 30 minutes after each vaccination.

Immune response was evaluated by determination of antibody titers (by ELISA) to HPV-l6 and HPV-18 on Study Days 0, 7, 28, 35 and 56. Serum for neutra1iziag antibody assays was collected on Study Days 0, 28 and 56. Cell mediated immunity (measured by lymphoproliferative assays and IL-5 and IFN-γ release) was evaluated on Study Days 0 and 56.

Efficacy: There were no efficacy endpoints.

Table 1A Study HPV-002: Treatment and Evaluation - Study Days 0 Through 56

		Study Day						
	Screen	**0**	**2***	**7**	**28**	**30***	**35**	**56**
Medical History	x							
Physical Examination	x							
ECG	x							
Randomization/Entry		x						
Pelvic Examination	x							
Pap Smear	x							
HPV-DNA	x							
HPV-16 and HPV-18 ELISA	x	x		x	x		x	x
HPV Neutralization		x			x			x
HPV CMI		x						x
Reserve Serum specimen		x		x	x		x	x
CBC, Differential, Platelets	x	x		x	x		x	x
Chemistry Screening Panel	x							
ALT, AST, BUN, Creatinine		x		x	x		x	x
Serum for Pool (15 mL)**								x
IgG, IgM, IgA	x							
Urinalysis	x	x			x			x
Hepatitis C and B, HIV-1	x							
Serum β-HCG	x							
Urine Pregnancy Test		x			x			x
Provide Diary Cards		x			x			
Site of Injection Examination				x			x	
Return of Diary Cards				x			x	
Assessment of Adverse Events		x***	x	x	x	x	x	x
Vital Signs****		x			x			
Vaccine Injection		x			x			

* *Telephone call (48-72 hours after injection) on Study 2 or 3 and on Study Day 30 or 31*

** Serum was collected to be used as a positive control in future studies

*** On Study Day 0, only adverse events occurring after the injection were noted as adverse events

**** Immediately prior to injection and 30 minutes after injection of study vaccine

Source: STN 125259/0: CSR HPV-002, Exhibit One, pp. 29-30

Table 2A Study HPV-002: Treatment and Evaluation Study Days 112 Through 140

	Study Day			
	112	114*	119	140
Medical History	x			
Physical Examination	x			
Cervical Secretions**				x
HPV-16 and HPV-18 ELISA	x		x	x
HPV Neutralization	x			x
HPV CMI	x			x
Reserve Serum Specimen	x		x	x
Serum for Pool (20 mL)***				x
CBC, Differential, Platelets	x			x
ALT, AST, BUN, Creatinine	x			x
Urinalysis	x			x
Urine Pregnancy Test	x			x
Provide Diary Cards	x			
Site of Injection Examination			x	
Return of Diary Cards			x	
Assessment of Adverse Events	x	x	x	x
Vital Signs****	x			
Vaccine Injection	x			

* Telephone call (48-72 hours after injection) on Study Day 114 or 115
** Cervical secretions collected only from volunteers who consented to this procedure
*** Serum was collected to be used as a positive control in future studies
**** Immediately prior to injection and 30 minutes after injection of study vaccine

Source: STN 125259/0: CSR HPV-002, Exhibit Two, pp. 30

Populations Analyzed: All subjects were included in the analysis.

Results

Disposition of Subjects: 24 females 18-30 years of age were randomized and completed the study. An additional 25 subjects were then enrolled to receive the HPV 16/18 L1 VLP vaccine. Two subjects who received HPV 16/18 vaccine did not complete the study: one withdrew consent at Day 56 after 2 doses of vaccine; and one subject received 2 doses of vaccine, but was lost to follow-up on day 33.

Data Analyzed

Safety analyses were based on all 49 subjects who received any dose of vaccine.
Immunogenicity analyses were performed on 48 subjects who received 2 doses of vaccine. (Immunogenicity analyses were performed in 49 subjects who received at least one dose of vaccine).

Demographics: The mean age (23-24) and other characteristics were similar for all 3 treatment groups. (Source: STN 125259/0, CSR HPV-002, Exhibit 5, p. 44, not shown here).

Safety Results

Table 3A-Study HPV-002: Number of Subjects with Solicited Adverse Events Within7 Days After Injection of Study Vaccine (Through Study Day 56)

	HPV-16 Vaccine	HPV-18 Vaccine	HPV 16/18 Vaccine
Total # of AEs	160	195	253
Number of Subjects with ≥ 1 AE	12 (100%)	12 (100%)	25 (100%)
Injection Site ARs			
Pain	12 (100%)	12 (100%)	25 (100%)
Redness	4 (33%)	5 (42%)	3 (12%)
Swelling	4 (33%)	4 (33%)	3 (12%)
General Reactions			
Fever	7 (58%)	3 (25%)	8 (32%)
Headache	6 (50%)	4 (33%)	13 (52%)
GI Symptoms	6 (50%)	5 (42%)	8 (32%)
Fatigue	5 (42%)	6 (50%)	12 (48%)
Rash	0 (0%)	0 (0%)	0 (0%)
Pruritus	1 (8%)	2 (17%)	2 (8%)

Source: STN 125259/0, CSR HPV-002, Exhibit 6, p. 45

All subjects experienced at least one adverse event in the 7 days after vaccination. The most common injection site adverse event was pain in all 3 treatment groups. The most commonly reported general symptoms were fatigue (42-50%) and headache (33-50%). Fever was defined as any T ≥ 37.5º F. Most of the adverse events were mild and resolved spontaneously. In general, there was no increase in intensity of adverse event with subsequent dosing.

When the adverse events were considered for all injections, the proportions were similar to when AEs were considered by subject.

Table 4A - Study HPV-002: Number of Injections with Solicited Adverse Events Within7 Days After Injection of Study Vaccine (Through Study Day 56)

	HPV-16 Vaccine N*=24	HPV-18 Vaccine N*=24	HPV 16/18 Vaccine N*=48**
Total # of AEs	160	195	253
Number of Subjects with ≥ 1 AE	24 (100%)	24 (100%)	45 (94%)
Injection Site ARs			
Pain	24 (100%)	24 (100%)	45 (94%)
Redness	5 (21%)	5 (21%)	3 (6%)
Swelling	5 (21%)	4 (17%)	5 (10%)
General Reactions			
Fever	10 (42%)	5 (21%)	10 (21%)
Headache	7 (29%)	5 (21%)	18 (38%)
GI Symptoms	6 (25%)	6 (25%)	8 (17%)
Fatigue	6 (25%)	10 (42%)	13 (27%)
Rash	0 (0%)	0 (0%)	0 (0%)
Pruritus	1 (4%)	2 (8%)	2 (4%)

*=total number of injections received

**= one volunteer did not receive dose 2 and one volunteer was lost to follow-up

Source: STN 125259/0, CSR HPV-002, Exhibit 14, p. 55

In the majority of cases, pain was grade 1 or 2 intensity, although 13 events were grade 3 in intensity. In most cases, the mean duration of events was similar across treatment groups for each event.

Table 5A – Study HPV-002: Summary of Unsolicited Adverse Events Reported by More than One Volunteer in any Treatment Group through Study Day 56

	HPV-16 Vaccine N=12	HPV-18 Vaccine N=12	HPV 16/18 Vaccine N=25
Total # of AEs	22	32	48
Number of Subjects with ≥ 1 AE	10 (83.3%)	11(91.7%)	18 (72.0%)
Pharyngitis	4 (33.3%)	5 (41.7%)	7 (28.0%)
Injection Site Reaction**	2 (16.7%)	5 (41.7%)	7 (28.0%)
Headache***	3 (25.0%)	1 (8.3%)	6 (24.0%)
Allergic Reaction ****	0 (0.0%)	4 (33.3%)	5 (20.0%)
Dysmenorrhea	2 (16,7%)	3 (25.0%)	4 (16.0%)
Nausea	0 (0.0%)	0 (0.0%)	2 (8.0%)

*In most cases, pharyngitis refers to URI
**Limited range of motion, induration, or bruising with onset between 0 and 4 days after injection
***Headaches with onset after the end of the period for collection of solicited AEs
****Seasonal allergies
Source: STN 125259/0, CSR HPV-002, Exhibit 16, p. 57

All unsolicited AEs were graded as mild to moderate in intensity. Two subjects experienced mild flu-like symptoms that were considered to be related to therapy (1 subject in the HPV-16 group and 1 subject in the HPV 16/18 group). No unsolicited AEs precipitated discontinuation from study participation.

Deaths and Serious Adverse Events: There were no deaths or SAEs reported in study HPV-002.

Clinical Laboratory Evaluation: There were no clinically significant changes reported for the parameters measured in chemistry tests, hematology tests, or urinalysis.

Vital Signs: There were no clinically meaningful changes in vital signs measured (BP, P, or Temperature) within 30 minutes of vaccination.

Immunogenicity Analyses
Anti-HPV-16 and anti-HPV-18 ELISA antibody midpoint titers were determined from specimens collected prior to each immunization and seven and 28 days after each immunization (on Study Days 0, 7, 28, 35, and 56). Overall, at day 56, there was no decrease in response to either of the individual HPV types 16 and 18 when the VLPs were administered together as compared to individually, and hence, no evidence of interference. (Source: STN 125259/0, CSR HPV-002, Exhibit 19, p. 62, not shown here).

Neutralization Assays: Neutralization titers were determined prior to vaccination, and at study day 28 (4 weeks after dose 1) and at study day 56 (4 weeks after dose 2). Neutralization titers which increased from < 1:100 to 1:100 or 1:1000 on Day 28 or Day 56 were observed for 3 subjects for HPV-16, for 12 subjects for HPV 18.

Cell mediated immunity (lymphoproliferative response and cytokine secretion-IL-5 and IFN-γ) was measured on study day 0 and study day 56. The majority of subjects in all three groups showed lymphoproliferative responses to 10 mcg HPV-16 VLPs and/or 10 mcg/mL HPV-18 VLPs. No statistical correlation could be demonstrated between anti-HPV 16 or HPV 18 antibody levels and lymphoproliferative responses.

Safety after 3rd dose HPV16 vaccine: In 8 subjects who received a 3rd dose of HPV 16 vaccine, there was no increase in proportion of subjects with local or general adverse events with the successive doses nor in duration of symptoms through Day 140. No clinically relevant changes in CBC, Cr, AST or ALT were noted Days 112-140.

Immunogenicity after 3rd dose HPV-16 vaccine: For all 8 subjects who received dose 3 of HPV-16 vaccine, measurable anti-HPV 16 antibody responses were observed on Study Day 119, 7 days after dose 3, with increases in response noted from study Day 119 to study Day 140 for all subjects. For each of the 8 subjects, the anti-HPV 16 antibody response on study day 140 was greater than the response observed through Study day 56 for that volunteer. It was noted that one of the eight subjects had had no response through Day 56, and no anti-HPV 16 antibodies noted at Day 112, but did respond after dose 3.

HPV-16 neutralizing antibody endpoint titers: All eight of the subjects who received dose 3 had HPV-16 neutralizing antibody endpoint titers that rose from <1: l00 on Study Day 112 to 1:100 (one volunteer), 1:1000 (six subjects) or 1:10000 (one volunteer) on Study Day l40. Six of the 8 subjects had not shown neutralizing antibody titers through study day 56. The geometric mean neutralizing antibody endpoint titer on study day 140 was 1:1000.
Reviewer's Comment: Only after dose 3 did neutralizing antibody endpoint titers develop in 6/8 subjects.

Cell mediated immunity was measured after dose 3 of HPV-16 vaccine by determination of lymphoproliferative response and cytokine secretion (IFN-γ and 1L-5) on Study Days 112 (before the third injection of study vaccine) and 140 (28 days after injection). All three indicators of cell mediated immunity showed increased geometric mean responses to 10 mcg/mL HPV-16 VLPs after two injections of HPV-16 vaccine. These responses were further boosted after a third injection of the vaccine.

Study HPV-002, Annex 1
Subjects: Seven of the eight subjects who received dose 3 of the vaccine enrolled in this extension study.

Assays Used
The **Quantitative Binding ELISA for Antibody to HPV-16** VLPs is described by the sponsor.
----------b(4)---------- ----------

-----b(4)---------- ----------

Cell mediated immunity (CMI) was determined by **lymphoproliferation assays** and by **IFN-γ and IL-5 release** using ----------b(4)---------- The IFN-γ assays were carried out using the ----------b(4)----------. The -b(4)-

assays were carried out using the ----------b(4)----------

Results:
Binding ELISA: At Study Year 1.5, all subjects had detectable antibody titers against HPV- 16. Antibody levels declined through Study Year 4.5. All 3 subjects who continued through Study Year 4.5 had detectable HPV- 16 antibodies at Study Year 4.5. (Source: STN 125259/0, CSR 002 annex 1, Exhibit 3, p. 11, not shown here).

Inhibitory ELISA Levels: At Year 1.5, 5/7 (71.4%) subjects had detectable HPV-16 antibodies; at Year 3, 3/4 (75.0%) subjects had detectable HPV-16 antibodies, and at Year 4.5, 1/3 (33.3%) volunteer had detectable HPV-16 antibodies. (Source: STN 125259/0, CSR 002 annex 1, Exhibit 5, p. 13, not shown here).

Cell Mediated Immunity: HPV-16 and HPV-18 lymphoproliferative responses and specific IFN-γ and IFN-gamma responses appeared to remain elevated to one or another eliciting antigen concentrations used in the CMI assays above pre-vaccination levels in the 7 subjects followed for at least 2 to up to 4.5 years. Cross-reactivity with the heterologous antigen was observed in all three assays of cell-mediated immunity. (Source: STN 125259/0, CSR 002 annex 1, Listings 5, 6, 7, pp. 32-46 not shown here).

Study HPV-003
Safety: Solicited adverse events were followed for 7 days after each injection and were to be recorded on a diary card. Adverse events were collected from the time of the first study drug administration through 30 days after each injection. Serious adverse events were collected from the time of the first study drug administration through 30 days after the last scheduled administration of study vaccine (i.e., through Study Day 210). Adverse events and serious adverse events were graded by severity (mild, moderate, severe) and relationship to study drug (none, remote, possible, probable, definite) according to pre-specified definitions. Solicited adverse events included the presence of fever (recorded by oral Tempadot), pain, redness or swelling at the injection site, and the presence of headache, gastrointestinal symptoms, fatigue, rash and pruritus. In addition, routine laboratory test results were to be drawn on days 0, 30, and 210 and were graded (toxicity Grade 1, 2, 3) according to the adverse event grading table as specified in the protocol. Vital signs were taken prior to and at 30 minutes after each vaccination.

Immune response was evaluated by determination of quantitative antibody titers to HPV-l6 and HPV-18 on study days 0, 7, 30, 60, 180, 210, and 360. Titers of VLP-specific antibodies in immunized volunteer serum samples were calculated relative to a positive control reference pooled serum sample. The titers were reported as midpoint titers relative to the standard control curve.

HPV DNA Determination: Subjects were screened with the Hybrid Capture II HPV Test (Digene, Gaithersburg, MD) using the high-risk HPV Probe B (which contains RNA probes for HPV 16/18/31/33/35/39/45/ 51/52/56/58/59/68). Specific RNA probes were used for typing using a cut-off value of b(4) pg/mL. The cut-off value for positivity was lowered from 1 pg/mL (used in the standard assay) to b(4) pg/mL to ensure maximum sensitivity in identifying probe positive samples. Additional HPV-16 and/or -18 testing was done using the DDL PCR DNA assay and will be included in annex 1 report. Subjects were assessed for HPV DNA positivity of the same type present at study entry on study days 60, 210, and 360.

Table 6A – Study HPV-003: Treatment and Evaluation

		Study Visit (Study Day)								
	Screen	*1 (0)*	*2 (7)*	*3 (30)*	*4 (37)*	*5 (60)*	*6 (180)*	*7 (187)*	*8 (210)*	*9 (360)*
Screening Medical History	x	x[a]								
Screening Physical Examination	x	x[a]								
Pelvic Examination	x					x			x	x
Pap Smear	x					x			x	x
HPV DNA	x					x			x	x
Hepatitis C and B, HIV-1	x									
Urinalysis	x									
HPV-16 and -18 ELISA[b]	x	x	x	x		x	x		x	x
HPV-16 and -18 Neutralization		x				x			x	x
CBC, Differential, Platelets	x	x		x					x	
Chemistry Panel	x									
ALT, AST, Creatinine		x		x					x	
Serum β-HCG	x									
Urine Pregnancy Test		x		x			x		x	
Randomization		x								
Provide Diary Cards		x		x			x			
Return of Diary Cards			x		x			x		
Vital Signs[c]		x		x			x			
Vaccine Injection		x		x			x			
Assessment of Adverse Events[d]		x[e]	x	x	x	x	x	x	x	
Site of Injection Examination			x		x			x		

a Update from screening
b Includes collection of reserve serum specimen
c Immediately before injection and 30 minutes after injection of study vaccine
d Includes interim medical history and physical examination; adverse events will also be assessed by telephone 2 to 3 days after each injection of study vaccine
e On Study Day 0, only adverse events occurring after the injection will be noted as adverse events

Source: STN 125259/0, CSR 003, Exhibit 1, p. 26

Table 7A – Study HPV-003: Primary Safety Endpoints

Objective	Endpoints
Evaluate safety	Solicited AE rates through 7 days after each injection
	AE rates through 30 days after each injection
	SAE rates through 30 days after the last injection (Study Day 210)
	Site-of-injection assessment
	Laboratory assessments at Study Days 0, 30 and 210
	Vital signs

Source: STN 125259/0, CSR 003, Exhibit 2, p. 29

Table 8A – Study HPV 003: Secondary Endpoints

Objective	Endpoints
Evaluate DNA positivity	HPV DNA positivity (of the same type present at study entry) at Study Days 60, 210, and 360
Evaluate antibody (ELISA) response	Serum ELISA titers against HPV-16 and HPV-18 at Study Days 0, 7, 30, 60, 180, 210, and 360

Source: STN 125259/0, CSR 003, Exhibit 3, p. 29

Populations Analyzed: The populations analyzed are shown in Table 10 below.

Table 9A – Study HPV-003-Populations Analyzed

	Population			
	Randomized	All scheduled injections	All prior injections	At least one injection
Disposition	x			
Safety				x
Cytology				x
DNA Positivity		x	x	x
Serum ELISA		x	x	x
Cervical ELISA		x		

Source: STN 125259/0, CSR 003, Exhibit 4, p. 32

Interim Analysis: An interim analysis was performed on DNA positivity at Study Day 60 for the purpose of planning future studies. The Study Day 60 evaluation of DNA positivity consisted of a comparison of the fraction positive in each treatment group, but individual subjects were not unblinded at that time. This analysis was performed by the biostatistician and included tabular summaries which were unblinded for treatment groups, but blinded for individual subjects.

Sample Size Determination: The primary objective of this Phase I/II study was to provide initial safety data for HPV 16/18 VLP vaccine in healthy adult women who are HPV-16 or HPV-18 DNA positive. The sample size of 30 subjects per arm was calculated based on the assumptions of HPV DNA positivity rates for the secondary objective, which was to assess the effect of HPV 16/18 vaccine on DNA positivity. For the sample size calculation it was assumed that: at Study Day 60, the HPV positivity rates for the study population are 40% for the HPV 16/18 group and 80% for the control group; and a two-sided chi-square test would be performed with a = 0.05. Under these assumptions, a sample size of 25 subjects per arm yields 84% power to detect a difference. Based on a dropout rate of 15%, this sample size was increased to 30 subjects per arm.

Results:

Disposition of Subjects: A total of 61 subjects were randomized into the study between 11/22/99 and 6/27/00 at 27 sites in the United States. 31 subjects were randomized to receive HPV 16/18 VLP vaccine and 30 subjects were randomized to receive alum control. More subjects discontinued from the HPV 16/18 arm, but this was apparently due to a higher number of subjects lost to follow-up.

Table 10A – Study HPV-003: Disposition of Subjects

	HPV 16/18 L1 VLP Vaccine	Alum Control
Number of subjects enrolled	N=31	N=30
Completed study through study day 360	21 (68%)	26 (87%)
Discontinued	10 (32%)	4 (13%)
Lost to follow up	6 (19%)	0 (0%)
Withdrawal of consent	4 (13%)	3 (10%)
Death	0 (0%)	0 (0%)
Other	0 (0%)	1 (3%)

Source: STN 125259/0, CSR 003, Exhibit 7, p. 38

Data Analyzed

Safety analyses: Subjects receiving at least one injection were included in the safety analysis.

Immunogenicity and HPV-DNA status analyses: Subjects receiving at least one injection, subjects receiving all scheduled injections, and subjects receiving all prior injections were included in these analyses. One volunteer was not included in the analysis of HPV DNA status because she was negative for both HPV-16 and -18 upon study entry.

Demographics: The mean age of the subjects was 22-24. The treatment groups were generally balanced as to ethnic background.

Safety Analyses: A total of 25 (81%) and 27 (90%) subjects in the HPV 16/18 vaccine and alurninum hydroxide control groups, respectively, received all three injections of study vaccine. Nine subjects did not receive all three injections; none of these discontinued for adverse events.

Table 11A - Study HPV-003: Number of Subjects with Solicited Adverse Events

Adverse Event	HPV 16/18 Vaccine N=31	Alum Control N=30
Number of Subjects with ≥ 1 AE	28 (90.3%)	29 (96.7%)
Injection Site ARs		
Pain	28 (90.3%)	28 (93.3%)
Redness	17 (54.8%)	8 (26.7%)
Swelling	13 (41.9%)	8 (26.7%)
General Reactions		
Headache	16 (51.6%)	21 (70.0%)
GI Symptoms	18 (58.1%)	14 (46.7%)
Fatigue	20 (64.5%)	20 (66.7%)
Rash	2 (6.5%)	0 (0.0%)
Pruritus	8 (25.8%)	6 (20.0%)
Fever*	16 (51.6%)	16 (53.3%)

Fever ≥99.5°F

Source: STN 125259/0, CSR 003, Exhibit 10, p. 42

Pain at the injection site was the most common solicited adverse event and occurred in 28 (90.3%) subjects in the HPV 16/18 vaccine group and 28 (93.3%) subjects in the aluminum hydroxide control group. Redness and swelling at the injection site were reported more often by subjects in the HPV 16/18 vaccine group (54.8% and 41.9%, respectively) than by subjects in the

aluminum hydroxide control group (26.7% each). Headache, gastrointestinal symptoms, fatigue or fever were reported by more than 46% of the subjects in each study group.

Data for subjects with solicited adverse events were summarized by intensity grade. More subjects in the HPV 16/18 vaccine group (51.6%) than subjects in the aluminum hydroxide control group (33.3%) reported one or more Grade 3 solicited adverse events. Pain at the injection site was the most common Grade 3 solicited adverse event and was reported by 41.9% of subjects in the HPV 16/18 vaccine group and 33.3% of subjects in the alum group. All other Grade 3 events were infrequent and were reported to have occurred after <10% of injections.

The rate of reported Grade 3 solicited adverse events was similar for both groups after the first and third injections. In the aluminum hydroxide control group, the number of subjects reporting one or more Grade 3 solicited adverse events increased slightly from 20.0% after the first injection to 26.7% after the third injection. The number of subjects receiving HPV 16/18 vaccine did not report an increased number of Grade 3 solicited adverse events with subsequent injections but remained the same (29.0% after the first and third injections). After the second injection, 8 subjects (25.8%) in the HPV 16/18 vaccine group and 0 subjects in the aluminum hydroxide control group reported Grade 3 solicited adverse events.

The number of injections after which solicited adverse events occurred is presented in Table XX. Solicited adverse events occurred after more injections in the alum group than in the HPV 16/18 group (92.9% of injections in the alum group and 82.8% of injections in the HPV 16/18 group.) The percentage of pain was similar in both groups but redness and swelling at the injection site were more frequent in the HPV 16/18 group than in the alum group.

Table 12A - Study HPV-003: Number of Injections with Solicited Adverse Events

Adverse Event	HPV 16/18 Vaccine N=87	Alum Control N=85
Number of Injections after which a solicited AE occurred	72 (82.8%)	79 (92.9%)
Injection Site ARs		
Pain	69 (79.3%)	68 (80.0%)
Redness	23 (26.4%)	12 (14.1%)
Swelling	18 (20.7%)	10 (11.8%)
General Reactions		
Headache	27 (31.0%)	34 (40.0%)
GI Symptoms	30 (34.5%)	18 (21.2%)
Fatigue	37 (42.5%)	37 (43.5%)
Rash	2 (2.3%)	0 (0.0%)
Pruritus	14 (16.1%)	7 (8.2%)
Fever*	24 (27.6%)	26 (30.6%)

*N=Number of injections received
**Fever=Temperature ≥ 99.5 °F
STN 125259/0, CSR 003, Exhibit 13, p. 44

The number of subjects requiring treatment after a solicited adverse event was balanced between treatment groups (25.8% – 26.7%). No subjects in either group required treatment for any solicited injection-site reaction. The most common solicited adverse event requiring treatment was headache; the incidence was less in the HPV 16/18 vaccine group (16.1%) than in the alum group (26.7%)

Solicited adverse events were typically brief in duration (<4 days on average) and, for the most part, were balanced across treatment groups. In general, the durations of solicited adverse events in each study group were similar after each injection of study vaccine.

Unsolicited adverse events were collected through 30 days after each vaccine injection.

Table 13A- HPV-003: Summary of Unsolicited Adverse Events Reported by More than One Volunteer in any Treatment Group

	HPV 16/18 vaccine	Alum control
Total # of AEs	52	28
Number of Subjects with ≥ 1 AE	22 (71.0%)	16 (53.3%)
Body as whole	10 (32.2%)	8 (26.7%)
Cardiovascular System	0 (0.0%)	0 (0.0%)
GI System	4 (12.9%)	0 (0.0%)
Endocrine System	0 (0.0%)	0 (0.0%)
Hem and Lymphatic System	1 (3.2%)	1 (3.3%)
Metabolic and Nutritional Disorders	0 (0.0%)	0 (0.0%)
Musculoskeletal	1 (3.2%)	0 (0.0%)
Nervous System	5 (16.1%)	0 (0.0%)
Respiratory System	10 (32.3%)	6 (20.0%)
Skin and Appendages	1 (3.2%)	1 (3.3%)
Special Senses	1 (3.2%)	0 (0.0%)
Urogenital System	11 (35.5%)	8 (26.7%)

Source: STN 125259/0, CSR 003, Exhibit 16, p. 46

Unsolicited adverse events were reported by 22 (71.0%) subjects in the HPV 16/18 vaccine group and 16 (53.3%) subjects in the aluminum hydroxide control group. Unsolicited adverse events for the digestive system (diarrhea, dyspepsia, gastritis, and stomatitis) and nervous system (depression, dizziness, dry mouth) occurred only in the HPV 16/18 vaccine group.

The majority of unsolicited adverse events were mild or moderate in severity. Of the 7 severe unsolicited adverse events (headache, dizziness, abortion, and two cases of dysmenorrhea in the HPV 16/18 vaccine group; abdominal pain and ovarian disorder in the aluminum hydroxide control group), none were judged by the blinded investigators to be related to study vaccine.

Deaths and Serious Adverse Events: No deaths occurred in the study.
One volunteer in the HPV 16/18 vaccine group had an SAE during the study that was considered not related to study vaccine. Volunteer 441507 in the HPV 16/18 vaccine group received the first two doses of study vaccine and was found to have a positive urine pregnancy test at the Study Day 60 visit and was discontinued from further vaccination. She experienced a spontaneous abortion at 18.5 weeks gestation. This event was judged by the blinded investigator to be not related to study vaccine. Her estimated date of conception was the day before she received the second dose of HPV 16/18 vaccine. Assessments requiring a pelvic examination (Pap smear, HPV DNA) were not performed at Study Days 60 or 210, but were performed at Study Day 360. The volunteer was followed and considered healthy at Study Day 360 after this event. She completed the study.

Clinical Laboratory Evaluation: One creatinine value in the alum group increased from normal at Day 0 to Grade 1 toxicity at Day 210, but did not appear to be clinically significant. All other serum chemistry values were within the normal range. None of the changes in hematology parameters were judged to be clinically significant.

Vital Signs: Vital signs (temperature, pulse, respiration rate, systolic blood pressure, and diastolic blood pressure) were taken on Study Days 0, 30, and 180 at pre-injection and 30 minutes post- injection. Vital signs were similar across study groups at each time point, and there were no clinically meaningful difference between pre- and post-injection vital signs in any study group.

Injection-Site Examinations at 7 days after injection were provided. Nine (29%) of the subjects in the HPV 16/18 vaccine group reported injection- site reactions: 8 subjects reported a reaction on Study Day 7 and 1 volunteer reported a reaction on Study Day 37. In the HPV 16/18 vaccine group on Study Day 7, two (6.5%) subjects reported tenderness, 1 (3.2%) reported redness, 2

(6.5%) reported swelling and 3 (9.7%) reported other findings (e.g., bruising). On Study Day 37, one (3.2%) HPV 16/18 vaccine volunteer reported redness. No subjects in the HPV 16/18 vaccine group reported any injection-site reactions on Study Day 187. In the aluminum hydroxide control group, the only injection-site reaction reported on Study Day 7 was redness reported by one (3.3%) volunteer.

Pregnancies: Three subjects in the HPV 16/18 vaccine group became pregnant during the study despite using contraception (hormonal contraceptives or condoms with spermicides). All three subjects completed the study.

- Volunteer 201541 received all three injections of study vaccine. She had a positive urine β-HCG test result on 3/19/01 (Study Day 318). She had an uncomplicated pregnancy, completed the study and delivered a full-term healthy child.
- Volunteer 229516 received all three injections of study vaccine. She had a positive urine β-HCG test result on 3/16/01 (Study Day 360). She had an uncomplicated pregnancy and delivered a full-term healthy child.
- The third study (spontaneous abortion) was discussed in the SAE.

HPV DNA: Regardless of HPV DNA status at baseline (positive for either or both HPV-16 and HPV-18), approximately 50% of subjects in either treatment group available for evaluation retained their HPV DNA positive status after 2 or 3 injections. At study day 360, approximately 50% of subjects in either treatment group available for evaluation who were positive for HPV- 16 at baseline were still positive. Only 1 or 2 subjects in either treatment group who were positive at baseline for HPV-18, or HPV-16 and HPV-18 continued to be positive at Study Day 360. There was no evidence that immunization with HPV 16/18 vaccine enhanced clearance of HPV-16 or HPV-18 DNA from cervical specimens.

Table 14A- Study HPV-003: Summary of HPV DNA Status in Subjects Receiving All Prior Injections and Who Were Positive at Baseline Only for HPV-16

HPV DNA Status	HPV 16/18 Vaccine N at baseline =17*	Aluminum Hydorxide Control N at baseline = 15*
Negative for both HPV 16 & HPV 18		
Study Day 60**	6/15 (40.0%)	5/14 (35.7%)
Study Day 210***	5/12 (41.7%)	5.15 (33.3%)
Study Day 360	4/10 (40.0%)	7/13 (53.8%)
Positive for both HPV 16 only		
Study Day 60**	8/15 (53.3%)	7/14 (50.0%)
Study Day 210***	6/12 (50.0%)	7/15 (46.7%)
Study Day 360	4/10 (40.0%)	4/13 (30.8%)
Positive for both HPV 18		
Study Day 60**	0/15 (0.0%)	0/14 (0.0%)
Study Day 210***	1/12 (8.3%)	1/15 (6.7%)
Study Day 360	0/10 (0.0%)	1/13 (7.7%)
Positive for both HPV 16 & HPV 18		
Study Day 60**	1/15 (6.7%)	2/14 (14.3%)
Study Day 210***	0/12 (0.0%)	2/15 (13.3%)
Study Day 360	2/10 (20.0%)	1/13 (7.7%)
Missing Data		
Study Day 60	2 (11.8%)	1 (6.7%)
Study Day 210	5 (29.4%)	0 (0.0%)
Study Day 360	7 (41.2%)	2 (13.3%)

*Denominators exclude subjects with missing data for the specific time point
**Subjects who received 2 doses of study vaccine
***Subjects who received 3 doses of study vaccine
Source: STN 125259/0, CSR 003, Exhibit 18, p. 52

Table 15A- HPV-003: Summary of HPV DNA Status in Subjects Receiving All Prior Injections and Who Were Positive at Baseline Only for HPV-18

HPV DNA Status	HPV 16/18 Vaccine N at baseline =7*	Alum Control N at baseline = 9*
Negative for both HPV 16 & HPV 18		
Study Day 60**	2/4 (50.0)	5/8 (62.5%)
Study Day 210***	4/5 (80%)	1/8 (12.5%)
Study Day 360	2/5 (40.0%)	6/8 (75.0%)
Positive for both HPV 16 only		
Study Day 60**	0/4 (0.0%)	0/8 (0.0%)
Study Day 210***	0/5 (0.0%)	3/8 (37.5%)
Study Day 360	1/5 (20.0%)	1/8 (12.5%)
Positive for both HPV 18		
Study Day 60**	2/4 (50.0%)	3/8 (37.5%)
Study Day 210***	1/5 (20.0%)	3/8 (37.5%
Study Day 360	2/5 (40.0%)	1/8 (12.5%)
Positive for both HPV 16 & HPV 18		
Study Day 60**	0/4 (0.0%)	0/8 (0.0%)
Study Day 210***	0/5 (0.0%)	1/8 (12.5%)
Study Day 360	0/5 (0.0%)	0/8 (0.0%)
Missing Data		
Study Day 60	3 (42.5%)	1 (11.1%)
Study Day 210	2 (28.6%)	1 (11.1%)
Study Day 360	2 (28.6%)	1 (11.1%)

*Denominators exclude subjects with missing data for the specific time point
**Subjects who received 2 doses of study vaccine
***Subjects who received 3 doses of study vaccine
Source: STN 125259/0, CSR 003, Exhibit 19, p. 53

Table 16A- HPV-003: Summary of HPV DNA Status in Subjects Receiving All Prior Injections and Who Were Positive at Baseline for HPV-16 and HPV-18

HPV DNA Status	HPV 16/18 Vaccine N at baseline =7*	Alum Control N at baseline = 9*
Negative for both HPV 16 & HPV 18		
Study Day 60**	1/5 (20.0%)	2/3 (66.6%)
Study Day 210***	2/6 (33.3%)	2/4 (50.0%)
Study Day 360	3/5 (60.0%)	2/4 (50.0%)
Positive for both HPV 16 only		
Study Day 60**	2/5 (40.0%)	1/3 (33.3%)
Study Day 210***	1/6 (16.7%)	1/4 (25.0%)
Study Day 360	1/5 (20.0%)	0/4 (0.0%)
Positive for both HPV 18		
Study Day 60**	0/5 (0.0%)	0/3 (0.0%)
Study Day 210***	1/6 (16.7%)	1/4 (25.0%)
Study Day 360	0/5 (0.0%)	1/4 (25.0%)
Positive for both HPV 16 & HPV 18		
Study Day 60**	2/5 (40.0%)	0/3 (0.0%)
Study Day 210***	2/6 (33.3%)	0/4 (0.0%)
Study Day 360	1/5 (20.0%)	1/4 (25.0%)
Missing Data		
Study Day 60	1 (16.7%)	1 (25.0%)
Study Day 210	0 (0.0%)	0 (0.0%)
Study Day 360	1 (16.7%)	0 (0.0%)

*Denominators exclude subjects with missing data for the specific time point
**Subjects who received 2 doses of study vaccine
***Subjects who received 3 doses of study vaccine
Source: STN 125259/0, CSR 003, Exhibit 20, p. 54

Pap Smear Results: Cervical samples for Pap smear and HPV DNA hybridization (Hybrid Capture II) were obtained at baseline and at Study Days 60, 210 and 360. The majority of women in each group had Pap smear cytology determined to be normal or ASCUS at each time point. In the HPV 16/18 vaccine group, there were 3 (9.7%) and 2 (6.5%) subjects with LSIL at Study Days 60 and 210 respectively, and none that had LSIL at Study Day 360. In the aluminum

hydroxide control group, there were 5 (16.7%), 7 (23.3%) and 2 (6.7%) subjects that had LSIL at Study Days 60, 210 and 360 respectively. In the HPV 16/18 vaccine group there was 1 (3.2%) volunteer with HSIL at Study Day 360. No subjects in the alum control group had HSIL on any cytology sample. The cervical cytology for the majority of subjects in each group was judged to be normal or ASCUS at Study Days 60, 210 and 360.

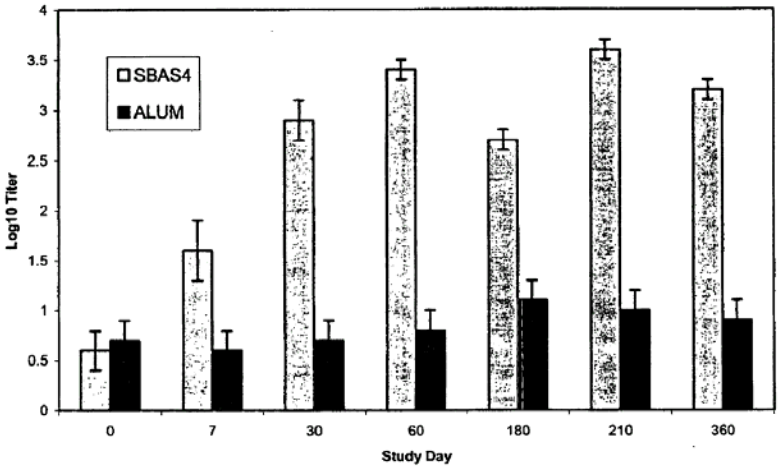
Table 17A- Study HPV-003: Summary of Cytology in Subjects Receiving at Least One Injection

HPV DNA Status	HPV 16/18 Vaccine N=31	Alum Control N=30
Normal		
Study Day 60	18 (58.1%)	15 (50.0%)
Study Day 210	15 (48.4%)	17 (56.7%)
Study Day 360	12 (38.7%)	16 (53.3%)
ASCUS*		
Study Day 60	4 (12.9%)	5 (16.7%)
Study Day 210	5 (16.1%)	3 (10.0%)
Study Day 360	6 (19.4%)	5 (16.7%)
LSIL*		
Study Day 60	3 (9.7%)	5 (16.7%)
Study Day 210	2 (6.5%)	7 (23.3%)
Study Day 360	0 (0.0%)	2 (6.7%)
HSIL*		
Study Day 60	0 (0.0%)	0 (0.0%)
Study Day 210	0 (0.0%)	0 (0.0%)
Study Day 360	1 (3.2%)	0 (0.0%)

Source: STN 125259/0, CSR 003, Exhibit 21, p.55

Immunogenicity Analyses: Among subjects receiving all scheduled injections, the $\log_{10}$ mean titers at each time point after injection 1 were higher in the HPV 16/18 vaccine group for both HPV-16 and HPV-18. Antibody titers increased through Study Day 60, declined until the third injection of study vaccine on Study Day 180 and peaked at Study Day 210. At Study Day 360 the titers were slightly below those seen at Study Day 60 but approximately 1000-fold higher than baseline titers. There were no increases in antigen-specific responses to HPV-16 or HPV-18 in the aluminum hydroxide control group.

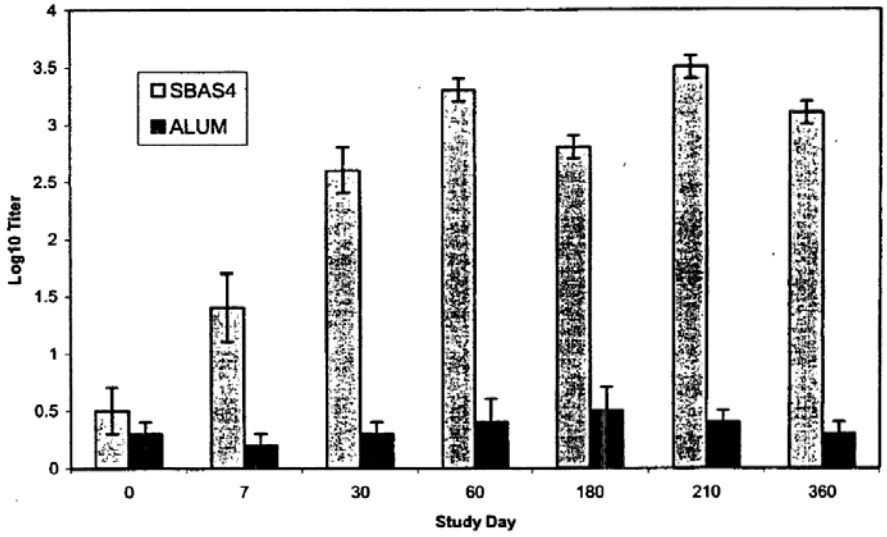
Figure 1A - StudyHPV-003: Log_{10} Mean HPV-16 ELISA Titers Results for Subjects Receiving All Injections



SBAS4=AS04
Source: STN 125259/0, CSR 003, Exhibit 22, p. 56

Similar results were seen for subjects who received all prior injections and for subjects who received at least one injection.

Figure 2A – Study HPV-003: Log_{10} Mean HPV-18 ELISA Titers Results for Subjects Receiving All Injections



SBAS4=AS04
Source: STN 125259/0, CSR 003, Exhibit 23, p. 57

Study HPV-004

Safety was assessed by clinical evaluation of adverse events for 30 days after each injection, evaluation of serious adverse events through 6 months after the third injection and evaluation of laboratory parameters at Study Days 0, 30, and 210. Specific solicited injection-site and general adverse events were collected on diary cards provided at each injection and completed daily by the volunteer for 7 days after each injection, at which time the diary cards were returned to the clinic and an injection site-examination was performed. Specific solicited local injection site (pain, redness, swelling) and general adverse event (headache, GI symptoms, fatigue, rash, pruritus and fever) data were collected on diary cards provided at each injection visit and recorded daily by the volunteer for 7 days. In addition, other adverse events could be reported. Each adverse event was graded and assessment as to relationship to vaccination was provided. Vital signs were assessed prior to and at 30 minutes after each vaccination.

Immune response was evaluated by determination of serum antibody titers (ELISA) to HPV-16 and HPV-18 at Study Days 0, 7, 30, 60, 180, 210, and 360; anti-HPV-16 and anti-HPV-18 neutralizing antibodies at Study Days 0, 60, 210, and 360, and cell-mediated immunity (CMI assays lymphoproliferation and IFN-γ and IL-5 release) at Study Days 0, 60, 210, and 360. Long-term follow-up for immune response through 48 months after the initial injection was also assessed and appears in the annex 3 report.

Efficacy: There were no efficacy endpoints.

Table 18A - Study HPV-004: Treatment and Evaluation - Study Days 0 Through 360

		Study Visit (Study Day)								
	Screen	1 (0)	2 (7)	3 (30)	4 (37)	5 (60)	6 (180)	7 (187)	8 (210)	9 (360)
Screening Medical History	x	x[a]								
Screening Physical Examination	x	x[a]								
Interim Gynecologic History[b]				x		x	x		x	x
Pelvic Examination	x								x	x
Pap Smear	x								x	x
HPV-DNA	x								x	x
Hepatitis C and B, HIV-1	x									
Urinalysis	x									
HPV-16 and -18 ELISA[c]	x	x	x	x		x	x		x	x
HPV-16 and -18 Neutralization		x				x			x	x
HPV-16 and -18 CMI		x				x			x	x
CBC, Differential, Platelets	x	x		x					x	
Chemistry Panel	x									
ALT, AST, Creatinine		x		x					x	
Serum β-HCG	x									
Urine Pregnancy Test		x		x			x		x	
Randomization		x								
Provide Diary Cards		x		x			x			
Return of Diary Cards			x		x			x		
Vital Signs[d]		x		x			x			
Vaccine Injection		x		x			x			
Assessment of Adverse Events, Serious Adverse Events[e]		x[f]	x	x	x	x	x	x	x	x[g]
Site of Injection Examination			x		x			x		

a Update from screening
b Query for information about scheduled or unscheduled gynecologic clinic visits and/or procedures since previous visit
c Includes collection of reserve serum specimen
d Immediately before injection and 30 minutes after injection of study vaccine
e Includes interim medical history and physical examination; adverse events collected for 30 days after each injection; serious adverse events collected from first injection through Study Day 360; adverse events were also assessed by telephone 2 to 3 days after each injection of study vaccine
f On Study Day 0, only adverse events occurring after the injection were noted as adverse events
g Record any new onset, chronic diseases, other medically significant conditions

Source: STN 125259/0: CSR HPV-004, Exhibit One, p. 32

Populations Analyzed: The populations analyzed are shown in Table 19A below. Subjects were analyzed as treated.

Table 19A - Study HPV-004: Populations Analyzed

	Population			
	Randomized	All scheduled injections	All prior injections	At least one injection
Disposition	X			
Safety				X
Cytology				X
DNA Positivity				X
Serum ELISA		X	X	X
Neutralizing antibody		X	X	X
CMI		X	X	
Cervical ELISA		X		

Source: STN 125259/0, CSR 003, Exhibit 4, p. 40

Sample Size Determination: The primary objectives of this Phase II study were to evaluate the safety of three formulations of HPV 16/18 vaccine as well as the immune response by ELISA 30 days after the third vaccine injection (Study Day 210). The sample size of 20 subjects per arm was considered adequate by the sponsor for the purpose of providing safety data. The sample size of 20 subjects per arm was also considered adequate for the purpose of evaluating the Study Day 210 ELISA data, based on the considerations below.

The only statistical analyses of immune response in this study were 95% confidence intervals for differences in mean $\log_{10}$ ELISA titers between treatment groups. The statistical power of such a comparison was estimated using interim data from the separate Phase II study, HPV-005 (MI-CP057). These data showed a difference in mean HPV-16 $\log_{10}$ titers of 0.3 between the 40 mcg HPV 16/18 vaccine with AS04 adjuvant and the 40 mcg HPV 16/18 vaccine with aluminum hydroxide arms after two injections, with a standard deviation of 0.5 logs. Assuming that this difference would increase to 0.5 1ogs after three injections, then a sample size of 17 subjects per arm would have 80% power to detect a difference. Assuming a dropout rate of 15% increases this sample size to 20 subjects per arm.

It is noted in the extended immunogenicity follow-up months 18-48, the neutralization assay was replaced with an inhibitory ELISA.

Results:

Disposition of Subjects: A total of 60 subjects were randomized into the study between 10/3/00 and 12/14/00 sites in the United States. Each site randomized between one and 21 subjects. Volunteer disposition is summarized by treatment group in Table 20A. Between 86% and 90% of the subjects in each treatment group completed the study. Two subjects in the no-adjuvant group were lost to follow-up. Five subjects (two in each of the AS04 and alum groups and 1 in the no-adjuvant group) withdrew consent during the study. In each case, the reason given for withdrawal of consent was either relocation or time constraints.

Table 20A- Study HPV-004: Disposition of Subjects

	HPV 16/18 AS04	HPV 16/18 Alum Control	HPV 16/18 no adjuvant
Number of subjects enrolled	N=20	N=18	N=22
Completed study through study day 360	18 (90%)	16 (89%)	19 (86%)
Discontinued			
Lost to follow up	0 (0.0%)	0 (0.0%)	2 (9.0%)
Withdrawal of consent		2 (11%)	1 (5.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: STN 125259/0, CSR 003, Exhibit 7, p. 44

Protocol Deviations: Two subjects were taking anti-depressants on Day 1. They elected to discontinue these medications and remained in the study.

Safety analyses: Subjects receiving at least one injection were included in the safety analysis.

Immunogenicity and HPV-DNA status analyses: Subjects receiving at least one injection, subjects receiving all scheduled injections, and subjects receiving all prior injections were included in these analyses.

Demographics: The mean age of subjects was 22-25 years. The majority of subjects were white (73-80%), 6-20% were black, and 5-11% were Hispanic.

Safety Analyses: Most of the subjects (91% to 100%) in each study group received all three injections of study vaccine. Three subjects did not receive all three injections; none of these discontinued for adverse events.

Table 21A - Study HPV-004: Number of Subjects with Solicited Adverse Events

Adverse Event	HPV 16/18 AS04 N=20	HPV 16/18 Alum N=18	HPV 16/18 No adjuvant N=22
Number of Subjects with ≥ 1 AE	20 (100%)	17 (94.4%)	22 (100%)
Injection Site ARs			
Pain	20 (100%)	15 (83.3%)	14 (63.6%)
Redness	11 (55.0%)	5 (27.8%)	8 (36.4%)
Swelling	11 (55.0%)	2 (11.1%)	7 (31.8%)
General Reactions			
Headache	13 (65.0%)	7 (38.9%)	14 (63.6%)
GI Symptoms	12 (60.0%)	8 (44.4%)	7 (31.8%)
Fatigue	11 (55.0%)	7 (38.9%)	12 (54.5%)
Rash	1 (5.0%)	0 (0.0%)	3 (13.6%)
Pruritus	6 (30.0%)	2 (11.1%)	3 (13.6%)
Fever*	8 (40.0%)	7 (38.9%)	6 (27.3%)

Fever ≥99.5°F

Source: STN 125259/0, CSR 004, Exhibit 10, p. 47

Pain at the injection site was the most common solicited adverse event and occurred in 20 (100%) subjects in the AS04 group, 15 (83.3%) subjects in the aluminum hydroxide group and 14 (63.6%) subjects in the no-adjuvant group. Redness and swelling at the injection site were reported more often by subjects in the AS04 group (55.0% each) than by subjects in the aluminum hydroxide group (27.8% and 11.1%, respectively) or the no-adjuvant group (36.4% and 31.8%, respectively). More than 30% of subjects in each study group had headache (38.9%-65.0%), gastrointestinal symptoms (31.8%-60.0%) or fatigue (38.9%-55.0%) within 7 days of receiving a vaccine injection.

Data for subjects with solicited adverse events were summarized by intensity grade. Most of the solicited adverse events reported in all 3 groups were of Grade 1 intensity. However, Grade 2 intensity injection-site pain was reported by 40% of subjects in the AS04 group and 50% of subjects in the aluminum hydroxide group. Grade 2 intensity headache was most common in the no-adjuvant group and was reported by 36% of subjects.

More subjects in the AS04 group (45.0%) than in the aluminum hydroxide group (16.7%) or the no-adjuvant group (22.7%) reported one or more Grade 3 solicited adverse events. Pain at the injection site was the most common Grade 3 solicited adverse event in the AS04 group reported by 35% of subjects. Injection-site pain of Grade 3 intensity was reported in <10% of subjects in the other two groups. General reactions of headache, gastrointestinal symptoms and fatigue were the most common Grade 3 solicited adverse events reported by 10%-20% of subjects in the AS04 group, 6%-11% of subjects in the aluminum hydroxide group, and 5%-14% of subjects in the no-adjuvant group.

The number of subjects reporting Grade 3 solicited adverse events is presented by injection number in Table 22A. The percentage of subjects reporting one or more Grade 3 solicited adverse events increased from 15% after the first injection to 35% after the third injection in the AS04 group. In contrast, fewer subjects receiving either the aluminum hydroxide or no-adjuvant formulations reported a Grade 3 solicited adverse event after the second and third injections than after the first injection.

Table 22A - Study HPV-004: Number of Subjects Reporting Solicited Adverse Events by Injection

Adverse Event	HPV 16/18 AS04 N=20	HPV 16/18 Alum N=18	HPV 16/18 No adjuvant N=22
After Injection 1	3 (15.0%)	2 (11.1%)	3 (13.6%)
After Injection 2	4 (20.0%)	1 (5.6%)	1 (4.5%)
After Injection 3	7 (35.0%)	1 (5.6%)	2 (9.1%)

Source: STN 125259/0, CSR 004, Exhibit 12, p. 48

Reviewer's Comment: The data tables were reviewed for the grade 3 solicited adverse events after each injection. These are presented in Table 23A below. Pain at the injection site was the most common Grade 3 adverse reaction experienced in the AS04 treatment group. Subjects in all 3 treatment groups had grade 3 headache after dose 3.

Table 23A- Study HPV-004: Number of Subjects Reporting Solicited Adverse Events by Injection

Adverse Event	HPV 16/18 AS04 N=20	HPV 16/18 Alum N=18	HPV 16/18 No adjuvant N=22
After Injection 1	3 (15.0%) Pain (2) Headache (1)	2 (11.1%) Pain (1) Headache (1) GI (1) Fatigue (1) Fever (1)	3 (13.6%) Pain (1) GI (1) Fatigue (2)
After Injection 2	4 (20.0%) Pain (2) Headache (1) Fatigue (1)	1 (5.6%) Headache (1) Fatigue (1)	1 (4.5%) Fatigue (1)
After Injection 3	7 (35.0%) Pain (6) Headache (2) GI (2) Fatigue (1)	1 (5.6%) Headache (1)	2 (9.1%) Pain (1) Headache (1)

Source: STN 125259/0, CSR 004, Exhibit 12, p. 48;
Tables 7, 8, and 9, pp. 84-86
A subject may have had more than 1 Grade 3 AE

Solicited adverse events were <3 days on average in duration and generally balanced across treatment groups. (Source: STN 125259/0, CSR 004, Exhibit 15, p. 50, not shown here). For the most part, the durations of solicited adverse events in each study group were similar after each injection of study vaccine. No injection-site reaction persisted beyond 6 days in the AS04 or alum groups; only 1 volunteer in the no-adjuvant group had swelling or redness at the injection site lasting more than 6 days. (Source: STN 125259/0, CSR 004, Table 17, p. 94-96, not shown here).
Reviewer's Comment: From review of the table for duration of adverse reaction by injection number, there was no consistent difference among the treatment groups.

Unsolicited adverse events were also collected through 30 days after each vaccine injection.

Table 24A – Study HPV-004: Summary of Unsolicited Adverse Events Reported by More than One Volunteer in any Treatment Group

	HPV 16/18 AS04 N=20	HPV 16/18 Alum N=18	HPV 16/18 No adjuvant N=22
Total # of AEs	32	30	51
Number of Subjects with ≥ 1 AE	11 (55.0%)	14 (77.8%)	17 (77.3%)
Body as whole	5 (25.0%)	6 (33.3%)	12 (54.5%)
Cardiovascular System	1 (5.0%)	1 (5.6%)	0 (0.0%)
GI System	3 (15.0%)	5 (27.8%)	1 (4.5%)
Endocrine System	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hem and Lymphatic System	0 (0.0%)	0 (0.0%)	1 (4.5%)
Metabolic and Nutritional Disorders	1 (5.0%)	1 (5.6%)	0 (0.0%)
Musculoskeletal	0 (0.0%)	0 (0.0%)	2 (9.1%)
Nervous System	2 (10.0%)	1 (5.6%)	2 (9.1%)
Respiratory System	5 (25.0%)	9 (50.0%)	9 (40.9%)
Skin and Appendages	2 (10.0%)	0 (0.0%)	1 (4.5%)
Special Senses	0 0.0%)	1 (5.6%)	1 (4.5%)
Urogenital System	4 (20.0%)	2 (11.1%)	5 (22.7%)

Source: STN 125259/0, CSR 004, Exhibit 16, p. 51

Unsolicited adverse events were reported by 11 (55%) subjects in the AS04 group, 14 (77.8%) subjects in the aluminum hydroxide group, and 17 (77.3%) subjects in the no-adjuvant group. In general, unsolicited adverse events reported for each body system were balanced for frequency and severity across treatment groups.

The majority of unsolicited adverse events were mild or moderate in severity. There were 5 subjects who reported a total of 6 unsolicited severe adverse events (bacterial infection, migraine, and URI in the AS04 group; accidental injury and asthma [2 events in 1 study] in the no-adjuvant group). None of these events was judged by the investigator to be related to study vaccine.

Deaths and Serious Adverse Events: No deaths occurred in the study. No serious adverse event which resulted in discontinuation of study was reported.

Clinical Laboratory Evaluation: One volunteer (# 0431617) in the AS04 group had a transiently elevated SGOT (50 IU/L) on Study Day 30 that was not considered to be clinically significant. None of the changes in hematology parameters were judged to be clinically significant. (Source: STN 125259/, CSR 004, Tables 33 and 34, pp. 128-131, not shown here).
Reviewer's Comment: The vast majority of lab values were graded as grade 0 in all groups (no abnormality).

Vital Signs: Vital signs (temperature, pulse, respiration rate, systolic blood pressure, and diastolic blood pressure) were taken on Study Days 0, 30, and 180 at pre-injection and 30 minutes post- injection. Vital signs were similar across study groups at each time point. There was no clinically meaningful difference between pre- and post-injection vital signs in any study group.

Injection-Site Examinations at 7 days after injection were provided. None of the subjects in the AS04 group were found to have injection-site reactions on Study Days 7, 37, or 187. In the aluminum hydroxide group, redness was noted in one volunteer on Study Day 7, and tenderness and swelling were each seen once on Study Day 187. In the no-adjuvant group, bruising was seen in one volunteer on Study Days 7 and 187, and swelling was found in one volunteer on Study Day 187.

Pap Smears: Nearly all women in each group had normal Pap smear cytology on Study Days 210 and 360. In the AS04 group, one (5.0%) subject had atypical squamous cells of undetermined significance (ASCUS). In the aluminum hydroxide group, 1 (5.6%) subject had ASCUS at Study Day 360, 3 (16.7%) had low-grade squamous intraepithelial lesion (LSIL) on Study Day 210 and 1 (5.6%) had LSIL on Study Day 360. In the no-adjuvant group, 3 (13.6%) subject had ASCUS at Study Day 210.
Reviewer's Comment: Pap tests are < 100% sensitive as to ascertainment of HPV related disease.

HPV DNA: A summary of the HPV DNA hybridization results at Study Days 210 and 360 in subjects who received at least one injection of study vaccine is presented. Samples were screened by DNA hybridization using Probe B, (detects high-risk HPV types 16/18/31/33/35/39/45/51/52/56/58/59/68). Those that were positive by Probe B were further tested by DNA hybridization using probes specific for HPV-16 and HPV-18. The majority of women were negative for HPV-16 or 18 DNA by PCR at Study Days 210 and 360. In the AS04 group, 2 (10.0%) subjects were Probe B positive at Study Day 210 and 4 (20.0%) were Probe B positive at Study Day 360, One of these subjects was positive for HPV-18 at Study Day 360. In the alum group, 2 (11.1%) subjects were Probe B positive at Study Day 210 and were also positive for both HPV-16 and 18. Three (16.7%) subjects were Probe B positive at Study Day 360: one who was positive for only HPV-16 and another who was positive for only HPV-18. In the no-adjuvant group, 1 (4.5%) volunteer was Probe B positive at Study Day 210 but none positive for either HPV-16 or 18. Two (9.1%) subjects were Probe B positive at Study Day 360; but neither was positive for HPV-16 or 18. (Source: STN 125259/0, CSR 004, Exhibit 19, p. 57, not shown here.)

Reviewer's Comment: Subjects who received vaccine possibly developed an infection with a non-vaccine HPV type.

Pregnancies: Four subjects (2 in the aluminum hydroxide group and 2 in the no-adjuvant group) became pregnant during the study. None of the subjects had SAEs. All four women had uncomplicated pregnancies and each delivered a full term healthy child. Narratives for the four subjects are provided below.

- **Subject 221603** in the aluminum hydroxide group received the first injection of study vaccine. She had a positive urine β-HCG pregnancy test on Study Day 30 and did not receive the next two injections of study vaccine. The subject delivered a healthy baby on -b(6)--- and completed the study.
- **Subject 363602** in the aluminum hydroxide group received all 3 injections of study vaccine. She had a positive β-HCG urine pregnancy test on Study Day 210. The subject completed the study and delivered a healthy baby boy on -b(6)-.
- **Subject 363608** in the no-adjuvant group received all 3 injections of study vaccine. Approximately 4 months (8/9/01) after receiving the third dose of study vaccine she had a positive urine pregnancy test. The subject completed the study and delivered a healthy baby boy on -b(6)-.
- **Subject 431620** in the no-adjuvant group received the first two injections of study vaccine. She had a positive β-HCG urine pregnancy test on Study Day 180 and did not receive the third injection of study vaccine. The subject completed the study and delivered a healthy baby on -b(6)-.

Immunogenicity Analyses:
The **primary immunogenicity endpoints** were HPV-16 and HPV-18 serum ELISA titers at Study Day 210 in each treatment group. Exploratory evaluations of the corresponding 95% confidence interval around the differences in the mean comparisons suggested that the Study Day 210 $\log_{10}$ mean ELISA titer to HPV-16 and HPV 18 in the AS04 group was higher than that in either the alum or no-adjuvant group. This is shown in Table 25A below.

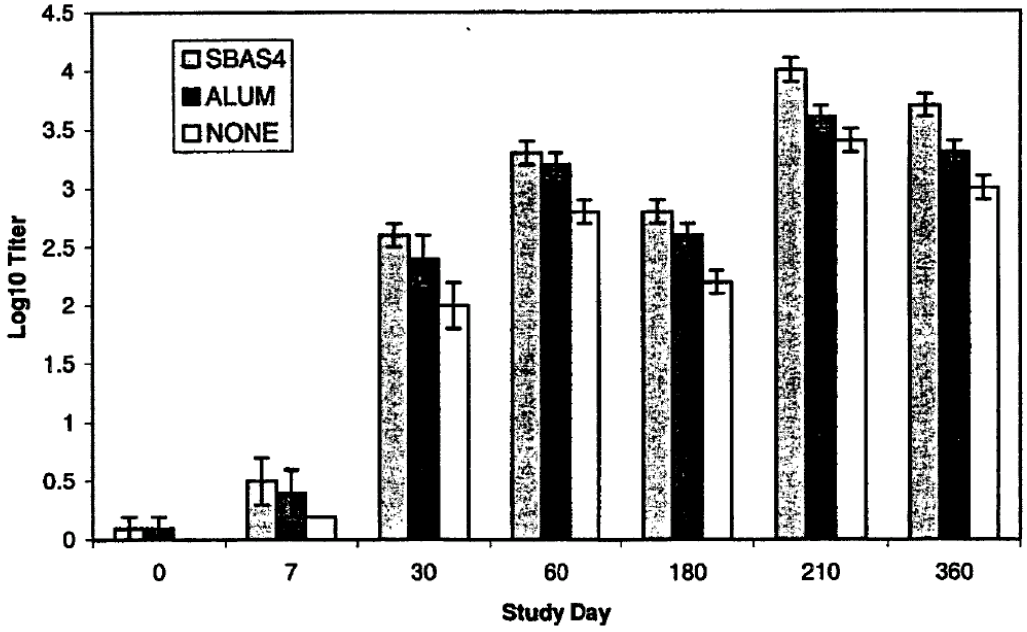
Table 25A- Study HPV-004: ELISA titers to HPV 16 and HPV 18 at Study Day 210 in Subjects Who Received All Scheduled Vaccinations

	HPV 16			HPV 18		
Statistic	AS04	Aluminum Hydroxide	No adjuvant	AS04	Aluminum Hydroxide	No adjuvant
N	19	17	20	19	17	20
Geometric mean	11199	4076	2488	4794	1960	1305
Log 10 mean (SE)	4.0 (0.1)	3.6 (0.1)	3.4 (0.1)	3.7 (0.1)	3.3 (0.1)	3.1 (0.1)
Log 10 95% CI	3.9, 4.2	3.4, 3.8	3.3, 3.5	3.5, 3.8	3.1, 3.5	2.9, 3.3

*In computation of means, < LOQ were set to1.
Source: STN 125126/0, CSR 004, Exhibit 20, p. 59

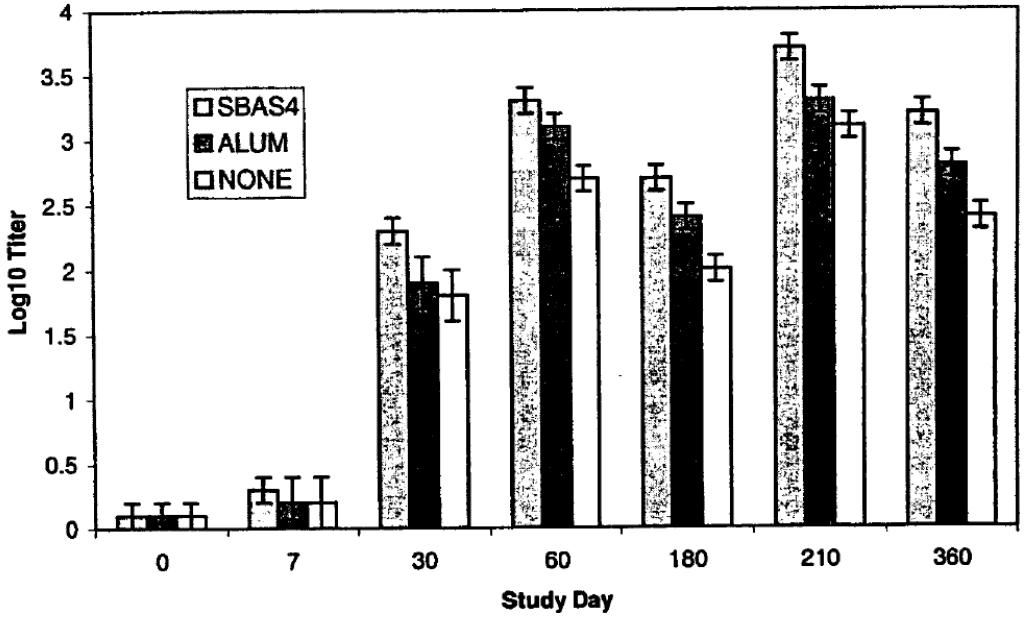
The ELISA results show that all subjects who received at least two doses of study vaccine seroconverted. In general, antibody titers increased through Study Day 60 and then declined until the third injection of study vaccine was received on Study Day 180. After the third injection, titers peaked at Study Day 210 and then declined. At Study Day 360, HPV-16 titers and HPV-18 titers remained elevated, at approximately 1000-fold higher than baseline levels. Among subjects receiving all scheduled injections, $\log_{10}$ mean titers at each time point tested were highest in the AS04 group for both HPV-16 and HPV-18, and higher in the aluminum hydroxide group than in the no- adjuvant group.

Figure 3A – Study HPV-004: Log_{10} HPV-16 ELISA Titers (+/- SE) for Subjects Receiving All Scheduled Injections



SBAS4=AS04
Source: STN 125259/0, CSR 004, Exhibit 21, p. 60

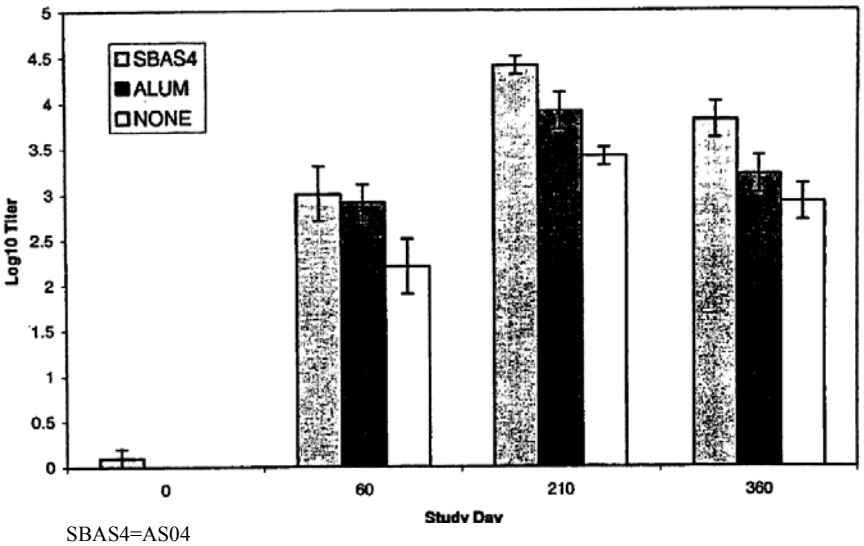
Figure 4A – Study HPV-004: Log_{10} HPV-18 ELISA Titers (+/- SE) for Subjects Receiving All Scheduled Injections



SBAS4=AS04
Source: STN 125259/0, CSR 004, Exhibit 22, p. 61

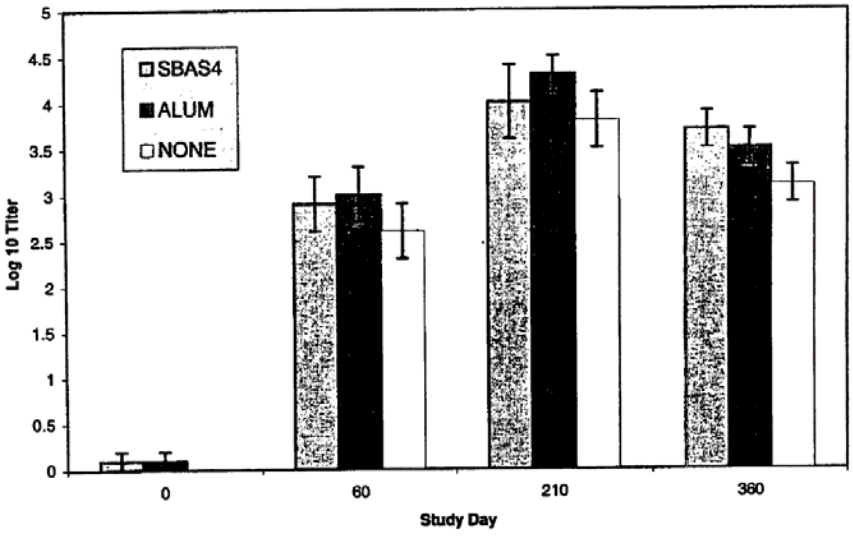
Serum Neutralizing Antibody Titers to HPV 16 and HPV 18: Peak neutralizing antibody log_{10} mean titers of 3.4 to 4.4 were observed on Study Day 210, and titers decreased but remained approximately 1000-fold elevated above pre- vaccination levels at Study Day 360. There was a trend for highest neutralizing responses to HPV-16 in the AS04 group at Study Days 210 and 360, whereas neutralizing responses to HPV-18 appeared similar at these time points in the AS04 and aluminum hydroxide groups. The lowest neutralizing antibody responses to HPV-16 and to HPV-18 at all time points were seen in the no- adjuvant group. See Figures 5A and 6A below.

Figure 5A- Study HPV-004: Log_{10} HPV 16 Neutralizing Titers (+/- SE) in Subjects Who Received All Three Injections



SBAS4=AS04
Source: STN 125259/0, CSR 004, Exhibit 23, p. 62

Figure 6A– Study HPV-004: Log_{10} HPV 18 Neutralizing Titers (+/- SE) in Subjects Who Received All Three Injections



SBAS4=AS04
Source: STN 125259/0, CSR 004, Exhibit 24, p. 63

Table 26A- Study HPV-004: Serum Neutralization Titers to HPV 16 and HPV 18 at Study Day 210 in Subjects Who Received All Scheduled Vaccinations

	HPV 16			HPV 18		
Statistic*	AS04	Aluminum hydroxide	No adjuvant	AS04	Aluminum hydroxide	No adjuvant
N	19	17	20	19	17	20
Geometric mean	26367	8733	2512	10000	19684	5623
Log 10 mean (SE)	4.4 (0.1)	3.9 (0.2)	3.4 (0.1)	4.0 (0.4)	4.3 (0.2)	3.8 (0.3)
Log 10 95% CI	4.2, 4.7	3.6, 4.3	3.1, 3.7	3.3, 4.7	3.9, 4.7	3.2, 4.3

*In computation of means, < LOQ were set to1.
Source: STN 125259/0, CSR 004, Exhibit 25, p. 63

Cell Mediated Immunity: Peripheral blood lymphocytes were collected from a subset of subjects on Study Days 0, 60, 210, and 360 for determination of CMI. Lymphoproliferative response and IFN-γ and IL-5 secretion following in vitro stimulation with purified HPV-16 and HPV-18 VLP antigen at concentrations of 10.0, 1.0, and 0.1 mcg/mL were evaluated.

- **Lymphoproliferative Response:** Proliferative responses were at background level prior to vaccination and in each study group increased 2- to 10-fold above baseline at 30 days after the second vaccination (Study Day 60). The third vaccination further boosted proliferative responses at Study Day 210. Antigen-specific cellular responses persisted for at least 6 months after the third vaccination (Study Day 360). Overall, the proliferative responses to HPV-16 and HPV-18 were greater in the AS04 and aluminum hydroxide groups compared with the no-adjuvant group. (Source: STN 125259/0, CSR 004, Exhibit 26, p. 65, not shown here)
- **IFN-γ Release**: Mean IFN-γ release were increased at 30 days after the second vaccination (Study Day 60) and were further boosted after the third vaccination. IFN-γ responses remained elevated at 6 months after the third vaccination (Study Day 360). A comparison of IFN-γ responses among the three treatment groups at Study Days 210 and 360 suggested that the magnitude of IFN-γ release after in vitro stimulation with HPV-16 and HPV- 18 was greater in the AS04 and aluminum hydroxide groups than in the no-adjuvant group. The largest increase in mean IFN-γ release from baseline after stimulation with HPV-16 or HPV-18 was observed in the aluminum hydroxide group. (Source: STN 125259/0, CSR 004, Exhibit 27, p. 66, not shown here)
- **IL-5 Release**: Mean IL-5 concentrations increased after the first two vaccinations, were further boosted by the third vaccination, and then decreased between Study Day 210 and Study Day 360. A comparison of IL-5 responses among the three treatment groups at Study Days 210 and 360 suggested that the magnitude of IL-5 release after in vitro stimulation with HPV-16 and HPV-18 was greater in the AS04 and aluminum hydroxide groups than in the no-adjuvant group. (Source: STN 125259/0, CSR 004, Exhibit 28, p. 67, not shown here)

Study HPV-004, Annex 2 and 3
Demographics of the 38 subjects in the extension study were similar to those in the parent study.

Procedures: Blood for immune response was collected beginning at 18 months (Study Year 1.5) after the primary injection with additional visits at 2, 3, and 4 years. HPV- 16 and HPV- 18 antibody responses were evaluated by specific ELISA and inhibitory ELISA. The inhibitory ELISA in the extension study replaced the neutralizing antibody assay that was used in the parent study. The antibody response to the major neutralizing epitopes of HPV- 16 and HPV- 18 (V5 or J4 epitopes, respectively) was determined using an inhibitory ELISA. Comparisons of performance of these inhibitory ELISAs compared with standard neutralization assays showed Kappa values of 0.89 (95% CI: 0.86 - 0.93) for HPV- 16 and 0.83 (95% CI: 0.79 - 0.88) for HPV-18. For group mean calculations, ELISA values below the limit of detection for HPV- 16 (< 20) and HPV- 18 (< 50) were set to 10 and 25, respectively. Additionally, specific cellular responses

to HPV 16/18 vaccine by lymphoproliferative assay and by IFN-γ and IL- 5 release were assessed.

Serum ELISA to HPV 16 and HPV 18: The analysis in annex 3 used the new ELISA binding assay includes only those subjects that returned for either a Study Year 3 (N= 25) or a Study Year 4 (N= 20) visit. These are designated by and "*" in the tables below. For all 4 years of the study, log_{10} mean HPV- 16 and HPV- 18 ELISA antibody levels were highest in the AS04 group; the lowest log_{10} mean HPV- 16 and HPV- 18 antibody levels were observed in the no adjuvant group. In the post- vaccination Study Years 1.5, 2, 3, and 4, log_{10} mean HPV- 16 and HPV- 18 antibody levels were maintained in the AS04 group at approximately 3.0. Log_{10} mean HPV- 16 and HPV- 18 antibody levels were lower in the aluminum hydroxide and no adjuvant.

Table 27A – Study HPV-004, Annex 2 and Annex 3:
Summary of ELISA Antibody Responses to
HPV 16 Log_{10} Mean (a), EU/mL (Log_{10} 95% CIs)

Study Visit	HPV 16/18 AS04 N=12 (b)	HPV 16/18 Aluminum hydroxide N=10 (b)	HPV 16/18 No adjuvant N=16 (b)
Day 0	0.1 (0.0, 0.4)	0.1 (0.0, 0.4)	0.0 (0.0, 0.0)
Day 7	0.3 (0.0, 0.1)	0.6 (0.0, 1.4)	0.1 (0.0, 0.4)
Day 30	2.7 (2.2, 3.2)	2.4 (1.8, 3.0)	1.9 (1.6, 2.2)
Day 60	3.4 (3.1, 3.7)	3.3 (3.0, 3.6)	2.9 (2.7, 3.0)
Day 180	2.9 (2.5, 3.2)	2.7 (2.4, 3.1)	2.2 (2.0, 2.4)
Day 210	4.0 (3.8, 4.2)	3.6 (3.3, 4.0)	3.4 (3.1, 3.6)
Day 360	3.7 (3.4, 3.9)	3.4 (3.0, 3.9)	2.9 (2.7, 3.1)
Year 1.5	3.4 (3.2, 3.7)	3.2 (2.7, 3.6)	2.6 (2.4, 2.8)
Year 2	3.2 (3.0, 3.5)	2.9 (2.5, 3.3)	2.4 (2.2, 2,6)
Year 3*	3.1 (2.9, 3.3)	2.6 (2.2, 3.1)	2.5 (2.2, 2.7)
Year 4*	3.2 (3.0, 3.4)	2.8 (0.7, 4.9)	2.3 (1.8, 2.7)

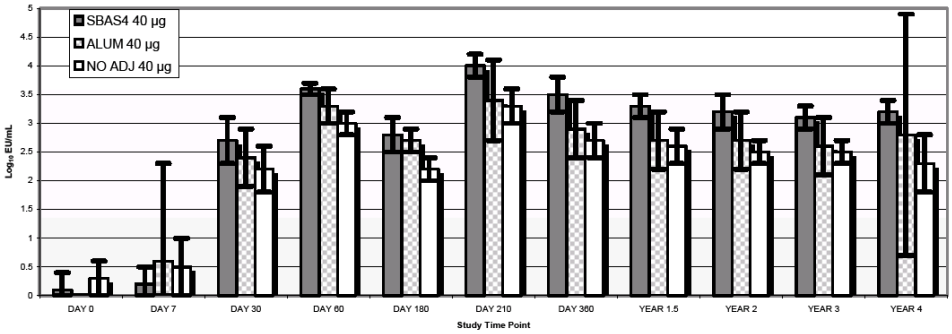
(a): For group mean calculations, values below limit were set to 1.
(b): N represents number of subjects who participated in at least 1 visit in the extension study.
Source: STN 125259/0, CSR 004 annex 2, Exhibit 2, p. 9 and annex 3, Exhibit 3, p. 11
*Years 3 and 4 were assayed with a new binding ELISA assay

Table 28A – Study HPV-004: Summary of ELISA Antibody Responses to HPV 18 Log_{10} Mean (a), EU/mL (Log_{10} 95% CIs)

Study Visit	HPV 16/18 AS04 N=12 (b)	HPV 16/18 Aluminum hydroxide N=10 (b)	HPV 16/18 No adjuvant N=16 (b)
Day 0	0.1 (0.0, 0.3)	0.0 (0.0, 0.0)	0.1 (0.0, 0.3)
Day 7	0.1 (0.0, 0.4)	0.2 (0.0, 0.7)	0.2 (0.0, 0.7)
Day 30	2.4 (2.0, 2.8)	1.7 (1.1, 2.3)	1.8 (1.3, 2.4)
Day 60	3.4 (3.2, 3.7)	3.1 (2.8, 3.4)	2.7 (2.5, 3.0)
Day 180	2.8 (2.4, 3.1)	2.3 (2.0, 2.6)	2.0 (1.7, 2.2)
Day 210	3.7 (3.5, 3.9)	3.3 (3.3, 3.5)	3.0 (2.7, 3.3)
Day 360	3.2 (2.9, 3.5)	2.8 (2.5, 3.1)	2.2 (1.9, 2.6)
Year 1.5	3.0 (2.7, 3.3)	2.6 (2.2, 2.9)	2.1 (1.8, 2.4)
Year 2	2.9 (2.5, 3.2)	2.4 (2.0, 2.8)	1.9 (1.6, 2.2)
Year 3*	2.9 (2.6, 3.2)	2.3 (1.9, 2.6)	2.2 (1.9, 2.6)
Year 4*	2.9 (2.5, 3.2)	2.4 (1.8, 3.0)	2.0 (1.6, 2.4)

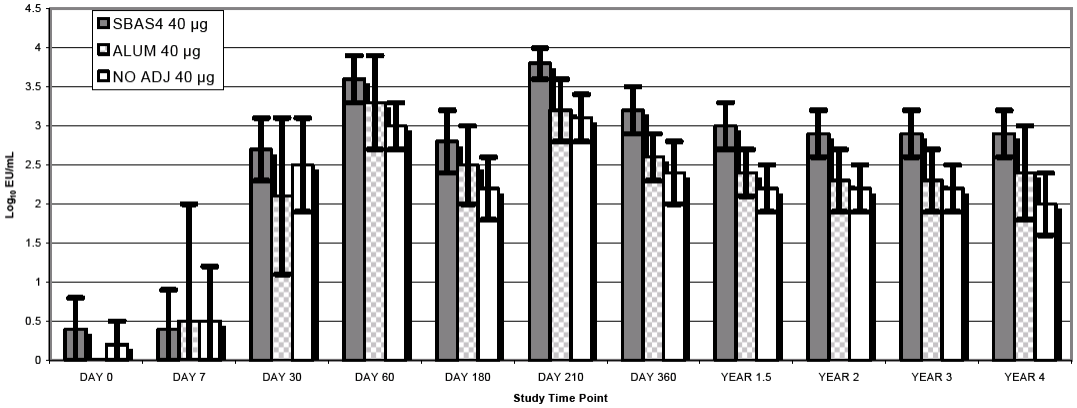
(a): For group mean calculations, values below limit were set to 1.
(b): N represents number of subjects who participated in at least 1 visit in the extension study.
Source: STN 125259/0, CSR 004 annex 2, Exhibit 3, p. 10 and annex 3, Exhibit 3, p. 9
*Years 3 and 4 were assayed with a new binding ELISA assay.

Figure 7A – Study HPV-004: Results of Binding ELISA Log10 Mean (95% Confidence Intervals) (HPV- 16)



SBAS4=AS04
Source: STN 125259/0, CSR 004, Exhibit 4, p. 12

Figure 8A - Study HPV-004: Results of Binding ELISA Log10 Mean (95% Confidence Intervals) (HPV- 18)

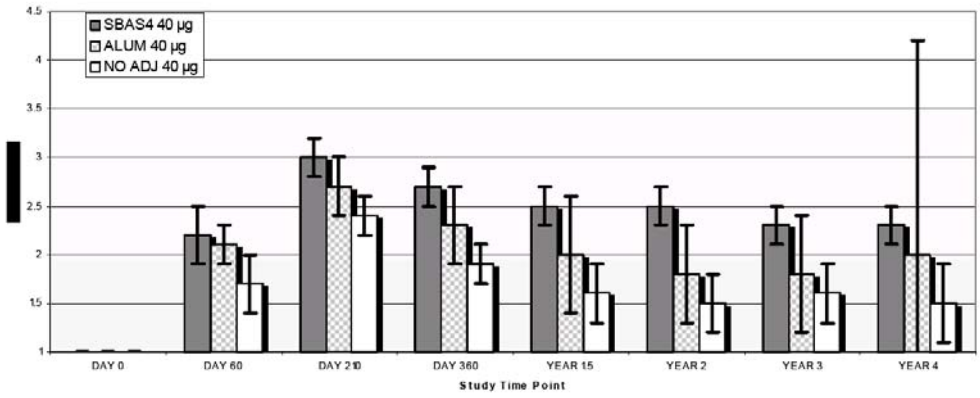


SBAS4=AS04
Source: STN 125259/0, CSR 004, Exhibit 5, p. 12

Serum Inhibitory ELISA Antibody to HPV- 16 and HPV- 18: In each group, peak HPV- 16 and HPV- 18 ELISA inhibitory antibody log_{10} mean titers were observed on Study Day 210 (30 days following the third dose of HPV 16/18 vaccine). There was a trend for highest inhibitory ELISA antibody responses to HPV- 16 and HPV- 18 in the AS04 groups at Study Day 210 (log10 mean titers of 2.9- 3.0). Thereafter, HPV- 16 and HPV- 18 titers decreased for each group with a trend for the higher antibody levels in the AS04 groups.

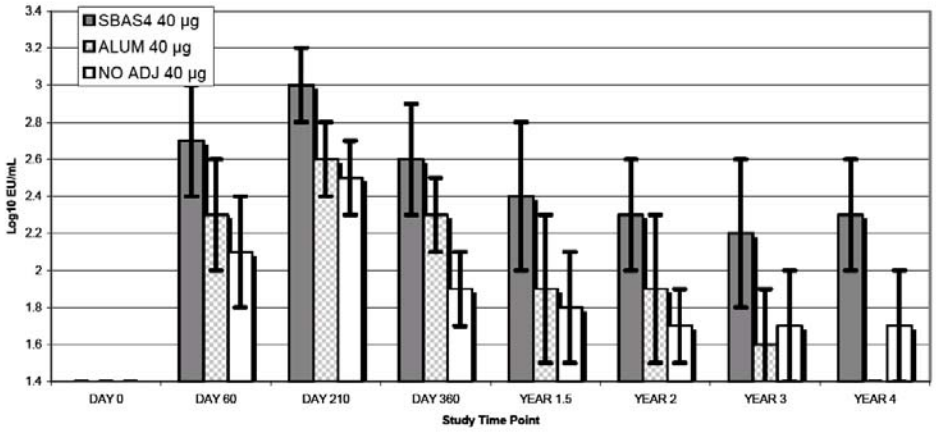
Log_{10} mean HPV- 16 and HPV- 18 antibody levels were highest in the AS04 treatment group at Study Years 3 and 4. At Study Year 3, the AS04 treatment group had log_{10} mean HPV- 16 and HPV- 18 antibody levels of 2.3 and 2.2, respectively, vs. 1.8 and 1.6 for the alum group and 1.6 and 1.7 for the no adjuvant group, respectively. At Study Year 4, the AS04 treatment group had log_{10} mean HPV- 16 and HPV- 18 antibody levels of 2.3 and 2.3, respectively, vs. 2.0 and 1.4 for the alum group and 1.5 and 1.7 for the no adjuvant group, respectively.

Figure 9A – Study HPV-004: Results of Inhibitory ELISA LOG10 Mean (95% Confidence Interval) (HPV- 16)



SBAS4=AS04
Source: STN 125259/0, CSR 004, Exhibit 7, p. 15

Figure 10A – Study HPV-004: Results of Inhibitory ELISA LOG10 Mean (95% Confidence Interval) (HPV- 18)



SBAS4=AS04
Source: STN 125259/0, CSR 004, Exhibit 8, p. 15

At Study Year 2, the proportion of subjects with detectable inhibitory antibody to HPV-16 and HPV-18 was higher for subjects receiving HPV 16/18 with AS04. Over 80% of subjects in this group had detectable inhibitory antibody to HPV- 16 and HPV- 18 at Study Year 2. In Year 2, 68% and 47% of those receiving HPV 16/18 with aluminum hydroxide had HPV- 16 and HPV-18 inhibitory antibody detected, respectively. In Year 2, the lowest response rates were observed in those receiving HPV 16/18 with no adjuvant (33% for HPV 16 and 40% for HPV 18).

Cell Mediated Immunity

- **Lymphoproliferative Responses** were detected at Years 1.5 and 2.0 in all 3 treatment groups. The HPV 16/18 with no adjuvant continued to have the lowest Stimulation Index (SI) as compared to either the AS04 adjuvanted group or the aluminum hydroxide adjuvanted group.
- **IFN-γ and IL-5 release** were measured at Years 1.5 and 2.0. The response was lowest in the group who received the non-adjuvanted group as compared to the AS04 and aluminum hydroxide adjuvanted group. For these two assays, the aluminum hydroxide adjuvanted vaccine elicited a higher response as compared to the AS04 adjuvanted vaccine.

Inclusion criteria included healthy subjects who agreed to use an effective method of birth control beginning 30 days before dose 1 and continuing through 60 days after the final dose; cervical specimen negative for high-risk HPV DNA using Digene Hybrid Capture II HPV test within 21 days of study entry; normal Pap test using Cytyc ThinPrep within 21 days of study entry; no evidence of anogenital HPV lesions and no physical findings suggestive of gynecologic pathogens on pelvic examination within 21 days of study entry; agreed not to receive other experimental therapy or vaccine until 30 days after the last study dose; and written informed consent..

Exclusion criteria include an acute illness or fever (T≥37.5ºC) at study entry; history of significant illness; pregnant or lactating; using immunosuppressive treatment as specified; history of cancer; history of substance abuse within 2 years; specified abnormal lab tests; receipt of immunoglobulin or blood products within 90 days prior to study entry; history of abnormal Pap test (other than single prior report of ASC-US or indeterminate Pap test); positive hepatitis C antibody, hepatitis B surface antigen, or HIV-1 antibody; prior receipt of an HPV vaccine; any treatment of genital warts or HPV related condition within 6 months of randomization; prior

receipt of MPL containing product; receipt of an experimental vaccine prior to study entry within 90 days of study entry (or experimental drug therapy within 30 days or 5 half-lives of experimental drug, whichever is longer.

Vaccination Schedule: Each subject's dose of study vaccine was selected by random assignment. Each subject was to receive an injection of study vaccine on Study Days 0, 30, and 180 by intramuscular injection in the deltoid muscle. Subjects and investigators were blinded as to treatment assignment.

Safety was assessed by clinical evaluation of adverse events for 30 days after each injection, and evaluation of serious adverse events through 30 days after dose 3 (study day 210). Specific solicited injection-site and general adverse events were collected on diary cards provided at each injection and completed daily by the volunteer for 7 days after each injection. Specific solicited 1ocal injection site (pain, redness, swelling) and general adverse event (headache, GI symptoms, fatigue, rash, pruritus and fever) data were collected on diary cards provided at each injection visit and recorded daily by the volunteer for 7 days. In addition, other adverse events could be reported. Each adverse event was graded and assessment as to relationship to vaccination was provided. Vital signs were assessed prior to and at 30 minutes after each vaccination. Laboratory tests including CBC with differential and platelet count, chemistry panel (including AST, ALT and Cr), urinalysis, serum β-HCG, Hepatitis C antibody, hepatitis B surface antigen, and HIV-1 antibody. Abnormal lab tests were graded according to a specified toxicity scale. Urine pregnancy tests were performed in the clinic.

Cytology was assessed by Pap smear at study entry and Study Days 210 and 360.

HPV DNA at screening was determined with the Hybrid Capture II HPV test (Digene) using the high risk probe B (RNA probes for High Risk (HR) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 59, and 68). On Study Days 210 and 360, DNA was collected and tested with HR probe B, as well as specific RNA probes for HPV 16 ad HPV 18 (Digene).

Immune response: Subjects were screened for antibody to HPV-16 and HPV-18 VLPs by using an ELISA assay developed at --b(4)----------. ELISA plates were coated with either HPV-16 or HPV 18 VLPs. Serum from sexually naïve adults and/or children were used as negative controls for HPV 16 or HPV 18 antibody reactivity. A serum dilution of –b(4)-- was used as the cutoff for seropositivity.

- **Quantitative ELISA for Antibody to HPV 16 and HPV 18 VLPs** were used to measure the antibody response to the study vaccine. Serum samples were serially diluted and assayed for the presence of HPV 16 VLP and HPV 18 VLP specific antibodies. Titers of VLP specific antibodies were calculated relative to a positive control (pooled serum sample). The titers were reported as midpoint relative to the standard control curve. These were evaluated at screening, Days 0, 7, 30, 60, 180, 210 and 360.
- **An assay for neutralizing antibody to HPV 16 and HP 18** using an ----------b(4)----------. Neutralization titers were reported as endpoint titers, defined as the highest serum dilution that inhibited the synthesis of the viral transcript. These were evaluated at Days 0, 60, 210, and 360.
- **Cell mediated immune responses** were determined by lymphoproliferation assays and by IFN-γ and IL-5 release using peripheral blood lymphocytes. These were evaluated in a subset of subjects at Days 0, 60, 210, and 360.

- **An assay for antibody in cervical secretions** was used for the evaluation of anti-HPV 16 and anti-HPV 18 antibodies (as described for the quantitative and neutralizing antibody assays above). These were evaluated at screening, Days 210 and 360.

Table 29A – Study HPV-005: Schedule of Evaluations

Procedure	Screen[a]	*Study Visit (Study Day)*								
		1 (0)	*2 (7)*	*3 (30)*	*4 (37)*	*5 (60)*	*6 (180)*	*7 (187)*	*8 (210)*	*9 (360)*
Screening medical history	X	X[b]								
Informed consent signed	X									
Verify eligibility criteria		X								
Screening physical exam	X	X[b]								
Randomize and assign PID		X								
Cervical secretions for Ab[c]	X								X	X
Pelvic exam w/ Pap smear	X								X	X
Cerv. swab for HPV-DNA[d]	X								X	X
Serum for HBsAg, HCV Ab, and HIV-1 Ab	X									
Urinalysis	X									
Serum for HPV-16 and 18 ELISA Antibody titer[e]	X	X	X	X		X	X		X	X
Serum for HPV-16 and 18 Neutralizing Antibody		X				X			X	X
Whole blood for CMI to HPV-16 and 18[c]		X				X			X	X
CBC, Differential, Platelets	X	X[f]		X					X	
Chemistry Panel[g]	X	X[f]		X					X	
Serum β-HCG	X									
Urine β-HCG[h]		X		X			X		X	
Provide diary cards		X		X			X			
Return of diary cards			X		X			X		
Vital Signs[i]		X		X			X			
Vaccine Injection		X		X			X			
Adverse Events[j]		X[k]	X	X	X	X	X	X	X	
Site of Injection Exam			X		X			X		

a Screening laboratory assessments were to be performed within 21 days before study entry.
b Any new findings since screening were to be documented.
c All volunteers at selected sites, approximately 20% of the volunteers in total, had blood cells collected for CMI and cervical secretions collected for antibody determination at these time points.
d A cervical swab was done for HPV-DNA determination using the Digene Hybrid Capture® II HPV test (high-risk types Probe B).
e A reserve serum specimen was also collected.
f Results obtained within 3 days before visit could be used for this visit.
g Screening serum chemistry included AST, ALT, GGT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, glucose, uric acid, calcium, total protein, albumin. Serum chemistry at other visits included ALT, AST, and creatinine only.
h On Study Days 0, 30, and 180, urine pregnancy test was to be negative before injection of study vaccine.
i Vital signs included temperature, blood pressure, pulse rate, and respiratory rate and were taken immediately before and 30 minutes after injection of study vaccine.
j Assessment of adverse events included interim medical history and physical examination. Volunteers were to be called 2 to 3 days after each injection to inquire about local and systemic reactions.
k On Study Day 0, only adverse events occurring after injection of study vaccine were to be recorded.

Source: STN 125259/0, CSR 005, Exhibit 1, p. 32

Primary Endpoint Variables

- **Primary Safety Variables:** These included solicited AEs for 7 days after each injection; unsolicited AEs for 30 days after each injection; SAEs from Day 0 through 30 days after dose 3; lab evaluations (CBC, AST, ALT and Cr) at baseline and 30 days after dose 1 and dose 3.
- **Primary Immunogenicity Variable** included serum antibody (ELISA titers) to HPV 16 and HPV 18 at 30 days after dose 3 in subjects who received HPV 16/18 with AS04.

Secondary Endpoint Variables

- **Secondary immunogenicity variables:** These included serum antibodies (ELISA titers) to HPV 16 ad HPV 18 through 30 days after dose 3; neutralizing antibody titers to HPv 16 amd HPV 18 through 30 days after dose 3; CMI in a subject of subjects through 30 days after dose 3; ELISA antibody response, neutralizing antibody response, and CMI through 360 days after

dose 1; antibody titers (ELISA and neutralizing) in cervical and vaginal secretions in a subset of subjects at 30 and 180 days after dose 3.

- **Other secondary variables:** Safety profiles and immune responses (ELISA titers, neutralizing antibody titers, antibodies in cervical secretions, and CMI) for the two 40 mcg formulations (one with alum and one with AS04).

Populations Analyzed: The populations analyzed are shown in Table 30A. Subjects were analyzed as treated.

Table 30A: Study HPV-005 – Populations Analyzed

	Population			
Summary	Randomized	All Scheduled Injections	All Prior Injections	At Least One Injection
Disposition	X			
Safety				X
Cytology				X
DNA Positivity				X
Serum ELISA		X	X	X
Neutralizing antibody		X	X	X
CMI		X	X	
Cervical ELISA		X		
Cervical neutralizing antibody		X		

Source: STN 125259/0, CSR 005, Exhibit 2, p. 40

Primary Endpoints

Safety

Primary safety endpoints included solicited AEs through 7 days after each dose of study vaccine; unsolicited AEs through 30 days after each injection of study vaccine; and SAEs through 30 days after dose 3 of study vaccine.

Other safety endpoints included injection site findings; toxicity grades and shift from baseline; toxicity grades for labe values at Days 30 and 210; VS (T, P, R, and BP).

No statistical testing was done for safety.

Immunogenicity

Primary immunogenicity endpoint was determination of serum ELISA titers against HPV 16 and HPV 18 at 30 days after dose 3.

Secondary immunogenicity endpoints included serum ELISA titers against HPV 16 and HPV 18 through study day 360; neutralizing antibody titers against HPV 16 and HPV 18 through study day 360; CMI through study day 360; and ELISA titers in cervical and vaginal secretions against HPV 16 and HPV 18 at study days 210 and 360.

Sample Size Determination: Dose comparisons and immune response were based primarily on descriptive statistics rather than statistical interference, clinical judgment was used in the selection of sample size.

Changes in the Conduct of the study

The study was amended as noted below.

Version 2 (1/7/99) included the following changes: history of genital warts and other HPV related conditions was removed as an exclusion criterion; any treatment of genital warts or other HPV-related condition within 6 months of randomization was added as an exclusion criterion; the lot numbers were updated. In addition, rhere were 3 amendment letters to version 2:

- **Amendment letter 1** (11/10/00) added blood collections for a subject of subjects to be used for assay development.

- **Amendment letter 2** (12/18/00) added blood collection for a subset of subjects for evaluation of immune response over a 3 year period after study day 360.
- **Amendment letter 3** (2/21/01) provided notification of new Medical Monitor.

Version 3 (9/4/02) included the following changes: for the extension years 2 through 4, the neutralization assay was replaced with an inhibitory ELISA; another new Medical Monitor was names; visit windows of +/-28 days were added to Years 2, 3, and 4 visits; of the events immediately reportable to --b(4)----- Investigational Drug Safety through study day 360, only withdrawals of consent were to be reported during Years 2, 3, and 4; and any volunteer with an abnormal Pap test at any time through Day 360 was referred to her own physician for follow-up care during Years 2, 3, and 4/

Changed in Planned Analysis: No changes were made to the planned analysis after the blind was broken. Interim analyses of immunogenicity data were performed by ---b(4)--------- biostatistician for the purpose of planning future studies. Tabular summaries were produced that contained data that were unblinded for study groups but blinded for individual subjects. No statistical adjustments were made because of the interim analyses.

Results

Disposition of Subjects: A total of 210 subjects were entered into the study between 10/29/99 and 5/1/00 at 25 sites in the US. Each site randomized between 2 and 32 subjects. (Source: STN 125259/0, CSR 005, Exhibit 3, p. 44, not shown here).

Subjects disposition is shown in Table 31A. Most of the subjects in each study group (78% to 92%) completed the study. Of the 35 subjects who discontinued from the study, 23 were lost to follow-up and 12 withdrew consent for the following reasons: 8 moved, 2 could not make the study visits, 1 had time constraints, and 1 refused to complete the study according to protocol. One volunteer who withdrew consent did so before receiving any study vaccine.

Table 31A – Study HPV-005: Disposition of Subjects

	12 mcg HPV 16/18 AS04	40 mcg HPV/18 AS04	120 mcg HPV 16/18 AS04	40 mcg HPV 16/18 aluminum hydroxide
Number of subjects enrolled	60	64	59	27
Completed study through study day 360	55 (92%)	50 (78%)	48 (81%)	22 (81%)
Discontinued	5 (8%)	14 (22%)	11 (19%)	5 (19%)
Lost to follow up	4 (7%)	9 (14%)	6 (10%)	4 (15%)
Withdrawal of consent	1 (2%)	5 (8%)	5 (8%)	1 (4%)

Source: STN 125259/0, CSR 005, Exhibit 4, p. 45

Protocol Deviations: Three subjects who enrolled in the study did not meet entry criteria.

- **Subject 176015** in the 40 mcg AS04 group had a history of 2 abnormal Pap tests (ASCUS), but was granted an exception by ---b(4)-------- because the investigator felt the presence of ASCUS was related to an IUD.
- **Subject 185001** in the 12 mcg AS04 group did not have a BUN at screening.
- **Subjects 430001** in the 12 mcg AS04 group was seropositive by ELISA within 21 days of study entry. In addition, she had a positive HR DNA Probe B within 21 days of study entry.

Errors

- Volunteer 170001 in the 12 mcg AS04 group received 2 doses of study vaccine before all screening lab tests were performed. The hepatitis virus result was not obtained until study day 60, at which time the test result was negative.

- One **randomization error** occurred during the study. Subject 431018 was assigned to the 40 mcg AS04 group in error. She should have been assigned to the 12 mcg AS04 group. She was included in tables as treated.
- One **dosing error** occurred during the study. Subject 171002 in the 120 mcg AS04 group received the incorrect study vaccine at study day 180 (alum alone). This subject was analyzed as randomized.
- Seven subjects received **excluded vaccinations** during the study.
  - --b(4)---------approved administration of typhoid vaccine for subjects 429012 in the 120 mcg AS04 group who required it for her job.
  - 3 subject in the 40 mcg AS04 group (176001, 187029, and 431012) and 1 subject in the 120 mcg AS04 group (431011) received hepatitis B vaccine during the study. None of the vaccines was received within 15 days of administration of study vaccine.
  - Subject 428012 in the 12 mcg AS04 group received a tetanus booster after a dog bite 12 days before dose 1 study vaccine.
  - Subject 429019 in the 12 mcg AS04 group had an influenza vaccine 20 days after receipt of dose 3 of study vaccine.

Datasets Analyzed
Safety analyses were conducted on all subjects who received at least 1 dose of vaccine (N=209). As noted, one subject withdrew prior to receipt of any vaccine.
Immunogenicity analyses were conducted in all subjects who received all scheduled injections, in those who received all prior injections, and in those who received at least one injection.

Demographics: The mean age was 23-24 years of age. Ethnic distribution was as follows: 81-91% of subjects were white, 3-15% were black, 0-7% were Hispanic, and 2-7% were Asian.

Safety Analyses: Most of the subjects (71% to 87%) in each study group received all 3 vaccinations.

Solicited Adverse Events
The numbers of subjects with solicited events are presented in Table 32A.

Table 32A- Study HPV-005: Number of Subjects with Solicited Adverse Events

Adverse Event	12 mcg HPV 16/18 AS04 N=60	40 mcg HPV/18 AS04 N=63	120 mcg HPV 16/18 AS04 N=59	40 mcg HPV 16/18 aluminum hydroxide N=27
Number of Subjects with ≥ 1 AE	59 (98.3%)	61 (96.8%)	59 (100.0%)	26 (96.3%)
Injection Site ARs				
Pain	59 (98.3%)	61 (96.8%)	59 (100.0%)	23 (85.2%)
Redness	32 (53.3%)	29 (46.0%)	28 (47.5%)	7 (25.9%)
Swelling	22 (36.7%)	25 (39.7%)	31 (52.5%)	5 (18.5%)
General Reactions				
Headache	42 (70.0%)	39 (61.9%)	36 (61.0%)	19 (70.4%)
GI Symptoms	25 (41.7%	28 (44.4%)	26 (44.1%)	15 (55.6%)
Fatigue	38 (63.3%)	38 (60.3%)	35 (59.3%)	15 (55.6%)
Rash	3 (5.0%)	3 (4.8%)	1 (1.7%)	0 (0.0%)
Pruritus	12 (20.0%)	11 (17.5%)	12 (20.3%)	8 (29.6%)
Fever*	29 (48.3%)	28 (44.4%)	29 (49.2%)	11 (40.7%)

Fever ≥99.5°F
Source: STN 125259/0, CSR 005, Exhibit 7, p. 49

In the 7 days after injection, most of the subjects in each study group had elicited AEs (96%-100%). Pain at the injection site was the most common solicited AE in the AS04 group (97%-100%). Among the AS04 dosages groups, the rate of injection site reactions was similar for

injection site swelling which occurred in 53% of subjects in the 120 mcg dose group as compared with 37% and 40% in the 12 mcg and 40 mcg dose group. Systemic reactions were reported in similar proportions for all treatment groups. The most common systemic AEs were headache and fatigue. Fever was reported in 40.&% to 49.2% of subjects.
Reviewer's Comment: Injection site AEs were reported by a lower proportion of subjects in the 40 mcg aluminum hydroxide group as compared to any of the AS04 formulation groups. Swelling and redness were noted in 18.5% and 25.9%, respectively, of subjects who received the alum formulation as compared to the proportions of subjects who received the AS04 formulations (36.7% - 52.5%, and 46.0% to 53.3%, respectively).

Data for subjects with solicited AEs were presented by injection number and intensity grade. The frequencies of solicited AEs with Grade 1 and 2 decreased from dose 1 to dose 3 in each treatment group. After dos 1, the frequencies of Grade 1 and 2 events were 78%-83% and 72%-76%, respectively, in the AS04 groups and 82% and 52%, respectively, in the aluminum hydroxide group. After dose 3, the frequencies of Grade 1 and 2 events were 54%-68% and 53%-57% in the AS04 groups, respectively, and 48% and 41% in the aluminum hydroxide group, respectively. The frequency of Grade 3 events decreased from dose 1 to dose 3 in the aluminum hydroxide group (from 30% to 4%) but was similar after each injection in the AS04 group (19%-25%).

The number of injections after which a Grade 3 AE occurred in presented in Table 33A. It is noted that 16.1%-18.1% of injections with any AS04 formulation was followed by Grade 3 pain, as compared to 8.2% in the aluminum hydroxide group. For systemic reactions, the proportions of subjects with Grade 3 systemic solicited events are similar across treatment groups.

Table 33A – Study HPV-005: Number of Injection After Which Grade 3 Solicited Adverse Events Occurred

Adverse Event	12 mcg HPV 16/18 AS04 N=168	40 mcg HPV/18 AS04 N=168	120 mcg HPV 16/18 AS04 N=155	40 mcg HPV 16/18 aluminum hydroxide N=73
# of injections after which a Grade 3 solicited AE occurred	39 (23.2%)	44 (26.2%)	38 (24.5%)	10 (13.5%)
Injection Site Reactions				
Pain	27 (16.1%)	38 (22.6%)	28 (18.8%)	6 (8.2%)
Redness	2 (1.2%)	0 (0.0%)	5 (3.2%)	0 (0.0%)
Swelling	1 (0.6%)	0 (0.0%)	2 (1.3%)	1 (1.4%)
General Reactions				
Headache	9 (5.4%)	2 (1.2%)	9 (5.8%)	2 (2.7%)
GI Symptoms	7 (4.2%)	6 (3.6%)	1 (0.6%)	1 (1.4%)
Fatigue	8 (4.8%)	5 (3.0%)	4 (2.6%)	2 (2.7%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fever*	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)

Source: STN 125259/0, CSR 005, Exhibit 9, p. 52

Solicited AEs were ≤ 4 days on average in duration. The longest mean durations were for pain at the injection site (2.4-3.5 days) and swelling at the injection site (2.3-3.0 days), and the mean duration of these events was shorter in the aluminum hydroxide group than in the AS04 groups. Mean duration for fever was also shorter in the aluminum hydroxide group. There were no apparent dosage effects seen in duration for solicited AEs in the AS04 group. (Source: STN 125259/0, CSR 005, Exhibit 10, p. 53, not shown here). Durations of solicited AEs in each treatment group were similar after each injection of study vaccine. The longest duration of any solicited AE in any group was 7 days (in very few subjects). (Source: STN 125259/0, CSR 005, Table 17, p. 109-111, not shown here).

Reviewer's Comment: From review of the table for duration of AEs by injection number, there was no consistent difference among treatment groups.

Unsolicited adverse events were collected through 30 days after each vaccination.

Table 34A – Study HPV-005: Summary of Unsolicited Adverse Events Reported by More than One Volunteer in any Treatment Group

	12 mcg HPV 16/18 AS04 N=60	40 mcg HPV/18 AS04 N=63	120 mcg HPV 16/18 AS04 N=59	40 mcg HPV 16/18 aluminum hydroxide N=27
Total # of AEs	106	87	95	50
Number of Subjects with ≥ 1 AE	38 (63.6%)	35 (55.6%)	(34 (57.6%)	19 (70.4%)
Body as whole	20 (33.3%)	20 (31.7%)	20 (33.9%)	7 (25.9%)
Cardiovascular System	3 (5.0%)	3 (4.8%)	1 (1.7%)	0 (0.0%)
GI System	3 (5.0%)	7 (11.1%)	7 (11.9%)	3 (11.1%)
Endocrine System	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hem and Lymphatic System	0 (0.0%)	0 (0.0%)	2 (3.4%)	1 (3.7%)
Metabolic and Nutritional Disorders	0 (0.0%)	1 (1.6%)	1 (1.7%)	1 (3.7%)
Musculoskeletal	2 (3.3%)	2 (3.2%)	3 (5.1%)	2 (7.4%)
Nervous System	12 (20.0%)	5 (7.9%)	7 (11.9%)	4 (14.8%)
Respiratory System	14 (23.3%)	15 (23.8%)	15 (25.4%)	7 (25.9%)
Skin and Appendages	4 (6.7%)	5 (7.9%)	3 (5.1%)	1 (3.7%)
Special Senses	2 (3.3%)	3 (4.8%)	4 (6.8%)	2 (7.4%)
Urogenital System	12 (20.0%)	5 (7.9%)	8 (13.6%)	7 (25.9%)

Source: STN 125259/0, CSR 005, Exhibit 11, p. 53

Unsolicited AEs were reported by 55.6%-63.6% of subjects who received AS04 formulations, and by 70.4% in aluminum hydroxide formulation recipients.

The majority (91%) of unsolicited AEs were mild or moderate in intensity. The incidence of severe unsolicited AEs was similar across study groups (8%-12%). Three subjects (2 in the 40 mcg AS04 formulation group and 1 in the 120 mcg AS04 group) had severe headache, 2 subjects (1 in the 12 mcg AS04 group and 1 in the aluminum hydroxide group) had spontaneous abortions assessed as severe, and 2 subjects (1 in the 12 mcg AS04 group and 1 in the aluminum hydroxide group) had severe bacterial infections (each had strep throat).

Deaths: No deaths occurred in the study.

Serious Adverse Events: Five subjects (2 in the 12 mcg AS04 and 3 in the aluminum hydroxide group) had 6 SAEs during the study. One SAE (subject 429013) was considered to be possibly related to study vaccine, and other SAEs were considered not related.

- **Subject 170002 (12 mcg AS04):** This subject had over-stimulated ovaries due to egg donation 5 months after receipt of dose 2 of vaccine. She was hospitalized for 2 days and the events resolved 2 days after discharge from the hospital. The investigator assessed this event as severe and not related to vaccine. The subject received dose 3 of study vaccine and completed the study.
- **Subject 429013 (12 mcg AS04):** This subject received dose 2 vaccine on 5/5/00 after a negative pregnancy test. She had a positive pregnancy test at Day 60 (6/6/00). She was discontinued from the study and referred to her private OB-GYN for care. She was diagnosed with a missed abortion on 6/22/00. On 7/11/00, she underwent a D&C. Two days later she was diagnosed with acute endometriosis due to retained products of conception and was started on oral antibiotics. On -b(6)-, she was hospitalized, and a second D&C was performed. The SAE (spontaneous abortion) was assessed by the investigator as possibly related to study material. The investigator stated that other concomitant medications (alprazolam, fluconazole,

Metabolife) taken during pregnancy might have contributed to the event. The subject completed the study.

- **Subject 200001 (40 mcg alum):** This subject had gastroenteritis 1 month after dose 2. She was hospitalized for 1 day and the event resolved the day of discharge from the hospital. The investigator assessed the event as severe and not related to study vaccine. The volunteer did not receive dose 3 on study day 180 due to a positive pregnancy test. She did complete the study. The volunteer had a healthy baby on -b(6)-.
- **Subject 200009 (40 mcg alum):** This subject had a positive urine β-HCG test on study day 21 (5/19/00) and did not receive dose 2. Following an altercation that occurred 4 months after dose 1 (8/20/00) she stated she had a spontaneous abortion of one of two (twin) fetuses. She was hospitalized for 2 days and recovered from the event. She had a positive pregnancy test on study day 180 (10/29/00) and did not receive dose 3. A healthy baby was born on -b(6)-, 17 days before the due date. There was no documentation of a loss of a twin during this pregnancy. The subject completed the study (late study day 210 visit).
- **Subject 428004 (40 mcg alum):** This subject had 2 episodes of cholecystitis after dose 2 of vaccine. The first episode occurred app. 5 months after the injection and the second dose occurred app. 2 weeks later. Both events required hospitalization (3 days and 2 days, respectively). The investigator assessed both events as moderate and not related to study vaccine. The volunteer had a positive β-HCG result at study day 180 and did not return for additional follow-up.

Adverse Events Resulting in Discontinuation of study vaccine: Three subjects (1 in each 40 mcg AS04, 1 in 120 mcg AS04, and 1 in 40 mcg aluminum hydroxide group) had AEs that resulted in discontinuation of study vaccine.

- **Subject 456007 (40 mcg AS04):** This subject had tachycardia (Pulse113 at 15 minutes) and throat tightness the day of dose 1 that resulted in the sponsor discontinuing medication. It could not be determined whether the event was a mild allergic reaction or a URI. The investigator assessed the event as mild and of probable relationship to study vaccine.
- **Subject 176017 (120 mcg AS04):** This subject first reported redness at the injection site at 8 days after dose 3 of vaccine that resulted in the investigator discontinuing further study vaccinations. The redness lasted for 3 days and was assessed as severe and definitely related to study vaccine.
- **Subject 326004 (40 mcg aluminum hydroxide):** This subject reported fatigue starting 2 days after dose 1, which was given 3/7/00. The fatigue progressed to grade 3 intensity on study days 5 and 6. The site investigator assessed the event as possibly related to study vaccine. The subject was being treated for depression and an eating disorder. After consultation with the medical monitor, the site investigator discontinued further study vaccinations. This symptom resolved 3/25/00.

Clinical Laboratory Evaluations: Ten chemistry values (<1%) collected during the study were abnormal, but most were Grade 1, were transient and resolved. Sixty-two (2%) hematology values were abnormal, the majority were Grade 1-2, and were transient.

Vital Signs: Vital signs (temperature, pulse, respiration rate, systolic blood pressure) were taken on study days 0, 30, and 180 at pre-injection and 30 minutes after injection. VS were similar across study groups at each time point. There were no apparent clinically significant differences pre- and post- vaccination.

Injection Site Examinations at 7 days after each vaccination were summarized. 37%-41% of subjects in each AS04 group ad 11% of subjects in the aluminum hydroxide group experienced

injection site reactions on study days 7, 37, and 187. Swelling was the most common injection site symptom and occurred in 2%-8% of subjects in each of the AS04 groups, and 0-4% in the alum group after each dose. Tenderness and redness occurred only in the AS04 groups, and the frequencies decreased with each injection of study vaccine.

Pap smear results at study days 210 and 360 for subjects who received at least one dose of study vaccine were summarized. On study day 210, 0%-5% of subjects in each study group had an abnormal Pap test. On study day 360, 0%-7% of subjects in each treatment group had abnormal Pap tests. One – 2 additional subjects in the 12 mcg AS04 group, 40 mcg AS04 group, and 40 mcg aluminum hydroxide group had abnormal Pap tests from study days 210 to 360. After day 210, there were no additional subjects in the 120 mcg AS04 group with ASCUS abnormalities and 2 fewer subjects with LSIL abnormalities. At both time points, a slightly greater percentage of subjects had ASCUS than had LSIL. Less than 10% of subjects had abnormal Pap tests (ASCUS or LSIL) on study day 210 or 360.

HPV DNA was collected on study days 210 and 360 from wither cervical cells in the Pap test specimen or from cervical cells in a separate specimen. A small percentage of subjects in the aluminum hydroxide group (0-4%) and AS04 groups (0-8%) were positive for HPV DNA at study day 210 or 360.

Pregnancies: A total of 11 subjects (2, 3, and 1 subjects in the 12, 40, and 120 mcg AS04 groups, respectively, and 5 subjects in the aluminum hydroxide group) became pregnant during the study. Four of these subjects (100001, 100009, 428004, and 429013) were included in the SAE section. Narratives for the remaining 7 subjects (176001, 1810002, 428010, 4300004, 431006, 431022, and 441004) are provided below. All but 1 (Subjects 428004 in the 240 mcg aluminum hydroxide group) of the 11 subjects who became pregnant completed the study.

- **Subject 431022 (12 mcg AS04):** This subject received 3 doses of study vaccine. This subject had a positive β-HCG test on 2/12/01, study day 292 or approximately 100 days after receipt of dose 3. On -b(6)-, she gave birth to a baby with Turner's syndrome. The site reported a positive screen for Turner's during pregnancy. She completed the study day 360 visit on 4/25/01.
- **Subject 176001 (40 mcg AS04):** This subject received 3 doses of vaccine. She had a positive pregnancy test on study day 217, 8/31/00, which was approximately 37 days after dose 3. She underwent an elective abortion on -b(6)- (fetus approximately 6 weeks gestation). She completed the study day 360 visit on 1/9/01.
- **Subject 428010 (40 mcg AS04):** This subject received 3 doses of vaccine and had a negative pregnancy test on study day 210 (9/26/00). Her LMP was mid-December 2000. The subject had a healthy baby on -b(6)-.
- **Subject 430004 (40 mcg AS04):** This subject missed study day 180 and rescheduled for 9/13/00 because of travel. Per ---b(4)--- approval, she had a late study day visit on 11/1/00 (app. 1.5 months late). She had a negative urine β-HCG that day and received dose 3. She had a negative pregnancy test on study day 210. On study day 360, she reported that she was 12 weeks pregnant. She had a healthy baby on -b(6)-.
- **Subject 441004 (120 mcg AS04):** This subject received the first two injections of study vaccine. She had a positive β-HCG on study day 180 and did not receive dose 3. The subject had a healthy baby on -b(6)-.
- **Subject 181002 (40 mcg aluminum hydroxide):** This subject received 2 doses of vaccine. She became pregnant on study day 30 (negative pregnancy test on that day). The subject had a healthy baby on -b(6)-.

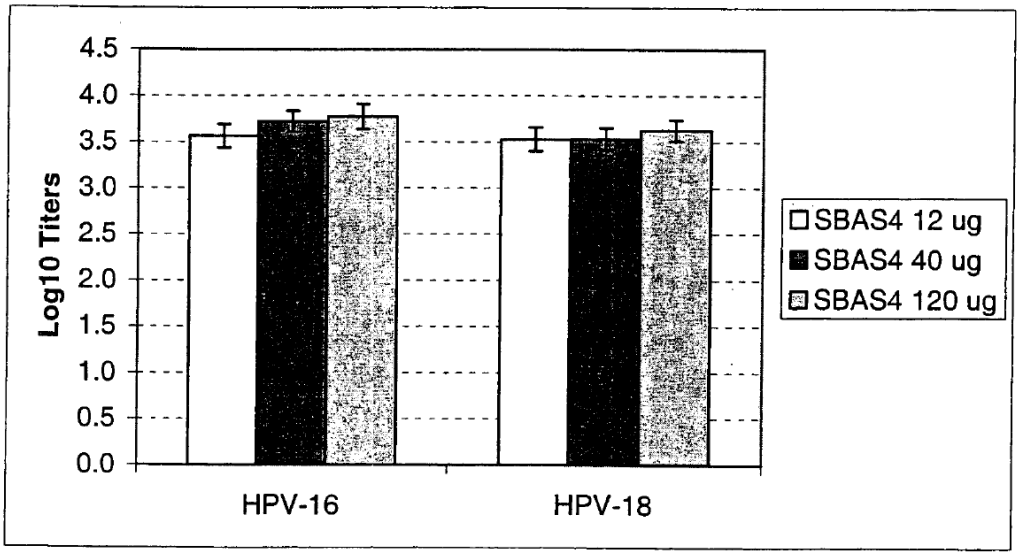
- **Subject 431006 (40 mcg aluminum hydroxide):** The subject received 3 doses of vaccine. She had a positive β-HCG test on study day 210 (8/16/00). She had a premature delivery resulting in neonatal death on -b(6)-. Pregnancy occurred within 30 days of dose 1 study vaccine.

Immunogenicity analyses: Immunogenicity data were analyzed for subjects who received all 3 doses, all prior injections, and at least one injection.

Populations Analyzed: These included subjects who received all doses of vaccine; subjects who received all prior doses of vaccine; and subjects who received at least one dose. At study days 0, 7, and 30, the population of subjects receiving all prior doses was the same as the population receiving at least one dose. At study days 210 and 360, the population of subjects receiving all prior injections was the same as the population of subjects receiving all scheduled vaccinations.

The primary immunogenicity endpoints were HPV 16 and HPV 118 serum ELISA titers at study day 210 in the AS04 groups. Among subjects receiving all scheduled injections, log_{10} mean titers were highest in the 120 mcg AS04 group for both HPV 16 and HPV 18. Log_{10} mean titers were higher in the 40 mcg AS04 group than in the 12 mcg AS04 group for HPV 16, but similar for HPV 18. The corresponding 95% CI in exploratory comparisons indicated there was a trend for a higher log_{10} mean ELISA titer to HPV 16 in the 120 mcg AS04 group as compared with the 12 mcg AS04 group. (Source: STN 125259/0, CSR 005, Table 42, p. 175-177, not shown here).

Figure 11A - Study HPV- 005: Log_{10} Mean ELISA Titers (with Log_{10} 95% CIs) to HPV 16 and HPV 18 at Study Day 210 for Subjects who Received All Scheduled Doses of Vaccine with AS04



SBAS4=AS04
Source: STN 125259/0, CSR 005, Exhibit 12, p. 65

Table 35A - Study HPV-005: ELISA Titers to HPV 16 and HPV 18 at Study Day 210 for Subjects who Received all Scheduled Vaccines with AS04 Adjuvant

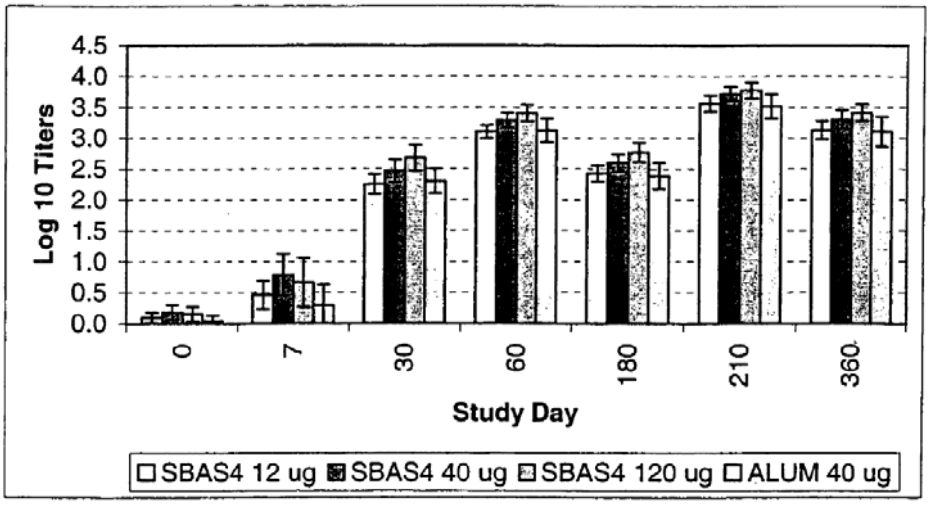
	HPV 16			HPV 18		
Statistic	12 mcg AS04	40 mcg AS04	120mcg AS04	12 mcg AS04	40 mcg AS04	120mcg AS04
N	51	47	42	51	47	42
Geometric mean	3655.7	5248.2	5944.5	3402.6	3443.4	4228.5
Log 10 mean (SE)	3.6 (0.1)	3.7 (0.1)	3.8 (0.1)	3.5 (0.1)	3.5 (0.1)	3.6 (0.1)
Log 10 95% CI	3.4, 3.7	3.6, 3.8	3.6, 3.9	3.4, 3.7	3.4, 3.7	3.5, 4.7

*In computation of means, < LOQ were set to1; Source: STN 125126/0, CSR 005, Exhibit 13, p. 66

Secondary Immunogenicity Analyses

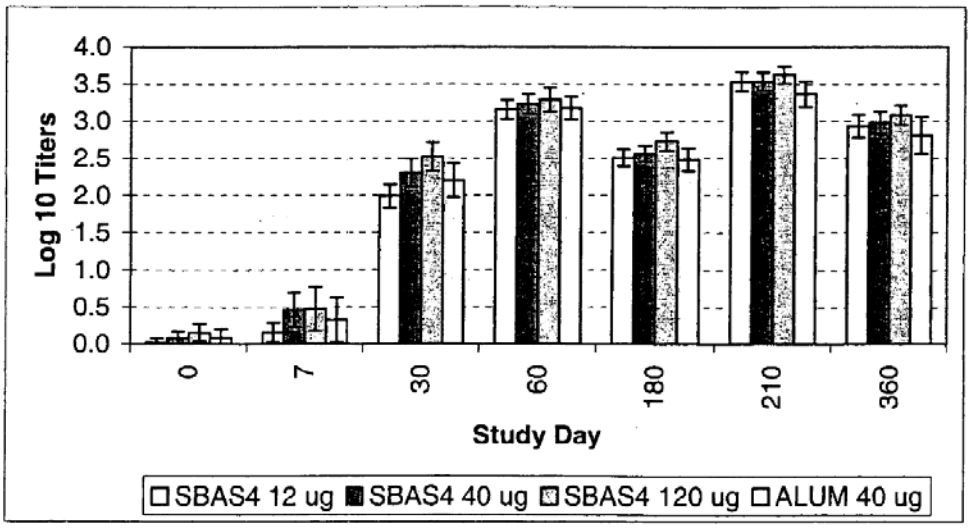
Serum ELISA Titers to HPV 16 and HPV 18: The ELISA results show that all subjects who received at least 2 doses of study vaccine seroconverted. Antibody titers in all study groups increased through study day 60 and then declined until dose 3 was received. After dose 3, titers peaked at study day 210 (log_{10} mean titer ranged from 3.4 – 3.8 across groups for HPV 16 and HPV 18 and then declined.) At study day 360, HPV 16 titers were similar to those seen at study day 60, and HPV 18 titers were slightly lower than those seen at study day 60.

Figure 12A - Study HPV-005: Log_{10} Mean ELISA Titers to HPV 16 (with Log_{10} 95% CIs) to HPV 16 for Subjects who Received All Scheduled Doses and Who Had Samples Collected at Each Analyzable Time Point



SBAS4=AS04
Source: STN 125126/0, CSR 005, Exhibit 14, p. 67

Figure 13A- Study HPV-005: Log_{10} Mean ELISA Titers to HPV 16 (with Log_{10} 95% CIs) To HPV 18 for Subjects who Received All Scheduled Doses and Who Had Samples Collected at Each Analyzable Time Point



SBAS4=AS04
Source: STN 125126/0, CSR 005, Exhibit 15, p. 67

Among subjects who received all scheduled doses of vaccine, log_{10} mean titers at study days 180, 210 and 360 followed a consistent pattern of 120 mcg AS04 ≥ 40 mcg AS04 ≥ 12 mcg AS04 ≥ 40 mcg aluminum hydroxide for both HPV 16 and 18. Exploratory 95% CIs around the differences between the log_{10} mean titers suggested there was a trend for higher ELISA titers to HPV 16 in the 120 mcg AS04 group compared to the 12 mcg AS04 group and 40 mcg aluminum hydroxide group at study days 180, 210 and 360. Similar exploratory analyses suggested that there was a trend for higher ELISA titers to HPV 18 in the 120 mcg AS04 group as compared to the aluminum hydroxide group at each time point and compared to all other groups at study day 180. When comparing the 40 mcg AS04 and 40 mcg alum groups, the log_{10} mean titers were higher in the 40 mcg AS04 group, but no statistical difference was suggested. (Source: STN 125259/0, CSR 005, Table 42, p. 175-177, not shown here).

Table 36A – Study HPV-005: ELISA Titers to HPV 16 and HPV 18 at Study Days 180, 210 and 360 for Subjects who Received all Scheduled Vaccines

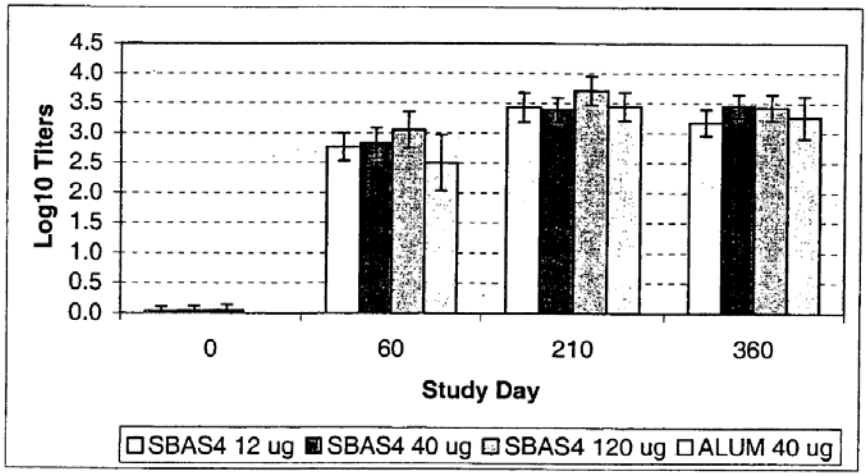
		HPV-16				HPV-18			
Study Day	Statistic*	12 mcg AS04	40 mcg AS04	120mcg AS04	40 mcg aluminum hydroxide	12 mcg AS04	40 mcg AS04	120mcg AS04	40 mcg aluminum hydroxide
180	N	50	48	42	21	50	48	42	21
	log_{10} mean	2.4	2.6	2.8	2.4	2.5	2.6	2.7	2.5
210	N	51	47	42	20	51	47	42	20
	log_{10} mean	3.6	3.7	3.8	3.5	3.5	3,5	3.6	3.4
360	N	50	46	42	19	50	46	42	19
	log_{10} mean	3.1	3.3	3.4	3.1	2.9	3.0	3.1	2.8

*In computation of means, < LOQ were set to1; Source: STN 125126/0, CSR 005, Exhibit 16, p. 68

erum Neutralizing Antibody Titers to HPV 16 and HPV 18

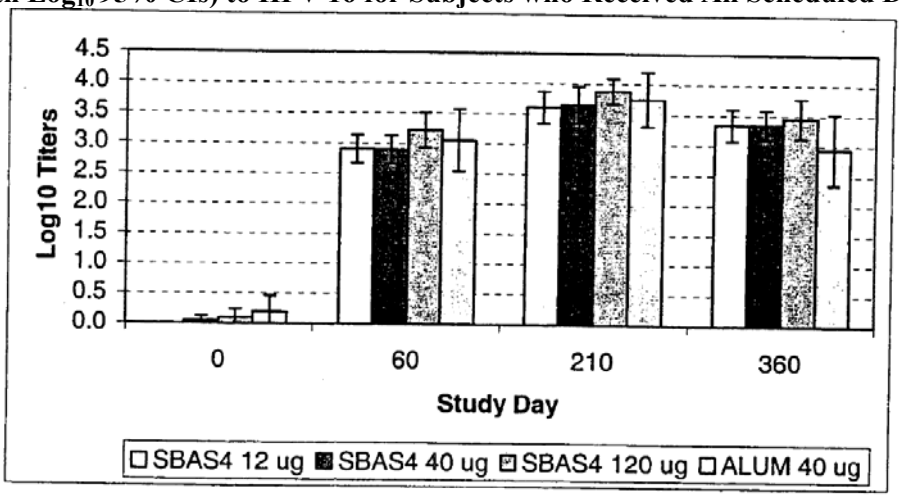
With one exception, the 120 mcg AS04 group had the highest log_{10} mean titers at study days 60, 210, and 360 for both HPV 16 and HPV 18. When comparing the 40 mcg AS04 group and 40 mcg aluminum hydroxide group, there was no obvious trend favoring either group.

Figure 14A- Study HPV-005: Log_{10} Mean Neutralizing Antibody Titers to HPV 16 (with Log_{10} 95% CIs) to HPV 16 for Subjects who Received All Scheduled Doses



SBAS4=AS04
Source: STN 125126/0, CSR 005, Exhibit 17, p. 69

Figure 15A – Study HPV-005: Log_{10} Mean Neutralizing Antibody Titers to HPV 18 (with Log_{10} 95% CIs) to HPV 16 for Subjects who Received All Scheduled Doses



SBAS4=AS04
Source: STN 125126/0, CSR 005, Exhibit 18, p. 70

Table 37A – Study HPV-005: Neutralizing Antibody Titers to HPV 16 and HPV 18 at Study Days 60, 210 and 360 for Subjects who Received all Scheduled Vaccines

		HPV-16				HPV-18			
Study Day	Statistic*	12 mcg AS04	40 mcg AS04	120mcg AS04	40 mcg aluminum hydroxide	12 mcg AS04	40 mcg AS04	120mcg AS04	40 mcg aluminum hydroxide
60	N	51	47	42	20	51	47	42	20
	log_{10} mean	2.8	2.8	3.0	2.5	2.9	2.9	3.2	3.1
210	N	51	46	42	20	51	46	42	20
	log_{10} mean	3.4	3.4	3.7	3.5	3.6	3.7	3.9	3.8
360	N	50	46	42	19	50	46	42	19
	log_{10} mean	3.2	3.5	3.4	3.3	3.3	3.3	3.5	2.9

*In computation of means, < LOQ were set to1; Source: STN 125126/0, CSR 005, Exhibit 19, p. 69

Cell Mediated Immune Responses to HPV 16 and HPV 18: Peripheral blood lymphocytes were collected from a subset of subjects on study days 0, 60, 210, and 360 for determination of CMI. Subjects enrolled at specific sites (326, 430, 431 440, and 456) for a total of 51 subjects were included in the subset. Lymphoproliferative response and IFN-γ and IL-5 secretion following in vitro stimulation with purified HPV-16 and HPV-18 VLP antigen at concentrations of 10.0, 1.0, and 0.1 mcg/mL were evaluated.

- **Lymphoproliferative Response:** Proliferative responses were at background level before vaccination and in each study group increased 3- to 10-fold above baseline at 30 days after dose 2 (study day 60). Dose 3 further boosted proliferative responses in most groups at Study Day 210, especially in the 40 mcg alum group. Antigen specific cellular responses persisted at least 6 months after dose 3 (study day 360). There was no clear evidence of a dose response among the AS04 groups. A comparison of lymphproliferative responses for the 40 mcg AS04 and 40 mcg aluminum hydroxide groups at study days 210 and 360 showed there were not consistent differences between formulations in increase in SI from baseline. After 2 doses (study day 60), it appeared that the 40 mcg AS04 formulation elicited higher SI with HPV 18 and HPV 16 than with the 40 mcg alum formulation. After 3 doses, the SI were similar for both treatment groups. (Source: STN 125259/0, CSR 005, Exhibit 20, p. 72, not shown here).
- **IFN-γ Release:** Mean IFN-γ concentration were markedly increase at 30 days after dose 2 (study day 60) and were for the most part boosted after dose 3. IFN-γ concentrations remained elevated at 6 months after dose 3 (study day 360). No consistent dose effect was demonstrated with AS04. The IFN-γ elicited responses for the 40 mcg AS04 and 40m mcg alum groups at study days 210 and 360 were similar for both HPV 16 and HPV 18. (Source: STN 125259/0, CSR 005, Exhibit 21, p. 73, not shown here).

Reviewer's Comment: A small number of subjects were included in these comparisons, so it is difficult to interpret the results.

- **IL-5 Release:** Mean IL-5 concentrations increased markedly after the first 2 doses of vaccine, were further boosted by dose 3, and for the most part, continued to increase between study days 210 and 360. In most study groups at most time points, IL-5 responses to HPV 18 were greater than those to HPV-16. In comparing the IL-5 responses for the 40 mcg AS04 group and the 40 mcg aluminum hydroxide group at study days 210 and 360, increases from baseline in mean IL-5 concentration after in vitro stimulation with HPV 16 or HPV 18 appeared to be greater in the alum group at both time points. (Source: STN 125259/0, CSR 005, Exhibit 22, p. 74, not shown here).

Results

At Study Day 210, after 3 doses of study vaccine, HPV-16 VLP specific activity in CVS was detected in 4/7 (57.1%), 9/10 (90.0%), 8/8 (100.0%) and 4/4 (100.0%) subjects in the AS04 12-µg, 40-µg, 120-µg and aluminum hydroxide 40-µg treatment groups, respectively. Similarly, at

Study Day 210, HPV-18 VLP specific activity in CVS was detected in 5/7 (71.4%), 8/10 (80.0%), 8/8 (100.0%), and 4/4 (100.0%) subjects in the AS04 12-µg, 40-µg, 120-µg and aluminum hydroxide 40-µg treatment groups, respectively. For the AS04 40-µg, 120-µg and aluminum hydroxide 40-µg treatment groups, all subjects with HPV-16 specific activity in the serum and all but one volunteer (in the AS04 40-µg group) with HPV-18 activity in the serum also had HPV-specific activity detected in CVS. At Study Day 360, there was a decline in the rate of detection of both HPV-16 and HPV-18 antibody in CVS in the AS04-immunized groups.

Study HPV-005, Annex 1

Table 38A- Study HPV-005 (Annex 1): Summary of Specific Activity*: HPV-16 and HPV-18 Responses in Serum and Secretions After HPV VLP Immunization

			Secretion			Serum		
Ab Type/ Treatment	Study Day	N	Positive n (%)	Geometric Mean (units/mL)	Min—Max (units/mL)	Positive n (%)	Geometric Mean (units/mL)	Min—Max (units/mL)
HPV-16								
SBAS4 12 µg	210	7	4 (57.1%)	0.040	0.008–0.23	6 (85.7%)	0.036	0.002–0.32
	360	5	3 (60.0%)	0.015	0.002–0.06	4 (80.0%)	0.030	0.008–0.14
SBAS4 40 µg	210	10	9 (90.0%)	0.076	0.029–0.17	9 (90.0%)	0.090	0.040–0.31
	360	6	4 (66.7%)	0.033	0.008–0.10	6 (100.0%)	0.036	0.015–0.16
SBAS4 120 µg	210	8	8 (100.0%)	0.130	0.038–0.53	8 (100.0%)	0.166	0.026–0.87
	360	5	3 (60.0%)	0.143	0.113–0.17	5 (100.0%)	0.092	0.034–0.24
Alum 40 µg	210	4	4 (100.0%)	0.108	0.041–0.24	4 (100.0%)	0.116	0.062–0.21
	360	2	2 (100.0%)	0.110	0.104–0.11	2 (100.0%)	0.067	0.058–0.07
HPV-18								
SBAS4 12 µg	210	7	5 (71.4%)	0.090	0.035–0.39	6 (85.7%)	0.079	0.002–0.39
	360	5	2 (40.0%)	0.067	0.060–0.07	4 (80.0%)	0.034	0.005–0.10
SBAS4 40 µg	210	10	8 (80.0%)	0.246	0.073–0.80	9 (90.0%)	0.175	0.033–0.63
	360	6	4 (66.7%)	0.061	0.013–0.15	6 (100.0%)	0.055	0.010–0.15
SBAS4 120 µg	210	8	8 (100.0%)	0.230	0.082–1.49	8 (100.0%)	0.312	0.050–0.94
	360	5	4 (80.0%)	0.147	0.124–0.16	5 (100.0%)	0.185	0.058–0.37
Alum 40 µg	210	4	4 (100.0%)	0.159	0.066–0.51	4 (100.0%)	0.175	0.091–0.47
	360	2	2 (100.0%)	0.130	0.073–0.23	2 (100.0%)	0.115	0.079–0.16

* Specific activity =reactivity per IgG

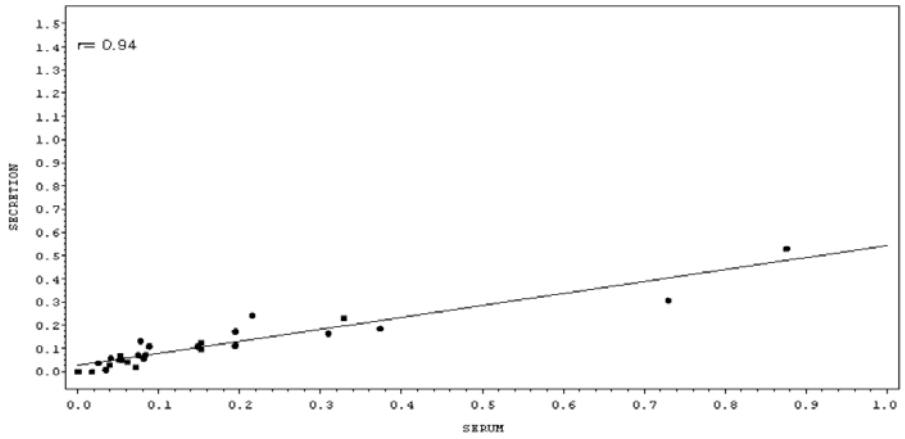
Note: For the summary of geometric mean, minimum and maximum, only values >0 were included.

SBAS4=AS04

Source: STN 125259/0, CSR 005-Annex 1, Exhibit 3

For the three AS04 dosage groups, the response appeared to be dose dependent. At Study Day 210 there appeared to be a correlation in the magnitude of the HPV-16 and HPV-18 IgG response in the CVS and serum. This finding was also seen at Study Day 360 (r=0.87 and r=0.80 for HPV-16 and HPV-18, respectively). (See figures 16A and 17A below.)

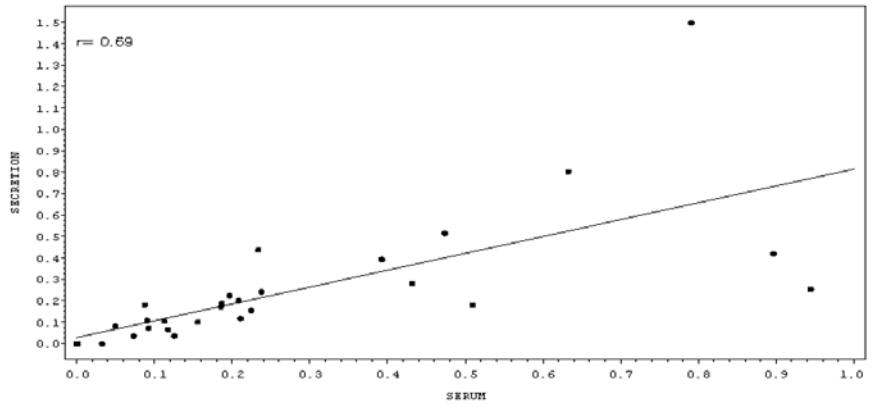
Figure 16A – Study HPV-005: Activity: IgG HVP-16 Responses in Serum and Secretions After HPV VLP Immunization at Study Day 210 (Standardized for Total IgG)



r=Estimate of Pearson correlation coefficient

Source: STN 125259/0, CSR 005-Annex 1, Exhibit 4, p. 12

Figure 17A – Study HPV-005: Activity: IgG HVP-18 Responses in Serum and Secretions After HPV VLP Immunization at Study Day 210 (Standardized for Total IgG)



r=Estimate of Pearson correlation coefficient

Source: STN 125259/0, CSR 005-Annex 1, Exhibit 5, p. 12

Study HPV-004 and HPV-005, pooled data

Study cohorts/data sets analyzed: The vaccine groups pooled from studies HPV-004 (MI-CP055) and HPV-005 (MI-CP057) were subjects vaccinated with 40 µg of HPV-16/18 vaccine with aluminium hydroxide [Al(OH)3 group] and those vaccinated with 40 µg of HPV-16/18 vaccine with AS04 [AS04 group].

- **Study Cohorts for Immunogenicity:** The immunogenicity analysis was performed on the Total Vaccinated Cohort; The persistence analysis was performed on the Kinetic Cohort defined as the cohort of subjects for whom at least one immunogenicity result was available at study Month 24.
- **Study Cohorts for CMI:** The analysis was performed on a subset of the Total Vaccinated Cohort of subjects initially seronegative by the anti-HPV (ELISA version 1) assay. Two cohorts were defined for the CMI analyses:
  - **HPV-16 Total Vaccinated Cohort**, including all subjects initially seronegative by anti-HPV-16 (ELISA version 1)

- **HPV-18 Total Vaccinated Cohort**, including all subjects initially seronegative by anti-HPV-18 (ELISA version 1)

Derived and transformed data

- A seronegative subject was a subject whose titer was below the cut-off value.
- A seropositive subject was a subject whose titer was greater than or equal to the cut-off value:
  - Anti-HPV16 (ELISA version 1) antibody titers ≥ 8 EU/ml
  - Anti-HPV18 (ELISA version 1) antibody titers ≥ 7 EU/ml
  - Anti-HPV16 (ELISA version 2) antibody titers ≥ 8 EU/ml
  - Anti-HPV18 (ELISA version 2) antibody titers ≥ 7 EU/ml
  - Anti-V5-HPV16 antibody titers ≥ -b(4)- EU/ml
  - Anti-V5-HPV16 antibody titers ≥ -b(4)- EU/ml
  - Anti-J4-HPV18 antibody titers ≥ -b(4)- EU/ml
  - Anti-J4-HPV18 antibody titers ≥ -b(4)- EU/ml
  - Anti-HPV16 (Pseudo-neutralization) antibody titers ≥ 40
  - Anti-HPV18 (Pseudo-neutralization) antibody titers ≥ 40

The **Geometric Mean Titers (GMTs)** calculations were performed by taking the anti-log of the mean of the log titer transformations.

Analysis of Immunogenicity: The following statistics were computed on both Total vaccinated and Kinetic cohorts and at all time points where data was available:

- Seropositivity rates with exactly 95 % confidence interval (CI) were calculated per pre-vaccination status
- Geometric mean antibody titers (GMTs) with 95 % CI were calculated per pre-vaccination status.
- Exploratory analysis was performed by computing p-values from the Wilcoxon's non-parametric test for the differences in GMTs between initially seronegative subjects in both groups. P-values <0.05 were considered to be an indicator of statistically significant difference between groups.
- For **CMI**, the following statistics were computed on the Total cohort of subjects initially seronegative for ELISA antibody titres to the corresponding HPV-16 or HPV-18 antigens at all time points where data was available: Geometric mean and median; Minimum and maximum; Q1 = 25th percentile and Q3 = 75th percentile; Exploratory analysis was performed by computing p-values from the Wilcoxon's non-parametric test for location differences between both groups. P-values <0.05 were considered to be an indicator of statistically significant difference between groups.

Results

Study dates: The first subject was enrolled in the study on 10/3/03 (First volunteer randomized HPV-004 [MI-CP055]) and 10/29/00 (First volunteer randomized HPV-005 [MI-CP057]). The last study visit was on 1/19/05 (Last volunteer completed study HPV-004 [MI-CP055]) and 9/905 (Last volunteer completed study HPV-005 [MI-CP057]).

Number and distribution of subjects: The numbers of subjects participating in each treatment group at each study entry for HPV-004 (MI-CP055) and HPV-005 (MI-CP057) are presented in Table 39A. A total of 38 subjects from HPV-004 were included in this analysis: 20 in the AS04 group and 18 in the aluminum hydroxide group. A total of 91 subjects from HPV-005 were

included in this analysis: 64 in the AS04 group (40 µg HPV-016/18 vaccine treatment group) and 27 in the aluminum hydroxide group.

Table 39A – Studies HPV-004 & HPV-005: Number of subjects participating per group and per study at study entry

Study	Treatment group		Total
	AS04	$Al(OH)_3$	
HPV-004 [MI-CP055]	20	18	38
HPV-005 [MI-CP057]	64	27	91
Total	84	45	129

Source: STN 125259/0, CSR 004 & 005, Table 3, p. 28

Demographics: The demographic profile of the two groups of subjects from the two studies was comparable with respect to mean age and racial distribution. The age of subjects ranged from 18 to 30 years, all subjects were female and the population was predominantly white/non-Hispanic.

Analysis of Total Vaccinated Cohort

Serum ELISA Antibody to HPV-16 and HPV-18: The data presented are for the results obtained using both the ELISA version 2 and the ELISA version 1. As had been previously noted, the initial binding ELISA assay was used for several years and was re-validated by GSK when supplies of reagents were exhausted. The new binding ELISA was used only on blood samples of subjects who completed either Year 3 and/or Year 4 study visits. All samples (from day 0 until the last study visit) of these subjects were retested using this new assay. The results of both assays are presented in this report. Regardless of the assays used (ELISA version 1 or 2), all subjects seroconverted one month after the first dose of vaccine (Day 30) to the HPV-16 antigen. Four years after the administration of the first vaccine dose, all subjects remain seropositive, except for one subject in the AS04 group. Using Wilcoxon's non-parametric test (p-value <5 %) to compare the anti-HPV-16 GMTs induced in initially seronegative subjects in the two study groups, the AS04 group showed a statistically significant higher GMT value of double or greater than those of the aluminum hydroxide group. (Source: STN 125259/0, CSR 004 & 005, Tables 4 and 5, p. 30-35, not shown here).

Similarly, regardless of the assays used (ELISA version 1 or 2), all subjects seroconverted one month after the full vaccination course dose of vaccine (Month 7) to the HPV-18 antigen. Four years after the administration of the first vaccine dose, all subjects remained seropositive except for one subject in the AS04 group. Using Wilcoxon's non-parametric test (p-value <5 %) to compare the anti-HPV-18 GMTs induced in initially seronegative subjects in the two study groups, the AS04 group had statistically significantly higher GMT value of double or greater than those of the aluminum hydroxide group. Both the AS04 and aluminum hydroxide group showed a peak HPV-16 and HPV-18 ELISA antibody response at Month 7 (30 days following the third dose of HPV-16/18 vaccine). (Source: STN 125250/0, CSR 004&005, Tables 6 and 7, p. 36-41, not shown here).

Serum Inhibitory ELISA Antibody to HPV-16 and HPV-18: Regardless of the cut-off value that is used, both the AS04 and aluminum hydroxide group showed a peak HPV-16 and HPV-18 ELISA inhibitory antibody titer at Month 7 (30 days following the third dose of HPV-16/18 vaccine). (Source: STN 125259/0, CSR 004&005, Tables 8, 9, 10, and 11, p. 43-50, not shown here.) For most time points, there was a statistically significant higher inhibitory ELISA antibody response to HPV-16 and HPV-18 in the AS04 group as compared to the aluminum hydroxide group.

Neutralizing Antibody responses to HPV-16 and HPV-18: Both the AS04 and aluminum hydroxide group showed a peak HPV-16 and HPV-18 ELISA neutralizing antibody response at Month 7 (30 days following the third dose of HPV-16/18 vaccine). (Source: STN 125259/0, CSR 004 & 005, Tables 12 and 13, not shown here).

Both at Months 7 and 12, there was a statistically significant difference in neutralizing antibody response to HPV-16 and HPV-18 in the AS04 group compared to the aluminum hydroxide group. (Source: STN 125259/0, CSR 004 & 005, Table 14, p. 54 and Table 15, p. 55, not shown here).

Results are similar in the Kinetic Cohort for the serum ELISA antibody to HPV-16 and HPV-18, (Source: STN 125259/0, CSR 004 & 005, Supplements 1, 2, 3, and 4, p. 72-83, not shown here); for serum inhibitory ELISA antibody to HPV-16 and HPV-18 (Source: STN 125259/0, CSR 004 & 005, Supplements 5, 6, 7, and 8, p. 84-91, not shown here); and for neutralizing antibody responses to HPV-16 and HPV-18 (Source: STN 125259/0, CSR 004 & 005, Supplements 9 and 10, p. 92-93, not shown here). Results of statistical comparison are also similar in this cohort. (Source: STN 125259/0, CSR 004 & 005, Table 16, p. 56 and Table 17, p. 57).

CMI Results:

- **Lymphoproliferative response:** Antigen specific proliferative responses were observed in both vaccine groups following vaccination. No statistical difference was observed between groups. (Source: STN 125259/0, CSR 004 & 005, Figures 1 & 2, p. 59-60, not shown here).
- **Cytokine production:** PBMCs collected before and following vaccinations were stimulated with VLP and cytokine production was measured. Cytokine production measured before vaccination showed marginal level of IFN-γ and IL-5 production (background level). PBMC samples collected post vaccination showed high level of IFN-γ production and lower IL-5 production level. No statistical difference was observed between groups. (Source: STN 125259/0, CSR 004 & 005, Tables 18-21, p. 61-64, not shown here).
- **Intracellular Cytokine Staining (ICS):** The cell-mediated immune response induced by HPV GSK vaccines was further characterised using ICS. The T-cell responses at pre-vaccination time points were at baseline levels. Post-vaccination, similar frequencies of CD4 specific for HPV-16 and HPV-18 L1 derived peptides were detected. (Source: STN 125259/0, CSR 004 & 005, Figures 3 & 4, p. 65-66, not shown here). Data for antigen specific CD4 and CD8 T cell responses for HPV-16 and HPV-18 were also presented. (Source: STN 125259/0, CSR 004 & 005, Supplements 13-15, p. 96-119, not shown here). Analyses of functionality of CD4 responses, upon short term in vitro stimulation, revealed that HPV-16 and 18 specific CD4 expressed mainly CD40L, produce IL-2, TNF-α and in a lower proportion IFN-γ. There were no apparent differences between the AS04 and aluminum hydroxide adjuvanted product. (Source: STN 125259/0, CSR 004 & 005, Figures 5 and 6, p. 67-68, not shown here). No specific CD8 were detected.
- **B-cell Response:** Memory B-cells specific to HPV-16 and HPV-18 were evaluated using the B-cell Elispot assay. HPV specific memory B-cells were at baseline before vaccinations. Significant frequencies of HPV-16 and 18 memory B-cells were detected upon vaccination. Although the number of subjects analyzed in B-cell Elispot was limited, the sponsor concluded that the AS04 adjuvanted product induced a higher frequency of memory B-cells directed against HPV-16 and 18 L1 than aluminum adjuvanted vaccine (at 1 month post-dose 3 at Month 7). Data for HPV-16 and HPV-18 B-cell responses were also presented, as well as data for HPV-16 and HPV-18 B-cell responses, respectively, proportion of subjects above 0. **Reviewer's Comment:** In the AS04 adjuvanted group, there was a somewhat higher frequency of HPV-16 and HPV-18 specific memory B cells/million when comparing the two groups, which is most noticeable at Month 7, but because of the small numbers of subjects, it

is difficult to state that this will translate into enhanced duration of protection. (Source: STN 125259/0, CSR 004&005, Figure 7, p. 69 and Figure 8, p. 70, not shown here).

Pooled Study HPV-004 and HPV-005, Annex 1
Statistical evaluation: The primary population for immunogenicity summaries consisted of subjects receiving at least one dose of study vaccine (Total Vaccinated Cohort). The immunogenicity analysis was performed on two study cohorts: on the Total Vaccinated Cohort and on the Kinetic Cohort (defined as the cohort of subjects for whom at least one immunogenicity result for any test was available at Study Year 2).

For the neutralizing assay, a seronegative subject was a subject whose titer was below the cut-off value. A seropositive subject was a subject whose titer was greater than or equal to the cut-off value (Anti-HPV-16 (Pseudo-neutralizing) antibody titers ≥ 40 and Anti-HPV-18 (Pseudo-neutralizing) antibody titers ≥ 40).

Neutralizing Antibody Responses to HPV 16 and HPV 18 Results: A total of 22 subjects were included in the aluminum hydroxide group analysis and a total of 31 subjects were included in the AS04 group analysis. The analysis was performed on the total vaccinated cohort and the kinetic cohort.

Total vaccinated cohort analysis: Both the AS04 and aluminum hydroxide groups showed a peak HPV-16 and HPV-18 neutralizing antibody response at Month 7 (30 days following the third dose of HPV-16/18 vaccine). In the initially seronegative subjects, the responses decreased with each subsequent year until Year 4. Seropositivity rates remained high throughout the follow-up period, up to Year 4, with 96% or more of subjects seropositive for both HPV 16 and HPV-18 neutralizing antibodies in the AS04 group and 95% or more of subjects seropositive in the aluminum hydroxide group. Tables 40A and 41A present results for pre-vaccination, Month 7 (1 month after dose 3), Month 12, and at Year 4. The GMTs are higher in the AS04 adjuvanted group as compared to the aluminum adjuvanted product, although the proportion of subjects who seroconverted are >95% in each group at each time point.

Table 40A – Studies HPV-004 & HPV-005: Seropositivity rates and GMTs for HPV-16 neutralizing antibodies (Total Vaccinated Cohort)

Group	Timing	n/N	Percent ≥ 40 ED50 (95% CI)	GMT 95% CI
AS04	PRE	2/31	6.5% (0.8, 21.4%)	22.3 (18.7, 26.6)
	MONTH 7	31/31	100% (88.8, 100%)	50786.4 (31534.6, 81781.2)
	MONTH 12	31/31	100% (88.8, 100%)	13823.4 (8718.3, 21917.7)
	YEAR 4	25/26	96.2% (80.4, 99.9%)	5648.8 (3105.1, 10276.3)
Aluminum Hydroxide	PRE	2/22	9.1% (1.1, 29.2%)	22.8 (18.4, 28.3)
	MONTH 7	21/22	95.5% (77.2, 99.9%)	11056.2 (3943.7, 30996.1)
	MONTH 12	21/22	95.5% (77.2, 99.9%)	3514.3 (1508.8, 8185.8)
	YEAR 4	11/11	100% (71.5, 100%)	1892.3 (928.5, 3856.5)

AS04 group = 40 µg HPV-16/18 L1 vaccine with AS04
Aluminum hydroxide group = 40 µg HPV-16/18 L1 vaccine with aluminium hydroxide
ED 50 = Estimate Dose 50 % (the estimated serum dilution reducing the signal generated by viral infection by 50 %).
PRE = pre-vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95 % CI = 95 % confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 004 & 005-Annex 1, Table 3, p. 10

Table 41A - Studies HPV-004 & HPV-005: Seropositivity rates and GMTs for HPV-18 neutralizing antibodies (Total Vaccinated Cohort)

Group	Timing	n/N	Percent ≥ 40 ED50 (95% CI)	GMT 95% CI
AS04	PRE	1/31	3.2% (0.1, 16.7%)	22.4 (17.8, 28.2)
	MONTH 7	31/31	100% (88.8, 100%)	12211.0 (8063.3, 18492.1)
	MONTH 12	31/31	100% (88.8, 100%)	3455.1 (2269.8, 5259.5)
	YEAR 4	25/26	96.2% (80.4, 99.9%)	1221.6 (644.9, 2313.7)
Aluminum Hydroxide	PRE	1/22	4.5% (0.1, 22.8%)	21.8 (18.3, 25.9)
	MONTH 7	21/22	95.5% (77.2, 99.9%)	3396.0 (1654.5, 6970.4)
	MONTH 12	21/22	95.5% (77.2, 99.9%)	1584.9 (854.2, 2940.6)
	YEAR 4	11/11	100% (71.5, 100%)	546.2 (255.4, 1168.5)

AS04 group = 40 µg HPV-16/18 L1 vaccine with AS04
Alum group = 40 µg HPV-16/18 L1 vaccine with aluminium hydroxide
ED 50 = Estimate Dose 50 % (the estimated serum dilution reducing the signal generated by viral infection by 50 %).
PRE = pre-vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
95 % CI = 95 % confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259/0, CSR 004 & 005-Annex 1, Table 4, p. 11

The statistically significant differences observed between the aluminum hydroxide and AS04 groups for HPV-16 at each measured time point from Month 7 to Year 4 and for HPV-18 at Month 7, Month 12 and Year 2 are presented in Tables 42A and 43A.

Table 42A - Studies HPV-004 & HPV-005, Annex 1: P-values of Wilcoxon's non-parametric test between both vaccine groups for HPV-16 antibodies at each time point (Total Vaccinated Cohort)

Timing	P value
PRE	1.000
Month 7	**0.0082**
Month 12	**0.0026**
Year 2	**0.0118**
Year 3	**0.0019**
Year 4	**0.0062**

The values are in bold when the null hypothesis is rejected (α = 5 %).
Source: STN 125259/0, CSR 004 & 005-Annex 1, Table 5, p. 12

Table 43A – Studies HPV-004 & HPV-005, Annex 1: P-values of Wilcoxon's non-parametric test between both vaccine groups for HPV-18 antibodies at each time point (Total Vaccinated Cohort)

Timing	P value
PRE	1.000
Month 7	**0.0043**
Month 12	**0.0195**
Year 2	**0.0078**
Year 3	**0.1643**
Year 4	**0.1182**

The values are in bold when the null hypothesis is rejected (α = 5 %).
Source: STN 125259/0, CSR 004 & 005-Annex 1, Table 6, p. 12

Analysis of Kinetic cohort: The persistence analysis was performed on the Kinetic Cohort defined as the cohort of subjects for whom at least one serological result was available at study Year 2. The analysis was stratified according to the pre-vaccination status (seronegative or seropositive).

Neutralizing Antibody responses to HPV-16 and HPV-18: Both the AS04 and aluminum hydroxide groups showed a peak HPV-16 and HPV-18 neutralizing antibody response at Month 7 (30 days following the third dose of HPV-16/18 vaccine). In the initially seronegative subjects, this response then decreased with each subsequent year until Year 4. Seropositivity rates remained high throughout the follow-up period, up to Year 4, with 96% or more of subjects seropositive for both HPV-16 and HPV-18 neutralizing antibodies in the AS04 group and 100% of subjects seropositive in the aluminum hydroxide group.

Reviewer's Comment: The overall results were similar to those noted in the Total Vaccinated Cohort. (Source: STN 125259/0, CSR 004 & 005-Annex 1, Table 7, p. 13 and Table 8, p. 14). As noted in the Total Vaccinated Cohort, statistically significantly higher responses are noted for all time points for HPV 16 neutralizing antibodies. For HPV-18, neutralizing antibodies were statistically higher for HPV 18 at Year 2, but not at Years 3 or 4.

Table 44A – Studies HPV-004 & HPV-005, Annex 1: P-values of Wilcoxon's non-parametric test between both vaccine groups for HPV-16 antibodies at each time point (Kinetic Cohort)

Timing	P value
PRE	1.0000
Month 7	0.1534
Month 12	**0.0410**
Year 2	**0.0118**
Year 3	**0.0019**
Year 4	**0.0062**

The values are in bold when the null hypothesis is rejected ($\alpha = 5\ \%$).
Source: STN 125259/0, CSR 004 & 005-Annex 1, Table 9, p. 15

Table 45A – Studies HPV-004 & HPV-005-Annex 1: P-values of Wilcoxon's non-parametric test between both vaccine groups for HPV-18 antibodies at each time point (Kinetic Cohort)

Timing	P value
PRE	1.000
Month 7	**0.0123**
Month 12	0.1143
Year 2	**0.0078**
Year 3	0.1643
Year 4	0.1182

The values are in bold when the null hypothesis is rejected ($\alpha = 5\ \%$).
Source: STN 125259/0, CSR 004 & 005-Annex 1, Table 10, p. 15

APPENDIX B-OVERVIEW OF SAFETY: ADDITIONAL TABLES AND NARRATIVES

Table 1B-Terms to Identify New Onset Chronic Diseases (NOCD)

Disease/Disorder		MedDRA Level	MedDRA Code
Autoimmune disorders		HGLT	10003816
B'cod autoimmune disorder		HLT	10003817
	Anaemia haemolytic autoimmune	PT	10002046
	Antiphospholipid syndrome	PT	10002817
	Cold type haemolytic anaemia	PT	10009868
	Coombs positive haemolytic anaemia	PT	10010941
	Idiopathic thrombocytopenic purpura	PT	10021245
	Pernicious anaemia	PT	10034695
	Warm type haemolytic anaemia	PT	10047822
	Autoimmune thrombocytopenia	PT	10050245
	Evan's syndrome	PT	10053873
	Autoimmune neutropenia	PT	10055128
Endocrine autoimmune disorder		HLT	10003818
	Basedow's disease	PT	10004161
	Insulin autoimmune syndrome	PT	10022472
	Polyglandular autoimmune syndrome type I	PT	10036072
	Polyglandular autoimmune syndrome type II	PT	10036073
	Autoimmune thyroiditis	PT	10049046
	Diabetic mastopathy	PT	10059134
	Lymphocytic hypophysitis	PT	10063685
	Polyglandular autoimmune syndrome type III	PT	10064115
Hepatic autoimmune disorder		HLT	10003820
	Autoimmune hepatitis	PT	10003827
	Biliary cirrhosis primary	PT	10004661
Muscular autoimmune disorder		HLT	10003821
	Myasthenia gravis	PT	10028417
	Myasthenia gravis neonatal	PT	10028419
	Polymyalgia	PT	10036097
	Polymyalgia rheumatica	PT	10036099
	Polymyositis	PT	10036102
	Ocular myasthenia	PT	10049168
	Myasthenia gravis crisis	PT	10062758
Lupus erythematosus and associated conditions		HLT	10025136
	Lupoid hepatic cirrhosis	PT	10025129
	Lupus encephalitis	PT	10025130
	Lupus nephritis	PT	10025140
	SLE arthritis	PT	10040968
	Systemic lupus erythematosus	PT	10042945
	Systemic lupus erythematosus rash	PT	10042946
	Lupus-like syndrome	PT	10050551
	Cutaneous lupus erythematosus	PT	10056509
	Lupus pneumonitis	PT	10057461
	Neonatal lupus erythematosus	PT	10057887
	Lupus vasculitis	PT	10058143
	Pericarditis lupus	PT	10058149
	Lupus endocarditis	PT	10058225
	Peritonitis lupus	PT	10062898
	Neuropsychiatric lupus	PT	10063663
Autoimmune disorders NEC		HLT	10003816
	Ankylosis spondylitis	PT	10002556
	Cryoglobulinaemia	PT	10011474

Table 1B- Terms to Identify New Onset Chronic Diseases (NOCD) [CONT]

Disease/Disorder		MedDRA Level	MedDRA Code
	Gastritis atrophic	PT	10017860
	Goodpasture's syndrome	PT	10018620
	Keratoconjunctivitis sicca	PT	10023350
	Keratoderma blenorrhagica	PT	10023358
	Mixed connective tissue disease	PT	10027754
	Reiter's syndrome	PT	10038294
	Sicca syndrome	PT	10040633
	Sjogren's syndrome	PT	10040767
	Sympathetic ophthalmia	PT	10042742
	Leukoencephalomyelitis	PT	10048999
	Toxic oil syndrome	PT	10051222
	Cryofibrinogenaemia	PT	10051229
	Encephalitis allergic	PT	10056387
	Nephritis autoimmune	PT	10058948
	Acute haemorrhagic leukoencephalitis	PT	10058994
	Autoimmune disorder	PT	10061664
Rheumatoid arthritis and associated conditions		HLT	10021428
	Felty's syndrome	PT	10016386
	Rheumatoid arthritis	PT	10039073
	Rheumatoid lung	PT	10039081
	Rheumatoid vasculitis	PT	10048628
	Rheumatoid nodule	PT	10048694
	Juvenile arthritis	PT	10059177
	Laryngeal rheumatoid arthritis	PT	10059669
Scleroderma and associated disorders		HLT	10039711
	CREST syndrome	PT	10011360
	Morphoea	PT	10027982
	Scleroderma	PT	10039710
	Systemic sclerosis	PT	10042953
	Systemic sclerosis pulmonary	PT	10042954
	Scleroderma renal crisis	PT	10062553
Skin autoimmune disorders NEC		HLT	10052738
	Benign familial pemphigus	PT	10004265
	Dermatitis herpetiformis	PT	10012468
	Dermatomyositis	PT	10012503
	Eosinophilic fasciitis	PT	10014954
	Herpes gestationis	PT	10019939
	Linear IgA disease	PT	10024515
	Pemphigoid	PT	10034277
	Pemphigus	PT	10034280
	Vitiligo	PT	10047642
Acute and chronic thyroiditis		HLT	10043779
	Thyroiditis	PT	10043778
	Thyroiditis acute	PT	10043780
	Thyroiditis chronic	PT	10043781
	Thyroiditis subacute	PT	10043784
	Autoimmune thyroiditis	PT	10049046
Optic neuritis	Optic neuritis	PT	10030942
	Optic neuritis retrobulbar	PT	10030945
	Vision blurred	PT	10047513
	Blindness	PT	10005159
	Visual acuity reduced	PT	10047531
	Visual evoked potential abnormaly	PT	10047549

Table 1B-Terms to Identify New Onset Chronic Diseases (NOCD) [CONT]

Disease/Disorder		MedDRA Level	MedDRA Code
Multiple sclerosis	Multiple sclerosis	PT	10028245
	Demyelineting disorder	HLGT	10012303
	Gait disturbances	HLT	10017578
	Muscle weakness	LLT	10028350
	Paresthesias	PT	10033775
	(Cognitive impairment)	LLT	10009846
	(Nuclear magnetic resonance imaging brain abnormal)	PT	10029818
Transverse myelitis	Myelitis Transverse	PT	10028527
	Muscle weakness	LLT	10028350
	Low back pain	LLT	10024891
	Paraesthesias and dysaesthesias	HLT	10033768
	Paralysis	PT	10033799
	(Urinary retention)	PT	10046555
	(Neurogenic bladder)	PT	10029279
Guillain-Barre syndrome	Guillain-Barre syndrome	PT	10018767
	Muscle weakness	LLT	10028350
	Paraesthesias and dysaesthesias	HLT	10033768
Diabetes mellitus insulin-dependent	Diabetes mellitus	PT	10012601
	Diabetes mellitus (incl. subtypes)	HLT	10012602
	Glucose metabolism disorders (incl. diabetes mellitus)	HLGT	10018424
Uveitis	Uveitis	PT	10046851
	Eye pain	PT	10015958
	Eye redness	LLT	10015963
	Photophobia	PT	10034960
Glomerulonephritis	Lupus nephritis	PT	10025140
	Proteinuria	PT	10037032
	Haematuria	PT	10018867
	Glomerular filtration rate decreased	PT	10018358
	(Hypoproteinemia)	PT	10021083
	(Oedema)	PT	10030095
	Blood urea increased	PT	10005851
	Blood creatinine increase	PT	10005483
Hepatitis	*already identified as "hepatitis autoimmune" above*	PT	
Inflammatory bowel disease	Inflammatory bowel disease	PT	10021972
Crohn's disease	Crohn's disease	PT	10011401
Ulcerative colitis	Ulcerative colitis	PT	10009900
	Rectal bleeding	LLT	10038035
Coeliac disease	Coeliac disease	PT	10009839
Sarcoidosis	Sarcoidosis	PT	10039486
	Angiotensin converting enzyme increased	PT	10049530
Asthma	Asthma	PT	10003553
Allergies	Immune system disorders	SOC	
	Allergic conditions	HLGT	10001708
Auto immunity analyses		HLT	10003828

HLGT = High Level Group Term (for analysis purposes, includes all Preferred Terms under this category)
HLT = High Level Term (for analysis purposes, includes all Preferred Terms under this category)
LLT = Low Level Term (for analysis purposes, includes all Preferred Terms under this category)
PT = Preferred Term.
SOC = System Organ Class
Source: STN 125259.48, CSR 007, Month 36, Supplement 196, p. 446-448

Table 2B: Study discontinuations due to adverse events for studies included in BLA [Studies HPV-001, 003, 004, 005, 007, 008, 009, 012 (including extension), 013 (including extension), 014 (including extension), 015, 016] classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort, data lock-point of August 31, 2008) [CERVARIX]

Primary System Organ Class (code)	Primary Preferred Term (code)	Treatment allocation	Subject no	Study	Symptom type	Intensity*	Dose/Days to onset/outcome
Blood and lymphatic system disorders	Lymphadenopathy	HPV	57	HPV-016	Unsolicited AE	3	2/106/R
Gastrointestinal disorders	Crohn's disease	HPV	389954	HPV-009	SAE	3	2/441/F
Gastrointestinal disorders	Nausea	HPV	1517	HPV-012	Unsolicited AE	3	1/0/R
General disorders and administration site conditions	Fatigue	HPV	137012A	HPV-009	Solicited AE	1	1/7/R
General disorders and administration site conditions	Fatigue	HPV	297312A	HPV-009	Solicited AE	1	1/2/R
General disorders and administration site conditions	Fatigue	HPV	262	HPV-012	Solicited AE	U	1/1/NA
General disorders and administration site conditions	*Fatigue*	*HPV*	*8373*	*HPV-015*	*Solicited AE*	*3*	*2/0/NA*
General disorders and administration site conditions	*Fatigue*	*HPV*	*8839*	*HPV-015*	*Solicited AE*	*3*	*1/0/NA*
General disorders and administration site conditions	Injection site pain	HPV	17037	HPV-008	Solicited AE	3	2/0/NA
General disorders and administration site conditions	Injection site pain	HPV	2027	HPV-012	Solicited AE	2	2/1/NA
General disorders and administration site conditions	Injection site pain	HPV	1294	HPV-014	Solicited AE	2	2/0/NA
General disorders and administration site conditions	Malaise	HPV	137012A	HPV-009	Solicited AE	1	1/7/R
General disorders and administration site conditions	Malaise	HPV	297312A	HPV-009	Solicited AE	1	1/2/R
Infections and infestations	*Bronchopneumonia*	*HPV*	*7748*	*HPV-015*	*Unsolicited AE*	*3*	*1/14/R*
Infections and infestations	Candida sepsis	HPV	369716	HPV-009	SAE	3	1/609/F
Infections and infestations	Cystitis	HPV	1278	HPV-014	Unsolicited AE	2	2/133/R
Infections and infestations	Erysipelas	HPV	149	HPV-016	Unsolicited AE	3	1/2/R
Infections and infestations	Herpes zoster	HPV	189	HPV-016	Unsolicited AE	3	1/26/R
Infections and infestations	HIV infection	HPV	237484	HPV-009	SAE	3	1/254/F
Infections and infestations	Influenza	HPV	399034	HPV-009	Unsolicited AE	2	1/29/R
Infections and infestations	Pneumococcal sepsis	HPV	89479	HPV-008	SAE	3	3/770/F

Table 2B: Study discontinuations due to adverse events for studies included in BLA [Studies HPV-001, 003, 004, 005, 007, 008, 009, 012 (including extension), 013 (including extension), 014 (including extension), 015, 016] classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort, data lock-point of August 31, 2008) [CERVARIX] [Cont]

Primary System Organ Class (code)	Primary Preferred Term (code)	Treatment allocation	Subject no	Study	Symptom type	Intensity†	Dose/Days to onset/outcome
Infections and infestations	Sepsis	HPV	20945	HPV-008	SAE	3	3/758/F
Infections and infestations	Skin infection	HPV	22364	HPV-008	SAE	2	2/1/R
Injury, poisoning and procedural complications	Gun shot wound	HPV	18105	HPV-008	SAE	3	3/686/F
Injury, poisoning and procedural complications	Road traffic accident	HPV	317629	HPV-009	SAE	3	1/179/F
Musculoskeletal and connective tissue disorders	*Arthralgia*	*HPV*	*3352*	*HPV-015*	*Solicited AE*	*1*	*1-0/NA*
Musculoskeletal and connective tissue disorders	Arthritis reactive	HPV	160	HPV-016	Unsolicited AE	3	2/63/NR
Musculoskeletal and connective tissue disorders	Intervertebral disc protrusion	HPV	4582	HPV-016	SAE	3	1/19/R
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Breast cancer stage I*	*HPV*	*8347*	*HPV-015*	*SAE*	*3*	*2/51/R*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Adenocarcinoma of the cervix*	*HPV*	*9704*	*HPV-015*	*SAE*	*3*	*3-246/R*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast neoplasm	HPV	1318	HPV-014	Unsolicited AE	1	2/29/NR
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Cervix cancer metastatic*	*HPV*	*5322*	*HPV-015*	*SAE*	*3*	*3/205/F*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gestational trophoblastic tumor	HPV	76286	HPV-008	SAE	2	2/151/F
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Thyroid neoplasm	HPV	3950	HPV-015	Unsolicited AE	2	2/142/NR
Nervous system disorders	Headache	HPV	2740	HPV-008	Unsolicited AE	2	1/0/R
Nervous system disorders	Headache	HPV	271516	HPV-009	Solicited AE	1	2/1/R
Nervous system disorders	Headache	HPV	7240	HPV-015	Solicited AE (previously reported as Unsolicited AE)‡	3	2/0/NA
Nervous system disorders	Multiple sclerosis	HPV	1261	HPV-014	SAE	2	2/25/NR
Nervous system disorders	*Syncope*	*HPV*	*1446*	*HPV-015*	*Unsolicited AE*	*3*	*1/1/R*
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	HPV	8076	HPV-001-007	SAE	3	2/132/R
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous complete	HPV	18389	HPV-008	SAE	3	1/142/R
Pregnancy, puerperium and perinatal conditions	Abortion threatened	HPV	57	HPV-012	Unsolicited AE	2	1/37/R
Psychiatric disorders	*Completed suicide*	*HPV*	*9446*	*HPV-015*	*SAE*	*U*	*3-148/F*
Psychiatric disorders	*Depression*	*HPV*	*226*	*HPV-015*	*Unsolicited AE*	*1*	*1/1/R*
Psychiatric disorders	*Depression*	*HPV*	*4715*	*HPV-015*	*Unsolicited AE*	*3*	*3-111/NR*
Psychiatric disorders	*Emotional disorder*	*HPV*	*201*	*HPV-015*	*Unsolicited AE*	*3*	*1-1/R*

Table 2B: Study discontinuations due to adverse events for studies included in BLA [Studies HPV-001, 003, 004, 005, 007, 008, 009, 012 (including extension), 013 (including extension), 014 (including extension), 015, 016] classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort, data lock-point of August 31, 2008) [CERVARIX] [Cont]

Primary System Organ Class (code)	Primary Preferred Term (code)	Treatment allocation	Subject no	Study	Symptom type	Intensity*	Dose/Days to onset/outcome
Reproductive system and breast disorders	Ovarian cyst	HPV	76264	HPV-008	Unsolicited AE	1	1/41/NR
Reproductive system and breast disorders	*Vaginal discharge*	*HPV*	*7904*	*HPV-015*	*Unsolicited AE*	*2*	*2/17/R*
Reproductive system and breast disorders	Vaginal discharge	HPV	8897	HPV-015	Unsolicited AE	1	1/2/R
Respiratory, thoracic and mediastinal disorders	Asthma	HPV	245113	HPV-009	Unsolicited AE	2	1/4/R
Skin and subcutaneous tissue disorders	Acne	HPV	11600Ã	HPV-008	Unsolicited AE	1	1/18/R
Skin and subcutaneous tissue disorders	Pruritus	HPV	11600Ã	HPV-008	Unsolicited AE	1	1/21/R
Skin and subcutaneous tissue disorders	Rash	HPV	11600Ã	HPV-008	Solicited AE	1	1/1/NA
Skin and subcutaneous tissue disorders	Rash	HPV	206	HPV-012	Unsolicited AE	1	1/16/U
Skin and subcutaneous tissue disorders	Urticaria	HPV	586	HPV-008	Solicited AE	1	2/1/NA
Social circumstances	Homicide	HPV	8746	HPV-008	SAE	U	3/217/F

NA – not applicable No outcomes are reported for solicited AEs for GSK-sponsored studies.
U – unknown
No change = no change in the clinical database since the last DLP (September 30, 2007)
New info = information in the clinical database has been changed or completed since the last DLP (September 30, 2007)
New case = new withdrawal reported in the clinical database since the DLP of September 30, 2007
A = up-dated information
* Intensity scale = 1 (mild), 2 (moderate), 3 (severe)
‡ time to onset since vaccine dose"
ASubjects in whom two or more AEs/SAEs were reported as leading to study discontinuation Subject 11600 in Study HPV-008, Subject 13702, Subject 297312 and Subject 467850 in
Study HPV-009
Subject 456007 from Study HPV-005 received the final formulation of *Cervarix* This subject is not included in this table as she was withdrawn from vaccination rather than withdrawn
from the study
Cases in women > 25 years of age in italics.
Source: STN 125259.48, Supplemental safety update, Table 24, p. 82-90

Table 3B: Study discontinuations due to adverse events for studies included in BLA [Studies HPV-001, 003, 004, 005, 007, 008, 009, 012 (including extension), 013 (including extension), 014 (including extension), 015, 016] classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort, data lock-point of August 31, 2008) [CONTROL]

Primary System Organ Class (code)	Primary Preferred Term (code)	Treatment allocation	Subject no	Study	Symptom type	Intensity†	Dose/Days to onset/outcome
Cardiac disorders	*Cardiac valve disease*	*ALU*	*6594*	*HPV-015*	*SAE*	*3*	*3/67/F*
Congenital, familial and genetic disorders	*Heart disease congenital*	*HAV720*	*442976*	*HPV-009*	*SAE of Child§*	*3*	*3/444/F (child)*
Gastrointestinal disorders	*Abdominal pain*	*ALU*	*4641*	*HPV-015*	*SAE*	*3*	*1/12/NR*
Gastrointestinal disorders	*Dyspepsia*	*ALU*	*1414*	*HPV-015*	*Unsolicited AE*	*2*	*1/5/R*
Gastrointestinal disorders	*Enteritis*	*ALU*	*9740*	*HPV-015*	*SAE*	*3*	*1/25/R*
General disorders and administration site conditions	Death	HAV720	16201	HPV-008	SAE	3	3/817/F
General disorders and administration site conditions	Facial pain	HAV720	10302	HPV-008	Unsolicited AE	2	1/0/R
General disorders and administration site conditions	Fatigue	HAV720	467850Ã	HPV-009	Solicited AE	1	1/1/R
General disorders and administration site conditions	Injection site pain	HAV360	2782	HPV-013	Solicited AE	2	1/0/NA
General disorders and administration site conditions	Malaise	HAV720	467850Ã	HPV-009	Solicited AE	1	1/1R
Infections and infestations	Gastroenteritis	HAV720	8959	HPV-008	Unsolicited AE	2	U/U/R
Infections and infestations	*Renal abscess*	*ALU*	*9709*	*HPV-015*	*SAE*	*3*	*1/9/R*
Infections and infestations	*Sepsis*	*ALU*	*5258*	*HPV-015*	*SAE*	*3*	*3/650/F*
Injury, poisoning and procedural complications	Road traffic accident	HAV720	16505	HPV-008	SAE	3	2/101/F
Injury, poisoning and procedural complications	Road traffic accident	HAV720	1899	HPV-008	SAE	3	3/30/F
Injury, poisoning and procedural complications	Road traffic accident	HAV720	6054	HPV-008	SAE	3	3/317/F
Injury, poisoning and procedural complications	Road traffic accident	HAV720	211712	HPV-009	SAE	3	3/180/F
Injury, poisoning and procedural complications	Road traffic accident	HAV720	302780	HPV-009	SAE	3	3/862/F
Injury, poisoning and procedural complications	Road traffic accident (Previously reported as traumatic brain injury le	HAV720	3365	HPV-008	SAE	3	3/239/R
Metabolism and nutrition disorders	Diabetic ketoacidosis	HAV720	18876	HPV-008	SAE	3	1/154/F
Musculoskeletal and connective tissue disorders	*Arthralgia*	*ALU*	*8383*	*HPV-015*	*Solicited AE*	*2*	*1/1/NA*
Musculoskeletal and connective tissue disorders	Joint swelling	HAV360	3218	HPV-013	Unsolicited AE	2	2/76/NR
Musculoskeletal and connective tissue disorders	*Muscle spasms*	*ALU*	*9918*	*HPV-015*	*Unsolicited AE*	*3*	*1/4/NR*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bone sarcoma	HAV720	6726	HPV-008	SAE	3	3/165/F
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Cervix carcinoma stage 0*	*ALU*	*4011*	*HPV-015*	*SAE*	*3*	*1/21/R*

Table 3B: Study discontinuations due to adverse events for studies included in BLA [Studies HPV-001, 003, 004, 005, 007, 008, 009, 012 (including extension), 013 (including extension), 014 (including extension), 015, 016] classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort, data lock-point of August 31, 2008) [CONTROL||CONT]

Primary System Organ Class (code)	Primary Preferred Term (code)	Treatment allocation	Subject no	Study	Symptom type	Intensity*	Dose/Days to onset/outcome
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon cancer	HAV720	196354	HPV-009	SAE	3	2/112/F
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Neoplasm malignant*	*ALU*	*2734*	*HPV-015*	*SAE*	*3*	*3/49/recovering*
Nervous system disorders	Dizziness	ALU	6576	HPV-001-007	Unsolicited AE	2	1/6/R
Nervous system disorders	Headache	HAV720	263933	HPV-009	Solicited AE	2	1/0/R
Nervous system disorders	Hypoaesthesia	HAV720	3190	HPV-008	Unsolicited AE	3	1/12/R
Nervous system disorders	Migraine	ALU	6464	HPV-001-007	Unsolicited AE	2	1/1/R
Psychiatric disorders	Anorexia nervosa	HAV360	1507	HPV-013	SAE	3	2/93/NR
Psychiatric disorders	Intentional self-injury	HAV720	141567	HPV-009	SAE	3	1/136/F
Psychiatric disorders	Intentional self-injury	HAV720	312860	HPV-009	SAE	3	2/149/F
Psychiatric disorders	Mental disorder	ALU	6294	HPV-001-007	Unsolicited AE	2	2/170/U
Psychiatric disorders	Suicide attempt	HAV720	130431	HPV-009	SAE	3	2/680/F
Psychiatric disorders	Suicide attempt	HAV720	393049	HPV-009	SAE	3	3/49/F
Psychiatric disorders (previously reported under General disorders and administration site conditions)è	Completed suicide (previously reported as accidental death) è	HAV720	14290	HPV-008	SAE	3	3/817/F
Reproductive system and breast disorders	Uterine hemorrhage	HAV720	330691	HPV-009	Unsolicited AE	1	1/4/R
Reproductive system and breast disorders	Uterovaginal prolapse	ALU	1511	HPV-015	SAE	3	1/14/NR
Reproductive system and breast disorders	*Vaginal hemorrhage*	*ALU*	*7734*	*HPV-015*	*Unsolicited AE*	*1*	*1/2/R*

NA = not applicable No outcomes are reported for solicited AEs for GSK-sponsored studies.
U = unknown
No change = no change in the clinical database since the last DLP (September 30, 2007)
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New case = new withdrawal reported in the clinical database since the DLP of September 30, 2007
A = up-dated information
* Intensity scale = 1 (mild), 2 (moderate), 3 (severe)
‡ time to onset since vaccine dose"
ASubjects in whom two or more AEs/SAEs were reported as leading to study discontinuation: Subject 11600 in Study HPV-008, Subject 13702, Subject 297312 and Subject 467850 in
Study HPV-009
Subject 456007 from Study HPV-005 received the final formulation of *Cervarix*. This subject is not included in this table as she was withdrawn from vaccination rather than withdrawn from the study.
Cases in women > 25 years of age in italics.
Source: S1N 125259-48, Supplemental safety update, Table 24, p 82-90

Table 4b- Events considered as outcomes of interest and MedDRA terms and codes used for screening the databases for events of interest

CBER categories of diseases	CBER Verbatim Term	MedDRA Preferred Term	MedDRA code
Neuroinflammatory	Optic neuritis	Optic neuritis	10030942
		Optic neuritis retrobulbar	10030945
	Multiple sclerosis	Multiple sclerosis	10028245
	Demyelinating disease	Demyelination	10012305
	Myasthenia gravis	Myasthenia gravis	10028417
	Transverse myelitis	Myelitis Transverse	10028527
	Myelitis	Myelitis	10028524
		Leukoencephalomyelitis	10048999
	Encephalitis	Encephalitis	10014581
		Encephalitis post immunisation	10014602
	Guillain-Barré syndrome	Guillain-Barré syndrome	10018767
Musculoskeletal	Systemic lupus erythematosus	Systemic lupus erythematosus	10042945
		Systemic lupus erythematosus rash	10042946
	Sjogren's syndrome	Sjogren's syndrome	10040767
	Rheumatoid arthritis	Rheumatoid arthritis	10039073
	Juvenile rheumatoid arthritis	Juvenile arthritis	10059177
	Arthritis	Arthritis	10003246
	Reactive arthritis	Arthritis reactive	10003267
	Scleroderma	Scleroderma	10039710
Gastrointestinal	Inflammatory bowel disease	Inflammatory bowel disease	10021972
	Crohn's disease	Crohn's disease	10011401
	Ulcerative colitis	Ulcerative colitis	10009900
	Ulcerative proctitis	Proctitis ulcerative	10036783
	Coeliac disease	Coeliac disease	10009839
Thyroid	Graves' disease	Basedow's disease	10004161
	Thyroiditis	Autoimmune thyroiditis	10049046
		Thyroiditis	10043778
		Thyroiditis acute	10043780
		Thyroiditis subacute	10043784
	Hyperthyroidism	Hyperthyroidism	10020850
	Hypothyroidism	Hypothyroidism	10021114
	Goiter	Goiter	10018498
		Hypothyroidic Goiter	10059844
Skin	Cutaneous lupus	Cutaneous lupus erythematosus	10056509
	Dermatomyositis	Dermatomyositis	10012503
	Vitiligo	Vitiligo	10047642
	Erythema nodosum	Erythema nodosum	10015226
	Psonasis	Psoriasis	10037153
	Psoriatic arthropathy	Psoriatic arthropathy	10037162
	Stevens-Johnson syndrome	Stevens-Johnson syndrome	10042033
	Raynaud's phenomenon	Raynaud's phenomenon	10037912
Others	Autoimmune haemolytic anaemia	Anaemia haemolytic autoimmune	10002046
		Cold type haemolytic anaemia	10009868
		Coombs positive haemolytic anaemia	10010941
		Haemolytic anaemia	10018916
		Warm type haemolytic anaemia	10047822

Table 4b- Events considered as outcomes of interest and MedDRA terms and codes used for screening the databases for events of interest [CONT]

CBER categories of diseases	CBER Verbatim Term	MedDRA Preferred Term	MedDRA code
	Antiphospholipid syndrome	Antiphospholipid syndrome	10002817
	Insulin-dependent diabetes mellitus (IDDM)	Diabetes mellitus#	10012601
		Diabetes mellitus insulin-dependent	10012608
	Idiopathic thrombocytopenic purpura (ITP)	Idiopathic thrombocytopenic purpura	10021245
		Autoimmune thrombocytopenia	10050245
		Thrombocytopenia#	10043554
	Autoimmune hepatitis	Autoimmune hepatitis	10003827
	Nephritis	Nephritis	10029117
		Nephritis autoimmune	10058948
		Lupus nephritis	10025140
	Autoimmune Glomerulonephritis	Glomerulonephritis	10018364
	Uveitis	Uveitis	10046851
	Sarcoidosis	Sarcoidosis	10039486
	Addison's disease	Addison's disease	10001130
	Vasculitis	Leukocytoclastic vasculitis	10024377
		Vasculitis	10047115
		Behcet's syndrome	10004213

Source STN 125259 18, Table 4, p 26-27

META-ANALYSIS: LEVELS 1-4 ANALYSES

- **Level 1 analysis:** defined as the analyses of all IND and non-IND studies in the HPV vaccine program. These analyses were based on all serious adverse events (SAEs) and unsolicited adverse events, as well as on medically significant events (MsAEs) and new onset of chronic diseases (NOCDs), when available, reported in the HPV trials for events of interest. Studies included in Level 1 analyses were all studies conducted with the HPV-16/18 L1 VLP AS04 vaccine (IND b(4)), with the b(4) vaccine and with the b(4) b(4) vaccine (BB-IND b(4)).
- **Level 2 analysis:** defined as the analyses of all IND and non-IND studies in the 3 major programs which have evaluated vaccines adjuvanted with AS04, i.e., all studies included in Level 2 analyses were all studies already included in Level 1 analyses, as well as the studies performed with the HSV AS04-adjuvanted vaccine. b(4) -adjuvanted vaccine and with the HBV AS04-adjuvanted vaccine (licensed in Europe under the name Fendrix™). These analyses were based on all SAEs and unsolicited adverse events, as well as on MsAEs and NOCDs (when available), reported in the HPV, HSV and HBV trials for events of interest.
- **Level 3 analyses:** defined as the analyses of IND and non-IND studies sponsored by GSK or external collaborators with all prophylactic programs which have evaluated vaccines with MPL-containing adjuvants, i.e., studies included in Level 3 analyses are all studies already included in Level 2 analyses, as well as the studies performed with other vaccines containing MPL, such as Malaria vaccine b(4) and Influenza vaccine adjuvanted with b(4) , as well as other (smaller) vaccine programs using MPL-containing adjuvants. In addition to the adverse events specified for programs for programs included in the Level 1 and 2 analyses, Level 3 analyses include SAEs reported in these other prophylactic programs using MPL.
- **Level 4 analyses:** defined as the analyses of all IND and non-IND GSK and Corixa studies in all therapeutic vaccine programs, in (b)(4) vaccine programs and studies conducted by Corixa

which have used MPL-containing adjuvants. These analyses were run independent from the Level 1, 2 and 3 analyses, since the profile of most subjects included in these programs differs significantly from the healthy subjects included in other vaccine programs. These analyses only included SAEs obtained from either safety databases or study publications.

BRIEF NARRATIVE OF EVENTS ASSESSED AS CONFIRMED IMMUNE MEDIATED ILLNESS (EXPERT PANEL)

HPV GROUP 15-25 YEARS OF AGE

- **Subject 85619 (17y/008):** Complaint = unspecified reactive arthritis at 244 days after dose 3. Concurrent Chlamydia infection (joint edema reported before Chlamydia infection, reactive arthritis diagnosed after Chlamydia infection.) Corrected time to onset = 180 days, [time at risk] (History acne, adenoidectomy and tonsillectomy in 2004; father with myasthenia gravis).
- **Subject 123422 (19y/009):** Complaint =RA unspecified 61 days after dose 1. Pre-existing JRA, symptoms in elbows and hands around 2 months postdose 1, treatment with sulindac. Expert opinion- exacerbation of pre-existing juvenile idiolathic arthritis [pre-existing] (History RA at age 2; no family history rheumatologic disorders).
- **Subject 6336 (19y/001):** Complaint = fatigue (3/16/02-5/02); subject reported fibromyalgia. Medical history of juvenile arthritis since 1984, subject treated for this event, but not for fibromyalgia. No supporting data for fibromyalgia. Subject lost to follow-up in 007. [pre-existing] (Other medical history-myopia since 1994, migraines since 1996 and anxiety 2001, drug allergies to sulfa, phenergan and imitrex; no family history rheumatologic disorders).
- **Subject 216829 (19y/009):** Complaint =RA unspecified. Symptoms 2.5 months postdose 2, X-ray normal, RF not reported, treatment with prednisone, plaquenil, leflunomide. The additional expert noted that the subject experienced an increase of arthritis symptoms with JRA on 11/11/04. [pre-existing, 2001-2002] (Five year history of intermittent knee, elbow and wrist pain and swelling; no family history of rheumatologic disorders).
- **Subject 11150 (22y/008):** Complaint = RA. First symptoms 5-6 months postdose 3, RF−, anti-CCP negative, X-ray normal, hand and wrist US showed synovial thickening. Recovered with sequelae. Expert dx RA. Corrected time to onset = 180 days (instead of 194 days). [time at risk] (History of asthma, allergies to PCN and nuts; no family history rheumatologic disorders).
- **Subject 8416 (24y/008):** Complaint =RA. Medical history RA 2 months after dose 2 (no details); 9 months postdose 3 symptoms recurred, RF + (4891U). Corrected time to onset = 204 days, [anytime at risk] (No medical history reported; no family history rheumatologic disorders).
- **Subject 12833 (17y/008):** Complaint = RA. Symptoms started 1 year postdose 3, RF+, anti-CCP+. Not recovered. [anytime at risk] (History eczema as child; no family history rheumatologic disorders.).
- **Subject 13415 (17y/008):** Complaint = RA. First symptoms 11 months postdose 3, diagnosed 505 days after dose 3. Water Rose +, RF and anti-CCP not reported, became asymptomatic after treatment. Corrected time to onset = 330 days instead of 505 days. [anytime at risk] (history otitis media child, UTI, and dryness of eyes; family history positive – mother with oligoarthritis and grandmother with RA).
- **Subject 1546 (16y/012):** Complaint=Suspected RA. Pre-existing knee and back pain for years and Raynaud's around 2 years postdose 3. Evaluation started and **celiac disease** confirmed by anti-glutaminase antibody test. Fe deficiency anemia and biopsy (villous atrophy in duodenum). (History as above; no family history of rheumatologic disorders).
- **Subject 391654 (19y/009):** Complaint = localized scleroderma morphea. Hardened, darkened spot on leg around 9 months postdose 3; 4 months later, biopsy led to dx of scleroderma.

- **Subject 369716 (24y/009):** Complaint = SLE unspecified. Hospitalized 6 months after dose 1 with severe symptomatology including weight loss, pleural effusion, glomerulonephritis. SLE blood tests were positive on blood just before dose 1. SLE blood tests were positive. (Prior to vaccination). [pre-existing] (Medical history and family history not known).
- **Subject 2241 (24y/008):** Complaint = SLE. Severe pain 5 months postdose 3. ANA and anti-ds DNA positive 6-7 months postdose 3. Pre-existing joint pain and foot swelling (non specific). In review of the history, the additional expert reported the subject had joint pains after the birth of her first child in 1997 and fatigue, edema and athralgia following the birth of her second child in 2002. [pre-existing] (Had history pain, fatigue, swelling of feet joint pain; no family history rheumatologic conditions).
- **Subject 19518 (24y/008):** Complaint = SLE. Hospitalized 7 months postdose 3, ANA, anti-ds DNA, anti-sm positive, proteinuria. Event probably started earlier (180 days postdose 3). [anytime at risk] (No reported medical history; no family history rheumatologic conditions).

HPV GROUP > 25 YEARS OF AGE

- **Subject 2779 (35 y/015):** Complaint = arthritis symptom both hands 29 days after dose 3. Pre-existing recurrent undifferentiated arthritis in both hands, with increased complaints during a period of 7 months postdose 3. [pre-existing] (Since 1983, suffers from recurrent arthritis episodes in both hands, every 8-10 weeks, last approximately 1 week; family history positive for RA –mother and several relatives).
- **Subject 2371 (44y/015):** Complaint = reactive arthritis at 4 days after dose 1. Concomitant diarrhea. [time at risk] (No prior medical history; no family history for rheumatologic disorders).
- **Subject 85 (50 y/014):** Complaint = chronic arthropathy and serous rheumatoid arthritis at 470 days after dose 3. Polyarthritis 8 months postdose 3, RA diagnosed 19 months postdose 3 with RF and ACL+. (Additional expert assessed time to onset as 548 days after dose 3 instead of 470 days postdose 3). 2 events. [anytime at risk] (No prior history: no family history for rheumatologic disorders).

BRIEF NARRATIVES FOR SUBJECTS WHO RECEIVED CONTROL AND HAD ILLNESSES OF CONFIRMED IMMUNE-MEDIATED ETIOLOGY (EXPERT PANEL)
CONTROL GROUP 15-25 YEARS OF AGE

- **Subject 8050 (22y/008):** Complaint = SLE. 8 months postdose 3, differential dx of SLE or RA. RF+. Diagnosis of SLE by rheumatologist. Diagnosis of undifferentiated arthritis by experts, but autoimmune disorder probably present. [anytime at risk] (History of polyp, gastritis, allergies to ASA and foods; no family history rheumatologic disorders).
- **Subject 11954 (16/008):** Complaint = Joint inflammation at 380 days after dose 3. Undifferentiated arthritis for 3 weeks. [anytime at risk] (No medical history, no family history rheumatologic disorders).
- **Subject 88202 (19y/008):** Complaint – arthritis. Undifferentiated arthritis lasting 1 month, treated with ibuprofen and paracetamol. (Discussion re: start dates – revised onset 8/7/06 or 8 months after dose 3). [anytime at risk] (History of syncope as adolescent but last episode 8 years ago; mother with rheumatism lumbar region).
- **Subject 229946 (23y/009):** Complaint = RA unspecified. Symptoms around 2 months postdose 3, seronegative RA treated with prednisone MTX and Indocin. [time at risk] (No medical history reported; family history of RA and anemia).

- **Subject 15673 (16y/008):** Complaint = RA. Arthritis including hands. RF- and ANA- (no subtyping). Imaging normal. [anytime at risk] (No medical history, no family history rheumatologic disorders).
- **Subject 4140 (18y/008):** Complaint = RA. Symptoms 1.5 years postdose 2, no hand involvement, no RF or imaging, treatment with prednisone, MTX, Celebrex. Hx Type I diabetes mellitus. Expert dx = arthritis [anyime at risk] (History as above; no family history rheumatologic disorders).
- **Subject 7669 (20y/001):** Complaint = RA. Onset 4 years postdose 3. RF+, treated with chloroquine, free of symptoms 2 years after onset. Dx'd with idiopathic hypothyroidism 7/03. [anytime at risk] (History of drug and food allergies; no family history of rheumatologic disorders).
- **Subject 22297 (22y/008):** Complaint = SLE. Discoid rash and positive anti-dsDNA test 17-18 months postdose 3. [anytime at risk] (No other medical history; no family history rheumatologic disorders).

BRIEF NARRATIVES FOR SUBJECTS WHO RECEIVED CERVARIX AND HAD ILLNESSES OF UNCERTAIN ETIOLOGY (EXPERT PANEL)
HPV GROUP, 15-25 YEARS OF AGE

- Subject 1063 (12y/012): Complaint = arthritis. Knee pain, possibly mechanical (karate practice), preexisted to vaccination. (Knee pain prior to vaccination, onset date of swelling uncertain, possible mechanical origin; no family history of rheumatologic disorders).
- Subject 3022 (20y/050): Complaint=arthritis tight hand. Arthritis in hand for 2 weeks, insufficient data. (No other medical history; no family history for rheumatologic disorders).
- Subject 7706 (19y/008): Complaint = Knee inflammation. Reported knee inflammation for one week, swelling uncertain, vaginal discharge in the preceding weeks. (No other medical history: no family history rheumatologic disorders).
- Subject 5018 (24y/016): Complaint = arthritis knee. Knee arthritis for 1 month, medical history of knee desmorrhexis (rupture of ligament), uncertain if mechanical or due to inflammatory process; history of allergies to pollen, dust, animal fur; no medical history rheumatologic disorders).
- Subject 14118 (16y/008): Complaint = reactive arthritis. Symptoms of arthritis in large joints of lower limbs, rheumatoid factor 22 IU (normal value not communicated), HLA-B27 positive, chlamydia infection and streptococcal throat infection before the event, treated with methotrexate, prednisolone, sulfasalazine and corticoid. (No medical history; no family history rheumatologic disorders).
- Subject 160 (21y/016): Complaint = reactive arthritis. Polyarticular disease for 6 months, swelling uncertain, rheumatoid factor and anti-nuclear antibodies negative, treated with corticoid and salazopyrine. (Insufficient data to diagnose; no prior medical history; no family history rheumatologic disorders).
- **Subject 1623 (25y/048): Complaint = arthritis humeroscapularis. Shoulder pain for one week, mechanical cause. (history 10/01 development of arthropathy with instability patella and episodes pain swelling; no family history rheumatologic disorders).*
- Subject 1031 (15y/042): Complaint = Coxitis. Nonspecific effusion in hip joint for 3 weeks, viral cause not documented: Complaint = arthropathy. Unclear stimulation of right elbow. [2 events after 2 doses] (Transient synovitis uncertain: infection cannot be seen on US; no family history rheumatologic disorders).
- Subject 11747 (16y/008): Complaint = arthropathy reactive. Pain and swelling in multiple joints, rheumatoid factor and anti-nuclear antibodies negative, HLA-B27 positive, possible start of reactive arthritis or spondylathropathy of undefined type at time of reporting. (No other medical history reported; no family history of rheumatologic disorders).

- Subject 21505 (21y/008): Complaint = TMJ arthritis. Temporomandibular joint disorder lasting for a few weeks, no evidence of inflammation. (History of intervertebral disc and PID: no family history rheumatologic disorders).

**Subject 1623-reclassified as peri-arthritis*

HPV GROUP, > 25 YEARS OF AGE

- Subject 4101 (43y/015): Complaint = acute arthritis of Right knee and ankle joints. Uncertain inflammatory or mechanical disorder, pre-existing osteoarthritis. (Historyof cholecystectomy and pyelonephritis and past history of acute arthritis right knee; no family history rheumatologic disorders).

BRIEF NARRATIVES FOR SUBJECTS WHO RECEIVED CONTROL AND HAD ILLNESSES OF UNCERTAIN ETIOLOGY (EXPERT PANEL)

CONTROL GROUP, 15-25 YEARS OF AGE

- **Subject 230320 (25y/009): Complaint = RA. Ankle pain and swelling, no back pain, no X-ray results, reported treated with prednisone, indocin and sulfasalazine. Expert opinion = monoarthritis. (Medical history with back pain reported, no results of xrays: no family history of rheumatologic disease).*
- Subject 105646 (24y/009): Complaint = Ankylosing spondylitis. Rheumatoid arthritis according to symptoms, rheumatologist consulted, no lab tests reported, treated with methotrexate, sulfasalizine, plaquinyl, corticoid. (No medical history reported, no family history rheumatologic disorders).
- Subject 6595 (18y/001): Complaint = TMJ arthritis. Temporo-mandibular joint disorder lasting a few days, no more details. (No other medical history; no family history rheumatologic disorders.)

**Subject 230320-recoded as ankylosing spondylitis*

CONTROL GROUP, > 25 YEARS OF AGE

- Subject 1441 (44y/015): Complaint = arthritis. Knee pain x 4 days, no swelling or redness, spontaneously resolved. (History osteoarthritis as pre-existing condition, contact dermatitis, UTI, blood transfusion, history ovarian cystadenoma 1996; no family history rheumatologic disorders).

BRIEF NARRATIVES FOR SUBJECTS WHO RECEIVED CERVARIX AND HAD ILLNESSES NOT CONSIDERED TO BE IMMUNE MEDIATED (EXPERT PANEL)

HPV GROUP, 15-25 YEARS OF AGE

- Subject 86676 (16y/008): Complaint = knee joint inflammation. Transient joint pain treated for one month. Dx: Degenerative mechanical undefined disorder. (History hay fever, suspected migraines, UTI, allergies to cats and doge; no family history rheumatologic conditions).
- Subject 2018 (19y/050): Complaint = arthritis of jaw, TMJ syndrome. (History infectious mononucleosis 2004; no family history rheumatologic conditions).
- Subject 4023 (24y/051): Complaint = arthritis of right shoulder. Rotator cuff syndrome, degenerative disorder. Dx: Degenerative mechanical undefined disorder. (History of amygdylectomy and kidney stones; no family history of rheumatologic disorders).
- Subject 13140 (17y/008): Complaint =Fibromyagia. Fibromyalgia (uncertain-insufficient data). Fibromyalgia. (Bipolar affective disorder since 2000; mother has ankylosing spondylitis and maternal grandfather has ankylosing spondylitis and RA).
- Subject 14935 (16y/008): Complaint = Fibromyalgia. Fibromyalgia dx'd by rheumatologist. Fibromyalgia. (Iritis in childhood, migraine since childhood, maxillary sinusitis, asthmatic disorder (worsened 7/06); grandmother has Diabetes mellitus type II and other grandmother has heart disease; father with hypertension).

- Subject 15004 (17y/008): Complaint = fibromyalgia. Fibromyalgia, clinical diagnosis, pre-existing. Fibromyalgia. (History headaches; tension in neck, shoulder and back pain, pain in lower extremities from 2002/2003; no family history rheumatologic disorders).
- Subject 86618 (16y/008): Complaint = fibromyalgia. Dx: Post-traumatic disorder in ankle and undefined diffuse pain (probably has 2 disorders). Traumatic disorder. (History distortion left ankle in August 2004; father with history of iritis and rheumatological pain).
- Subject 294498 (21y/009): Complaint = fibromyalgia. Dx: Fibromyalgia uncertain. Fibromyalgia. (Medical history and family history not known).
- Subject 482958 (25y/009): Complaint=Rheumatism/unspecified/fibromyalgia/fibrositis. Fibromyalgia diagnosed by rheumatologist, no inflammatory arthritis, RF not clinically significant. Fibromyalgia. (History of right shoulder pain; father with thyroid disease).

CONTROL GROUP, 15-25 YEARS OF AGE

- Subject 17064 (23y/008): Complaint = arthritis in spine and foot. Post-traumatic disorder. Degenerative mechanical undefined disorder. (No other medical history, father with osteoarthritis knees and shoulders).
- Subject 7621 (18y/001): Complaint = trauma to left knee after fall 2 months after dose 2. ~5 years after dose 3 reported patellar arthropathy. Post-traumatic arthropathy. Traumatic disorder. Had corrective surgery 2007.

BRIEF NARRATIVES FOR SUBJECTS WHO RECEIVED CERVARIX AND HAD ILLNESSES NOT CONSIDERED TO BE IMMUNE MEDIATED (EXPERT PANEL)
HPV GROUP, >25 YEARS OF AGE
HPV GROUP, > 25 YEARS OF AGE

- Subject 237 (34y/014): Complaint = knee joint inflammation. Dx: mensical tear. Degenerative mechanical undefined disorder. (Osteoarthritis and meniscal tear: transient knee disorder: no family history rheumatologic disorders).
- Subject 731 (45y/014): Complaint= arthritis. Dx=meniscal tear and degenerative disorder. Degenerative mechanical undefined disorder. (History allergic rhinitis pollinosis, breast cancer; no family history rheumatologic disorders).
- Subject 9906:Complaint = arthritis worsening. Degenerative back disorder. Degenerative mechanical undefined disorder.
- Subject 60 (30y/035): Complaint = arthritis ankle. Post-traumatic disorder. Traumatic disorder. (History of bone fracture left foot in 1994; since then has had on and off joint pain: no family history rheumatologic disorders).
- **Subject 103 (44y/015): Complaint = arthropathy. Degenerative disc disorder, tendonitis shoulder. Dx: Degenerative mechanical undefined disorder. (History of lower back pain; assessed as exacerbation of pre-existing condition; no family history rheumatologic disorders).*
- Subject 4593 (36y/015): Complaint = Fibromyalgia. Dx: Fibromyalgia diagnosed by rheumatologist, pre-existing condition. Fibromyalgia. (History well-controlled asthma; brother had overactive thyroid and had thyroidectomy).
- **Subject 9162 (26y/015): Complaint = fibromyalgia. Dx: Fibromyalgia uncertain, pre-existing condition. Fibromyalgia. (No other medical history; no family history rheumatologic disorders).*

**Subject 103-now exacerbation of back pain*
**Subject 9162-AE deleted by investigator*

CONTROL GROUP, > 25 YEARS OF AGE

- Subject 10610 (42y/015): Complaint = osteoarthritis related to degenerative cartilage disorder in left knee. Degenerative mechanical undefined disorder. (History left knee injury; family history negative for rheumatologic disorders).
- Subject 4609 (59y/015): Complaint = osteoarthritis, degenerative disorder preexisting to vaccination. Degenerative mechanical undefined disorder. (History as above; mother and younger sister with arthritis).
- Subject 5471 (45y/015): Complaint = arthralgia for one day. Degenerative mechanical undefined disorder. (No medical history, no family history rheumatologic disorders).
- Subject 9906 (54y/015): Complaint = arthritis worsening. Degenerative back disorder. Degenerative mechanical undefined disorder. (Back and hip pain and was diagnosed with arthritis and bursitis app. 15 years ago; no family history rheumatologic disorders).
- **Subject 19 (64 y/015): Complaint =right metacarpal joint disorder. Probably post-traumatic. Traumatic disorder. (No other medical history, no family history rheumatologic disorders).*
- Subject 2423 (44y/019): Complaint = Fibromyalgia. Dx: Fibromyalgia uncertain. Fibromyalgia. (No medical history; family history - older sister recently diagnosed with fibromyalgia by neurologist).
- Subject 2508 (45y/010): Complaint = fibromyalgia. Dx: Fibromyalgia uncertain. Fibromylagia. (Not reviewed; no medical history reported; no family history of rheumatologic disorders).
- Subject 5288 (33y/015): Complaint = Fibromyalgia. Dx: Degenerative mechanical undefined disorder. (No medical history; no family history rheumatollgic disorders).
- Subject 9916 (38y/015): Complaint = fibromyalgia. Dx: Fibromyalgia uncertain, pre-existing condition. Fibromyalgia. (Has had cold sensitivity, chronic fatigue, poor sleep, cognitive difficulties with attention and memory for 4-5 years prior to vaccination; father had siblings with back pain).
- Subject 3613 (29y/015): Complaint = Fibromyalgia. Dx: Fibromyalgia uncertain. Fibromyalgia. (No other medical history; no family history rheumatologic disorders)
- Subject 57 (24y/016): Complaint = reactive arthritis. Arthralgia linked to viral syndrome. Viral syndrome. (No joint swelling; swollen glands supports diagnosis of viral infection and arthrlagia related to viral infection; no family history rheumatologic disorders).

**Subject 19 removed; event re-classified as hand fracture.*

Table 5b-Cases added to levels 1 analyses (3/09 submission)

Case number, Study, Age	Event	Time to Event	Intensity
		HPV-AS04	
15068, HPV-008	Non-specific arthritis	455 days after dose 3	Not Serious
71903, HPV-008	Pyoderma gangrenosum	555 days after dose 3	Serious-see deaths
4697, HPV-015	Weakness leg joints (arthropathy)	510 days after dose 3	Not serious
29594, HPV-008	Fibromyalgia	186 days after dose 3	Not serious
2322, HPV-010	Fibromyalgia	236 days after dose 3	Not serious
603, HPV-015	Drug-induced lupus erythematosus	212 days after dose 3	Serious
8416, HPV-008	Rheumatoid arthritis aggravated	269 days after dose 3	Serious (lasted 3 days)
482958, HPV-009	Rheumatoid arthritis	35 day after dose 1	Not serious
5208, HPV-015	Rheumatoid arthritis probable	155 days after dose 3	Not serious
457, HPV-031	Rheumatoid arthritis (History of joint pain, morning stiffness, malaise, joint stiffness since 1/07)	61 days after dose 2	Not serious
204, HPV-032	Rheumatoid arthritis	415 days after dose 3	Not serious
151265, HPV-009	SLE	773 days after dose 3	Not serious
110, HPV-016	Reactive arthritis-cerebral malaria	42 days after dose 3	Serious
2051, HV-048	Knee disorder (40 mcg each HPV 16 and 18 VLP)	10 days after dose 2	Not serious
		CONTROL	
15145, HPV-008	Arthritis (HAV 720)	1128 days after dose 3	Not serious
17284, HPV-008	Psoriatic arthritis (HAV 720)	39 days after dose 2	Not serious
3933, HPV-015	Arthritis knee (alum)	479 days after dose 3	Not serious
121, HPV-010	Sacro-iliac joint disease (Gardasil)	44 days after dose 3	Not serious
6528, HPV-008	Fibromyalgia (HAV)	521 days after dose 3	Not serious
144043, HPV-009	Rheumatoid arthritis (HAV)	225 days after dose 3	Not serious
5238, HPV-015	Rheumatoid arthritis (alum)	235 days after dose 3	Not serious
5270, HPV-015	Rheumatoid arthritis (alum)	302 days after dose 3	Not serious

Narratives for additional events (those considered serious)

HPV Group

Subject 0603 (39y/015): Received 3 doses Cervarix. 7 months after dose 3, developed viral exanthema vs. streptococcal infection. Subsequently she developed fever. After extensive work-up and multiple meds, history was obtained that rashes began 6 days after starting herbal tea (with Vitaplus). The tea and other meds were discontinued and she was treated with steroids. A skin biopsy was consistent with drug eruption.

Subject 8416 (25y/008): Received 3 doses Cervarix. Subject had a history of RA. No family history of rheumatologic disorders. 9 months after dose 3, the subject experienced myalgias, arthralgias, intense pain in left leg with swelling. She was hospitalized with exacerbation of RA. RF was =4891U and CRP 4.09. She withdrew consent and was after lost to follow-up.

Subject 110 (25y/016): Received 3 doses of Cervarix, 2 months after developed **cerebral malaria** and **typhoid fever** (travel to Ghana). She developed reactive arthritis knees and ankles. The subject recovered with sequelae.

Control

Subject 3933 (45y/015): Received 3 doses Cervarix. 16 months after dose 3, developed arthritis knee joint and was hospitalized. Resolved in 11 days. Considered unrelated to vaccination. CRP=1.85. (Medical history = hypertension and hypothyroidism). No family history reported.

Table 6b-Musculoskeletal events including events identified by external expert panel with corresponding MedDRA terms and codes used for screening the databases for events of interest [Extended terms]

CBER categories of diseases	CBER Verbatim Term	MedDRA Preferred Term	MedDRA code
Musculoskeletal	Systemic lupus erythematosus	Systemic lupus erythematosus	10042945
		Systemic lupus erythematosus rash	10042946
	Sjogren's syndrome	Sjogren's syndrome	10040767
	Rheumatoid arthritis	Rheumatoid arthritis	10039073
	Juvenile rheumatoid arthritis	Juvenile arthritis	10059177
	Arthritis	Arthritis	10003246
	Reactive arthritis	Arthritis reactive	10003267
	Scleroderma	Scleroderma	10039710
	Arthropathy	Arthropathy	10003285
	Spondyloarthropathy	Spondyloarthropathy	10051265
	Fibromyalgia	Fibromyalgia	10048439
Additional terms from other CBER categories of diseases considered by external experts to be relevant for an analysis of musculoskeletal disorders			
Skin	*Cutaneous lupus*	*Cutaneous lupus erythematosus*	*10056509*
	Dermatomyositis	*Dermatomyositis*	*10012503*
	Psoriatic arthropathy	*Psoriatic arthropathy*	*10037162*
	Raynaud's phenomenon	*Raynaud's phenomenon*	*10037912*
Others	*Antiphospholipid syndrome*	*Antiphospholipid syndrome*	*10002817*
	Vasculitis	*Leukocytoclastic vasculitis*	*10024377*
		Vasculitis	*10047115*
		Behcet's syndrome	*10004213*

STN 125259/48, Supplemental safety update, Table 96, p. 216

Table 7b: Reported neonatal and infant deaths from GSK-sponsored studies (data lock-point of August 31, 2008) [control]

Infant's Case ID		Infant's Gender	Infant's Age	Preferred Term	Time from last vaccination to EDC** (in days)	Treatment
b(6)		Male	Neonate	Death neonatal	-272	Al(OH)3 control
		Female	Neonate	Respiratory distress, Premature baby	-128	Al(OH)3 control
	*	Female	Neonate	Death neonatal, Premature baby, Placental transfusion syndrome	NA	Al(OH)3 control
	*	Female	Neonate	Death neonatal, Premature baby, Placental transfusion syndrome	NA	Al(OH)3 control
		Male	Neonate	Respiratory distress	-1425	Al(OH)3 control
		Male	Fetus	Intra-uterine death	-1577	Al(OH)3 control
		Male	Neonate	Sudden infant death syndrome	-510	HAV720 vaccine
	*	Male	Neonate	Premature baby	NA	HAV720 vaccine
	*	Male	Neonate	Premature baby	NA	HAV720 vaccine
		Male	72 Days	Pneumonia aspiration	NA	HAV720 vaccine
		Male	Neonate	Premature baby	-158	HAV720 vaccine
		Female	Neonate	Respiratory distress, Death neonatal	-25	HAV720 vaccine
		Male	Neonate	Hemorrhage intracranial	-144	HAV720 vaccine
		Male	Neonate	Premature baby, Respiratory distress	NA	HAV720 vaccine
		Male	Neonate	Premature baby	-584	HAV720 vaccine
		Male	Neonate	Neonatal respiratory distress syndrome	-14	HAV720 vaccine

*Twins

** Negative values indicate the number of days before the EDC, positive values indicate the number of days after the EDC

NA= Not available

EDC= Estimated date of conception

Sthis female fetus was born dead and premature by normal vaginal delivery, after 24 weeks of pregnancy.

Source: STN 125259.48, Supplemental safety summary, Table 51, p. 133-134

Table 8b: Reported neonatal and infant deaths from GSK sponsored studies (data lock-point of August 31, 2008) [Cervarix]

Infant's Case ID	Infant's Gender	Infant's Age	Preferred Term	Time from last vaccination to EDC** (in days)	Treatment
b(6)	Female	Neonate	Respiratory distress	-368	HPV-16/18 vaccine
	Male	Neonate	Premature baby	-686	HPV-16/18 vaccine
	Male	Neonate	Premature baby	-403	HPV-16/18 vaccine
	Female	Neonate	Premature baby	-403	HPV-16/18 vaccine
	Female	Neonate	Neonatal asphyxia	-647	HPV-16/18 vaccine
	Male	Neonate	Premature baby	11	HPV-16/18 vaccine
	Male	Neonate	Respiratory distress, Pleural effusion, necrotizing colitis, short bowel syndrome	-104	HPV-16/18 vaccine

*Twins
** Negative values indicate the number of days before the EDC, positive values indicate the number of days after the EDC
NA– Not available
EDC– Estimated date of conception
Sthis female fetus was born dead and premature by normal vaginal delivery, after 24 weeks of pregnancy.
Source: STN 125259.48, Supplemental safety summary, Table 51, p. 133-134

A brief description of these case fatalities is provided.

CONTROL GROUP

- b(6): This neonate was born after 28 weeks of pregnancy, by normal vaginal delivery. The infant had an unknown Apgar score, and died a few hours later. An autopsy was not performed.
- b(6): The neonate was born via partial breech extraction with an Apgar score 6-8, and weight 1 kg, after 29 weeks age of gestation and died due to acute respiratory distress syndrome and prematurity.
- b(6): The neonates were delivered prematurely after 21 weeks of pregnancy and subsequently died. The twins experienced twin-twin transfusion syndrome and severe oligohydramnios.
- b(6) After 25 weeks of pregnancy, the neonate was born by caesarean section. The infant's Apgar score, weight and height were not known. The newborn developed respiratory distress and died. The cause of death was respiratory distress. No autopsy was performed.
- b(6): The male fetus was born dead by normal vaginal delivery, after 24 weeks of pregnancy (weight: 655g). An autopsy was not performed.
- b(6): Two years after the mother's last vaccination and after 41 weeks of pregnancy, this male child was born by normal vaginal delivery. He had an unknown Apgar score, a weight of 3.2 kg and a height of 52 cm. When the infant was 2 months and 2 days-old, he was found unresponsive lying prone in his bassinet by his grandmother. The infant was last known alive approximately six hours prior, when he was fed formula. According to the mother, the child was on infant Tylenol drops for congestion, but had not had any of drops in the past 48 hours. The cause of death was described as interstitial pneumonitis. Examination of the lungs revealed wide spread chronic inflammation involving interstitium as well as few focal areas of acute inflammation. His recent symptoms of congestion correlated with the respiratory inflammation. The complete post-mortem disclosed no other anatomic, metabolic or toxicologic cause of death. No trauma or abnormalities were noted that would have caused or contributed to his death.

- b(6): These male neonates were born on after 23 weeks of pregnancy, with a birth weight of 0.470 kg and 0.420 kg, and an Apgar score of 2- 0 and 4-0, respectively. They died immediately after birth due to immaturity.
- b(6): This male child was born by normal vaginal delivery after 37 weeks of pregnancy. He had an Apgar score of 7-9 and a weight of 2.5 kg. The baby stayed in an incubator for 1 week. The baby was discharged after one week apparently stable. However, 72 days after delivery and seven months after his mother's last vaccination, the baby experienced aspiration pneumonia and died. According to the baby's mother, after breastfeeding the baby suddenly developed upwards rolling of eyeballs and cyanosis.
- b(6): This male child was born premature by normal vaginal delivery after 32 weeks of pregnancy. He was born presenting severe respiratory distress and died due to respiratory arrest.
- b(6): This female neonate was born premature (24 weeks of pregnancy, birth weigh: 0.550 kg) by an emergency caesarean section secondary to eclampsia in her mother. She was born presenting respiratory distress syndrome and died. No autopsy was performed.
- b(6): This male infant was born premature (weigh: 0.785 kg) after 24 weeks of pregnancy, and with an Apgar score of 2 - 6 - 6. On (b)(6) the neonate died in the hospital after 24 days of life. The cause of the death was intracranial hemorrhage. No necropsy was done.
- b(6): The neonate was born by vaginal delivery at home assisted by a traditional birth attendant after 28 weeks of pregnancy (weight: 1.8 kg). The baby showed signs of respiratory distress (cyanosis) and died.
- b(6) This neonate was delivered premature at 30 weeks of pregnancy and died 10 hours after birth due to respiratory distress.
- b(6): This male child was born premature by normal vaginal delivery after 32 weeks of pregnancy. He had a weight of 1.500 kg. He was diagnosed with respiratory distress syndrome secondary to prematurity and died after a few hours due to pulmonary complications. An autopsy was not performed.

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- b(6): The neonate was born at 24 weeks of gestation (birth weight: 724 grams) by caesarean section due to a placental abruption, had severe respiratory distress and died.
- b(6): This male child was born by vaginal delivery after 22 weeks of pregnancy. He had a weight of 0.5 kg and died on the same day. The cause of death is prematurity. An autopsy was not performed.
- b(6): The neonates were born after 28 weeks of pregnancy. The mother had a premature rupture of membranes and then gave birth to premature twin infants (one male and one female) by normal vaginal delivery. The infants had unknown Apgar scores, a weight of 2.000 kg for the baby boy and unknown for the baby girl. Both neonates died due to the prematurity.
- b(6): The neonate was born by normal vaginal delivery after 40 weeks of pregnancy. The infant had an unspecified Apgar score and a weight of 2.806 kg. The neonate experienced neonatal asphyxia and died at 10 hours of life.
- b(6) This male infant was born premature after 28 weeks of pregnancy by normal vaginal delivery weighing 1.100 kg and with unknown Apgar score. The neonate died on the same day due to lung immaturity.
- b(6) This male child was born premature by caesarean section after 26 weeks of pregnancy. He had an Apgar score of 5-9, a weight of 0.790 kg and a height of 32 cm. The child was diagnosed with respiratory distress syndrome, right pulmonary effusion and necrotizing enterocolitis. A colectomy with iliostomy was done. Afterwards the neonate

developed a short bowel syndrome and died at 183 days of age due to sepsis (hospital acquired infection).

Table 9b: Reported neonatal and infant deaths from study HPV-009 (data lock-point of August 31, 2008) [control]

Infant's Case ID	Infant's Gender	Infant's Age	Preferred Term	Time from last vaccination to EDC** (in days)	Treatment
b(6)	Female	Neonate	Congenital nephrotic syndrome	-92	HAV720 vaccine
	Female	Neonate	Death neonatal	-207	HAV720 vaccine
	Male	Neonate	Interstitial lung disease	-256	HAV720 vaccine
	Female	Neonate	Premature baby	-2	HAV720 vaccine
	Female	Neonate	Premature baby	-2	HAV720 vaccine

Table 10b: Reported neonatal and infant deaths from study HPV-009 (data lock-point of August 31, 2008) [Cervarix]

Infant's Case ID	Infant's Gender	Infant's Age	Preferred Term	Time from last vaccination to EDC** (in days)	Treatment
b(6)	Male	Neonate	Death neonatal	9	HPV-16/18 vaccine
	Male	Neonate	Premature baby	-858	HPV-16/18 vaccine
	Male	Neonate	Premature baby	-858	HPV-16/18 vaccine
	Female	Neonate	Death neonatal, Pulmonary arterial hypertension, Premature baby	-306	HPV-16/18 vaccine

Brief description of these case fatalities is provided.

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- b(6): The mother was exposed to the vaccine 92 days before the estimated date of conception. This female child was born by normal vaginal delivery. The infant had an Apgar score of 10, a weight of 2.91 kg and a height of 49 cm. The newborn experienced meconium aspiration. During this hospitalization the infant was very edematous, for which several studies were performed, among which proteinuria was detected. A renal biopsy was also performed as compatible with Finland's type Nephrotic Syndrome and Cytomegalovirus infection. Diagnosis: congenital nephrotic syndrome. On 25 January 2007 a sonogram revealed a mild increase of echogenicity of both kidneys. On 02 March 2007, she presented deterioration of her clinical condition and experienced a spontaneous peritonitis. On b(6) b(6), the infant presented a cardio respiratory arrest and died. An autopsy was performed. Cause of death: Primary Bacterial Peritonitis, septic shock and disseminate intravascular coagulation.
- b(6): The mother was exposed to the vaccine 207 days before the estimated date of conception. The female neonate was born by Caesarean section due to abruption placenta, after a term pregnancy. The neonate experienced tachycardia and died shortly after birth.
- b(6): The mother was exposed to the vaccine 256 days before the estimated date of conception. On 11 November 2005, this male neonate was born premature by uncomplicated vaginal delivery after 35 weeks of pregnancy. The neonate weighed 1,900 kg with a cephalic circumference of 31 cm and an Apgar score of 9 - 9. After birth, the neonate experienced frequent episodes of apnea. On b(6), the infant experienced cyanosis and was brought in respiratory arrest to the emergency room. Cardiopulmonary resuscitation was

performed without success. An initial diagnosis of sudden infant death syndrome was made. An autopsy was performed. According to the autopsy report, the cause of death was an interstitial pneumonitis. The abnormalities found were inflammatory pulmonary disease from viral origin (interstitial pneumonitis), with visceral congestion. From forensic point of view, it as a natural death. According to the neuropathology report, the diagnosis was mild cerebral edema and sequelae from neonatal hypoxic encephalopathy: periventricular leukomalacia, necrosis of white substance (old), cerebral and cerebellar subarachnoid hemorrhage (old) and old ventricular hemorrhage (remain).

- b(6): The mother was exposed to the vaccine 2 days before the estimated date of conception. On b(6) after 25.6 weeks of pregnancy, these twin neonates were born by Caesarean section due to transverse presentation. The first female infant had a weight of 620 g, a length of 29 cm and an Apgar score of 2-5. The second female infant had a weight of 520 g, a length of 29 cm and Apgar score of 1-5. The neonates had respiratory insufficiency syndrome due to hyaline membrane and both died shortly after birth. The cause of death was extreme prematurity and contributory cause was twin pregnancy.

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- b(6): This female neonate was born by Caesarean section due to fetal hypokinesia after 40 weeks of pregnancy. The mother was exposed to the HPV 16/18 vaccine 9 days after the estimated date of conception. The neonate had the umbilical cord around the neck, and was born alive but died approximately one hour later. No additional details were obtained.
- b(6): The mother was exposed to the vaccine 858 days before the estimated date of conception. The neonates were born prematurely after 23 weeks + 4 days of pregnancy and died on the same day due to the extreme prematurity.
- b(6): The mother was exposed to the vaccine 306 days before the estimated date of conception. This female child was born premature, after 29 weeks of pregnancy, by normal vaginal delivery. She had an Apgar score of 1-7, a weight of 1,94 kg. The neonate was born flaccid, hypotonic, hemodynamically unstable, with slow capillary perfusion and required resuscitation maneuvers. The neonate was diagnosed with respiratory distress, hyaline membrane, left pneumothorax, and pulmonary arterial hypertension. The neonate died 1 day later. Cause of death was pulmonary arterial hypertension and prematurity.

Table 11b: Cases that were exposed to study vaccine during pregnancy (data lock-point of August 31, 2008)

Treatment	Infant's Case ID	Infant's Gender	Infant's Age	Case Outcome	Preferred Term	Time from EDC to next vaccination (in days)
Al(OH)3 control	b(6)	Unknown	Fetus	Fatal	Anencephaly	15
Al(OH)3 control		Unknown	Fetus	Fatal	Trisomy 21	15
Hepatitis A vaccine		Female	Neonate	Unresolved	Apert's syndrome	11
Hepatitis A vaccine		Female	Neonate	Fatal	Anencephaly	14
Human papilloma type 16 – 18 vaccine		Female	Neonate	Resolved	Hip dysplasia	6
Human papilloma type 16 – 18 vaccine		Male	Neonate	Fatal	Multiple congenital abnormalities	1

EDC= Estimated date of conception

*One pregnancy with twins

STN 125259/48, Supplemental safety summary, Table 57, p. 149-150

Table 12b-Congenital anomalies in subjects who received Cervarix

TREATMNT	PTNAME	MPID	ISEX	IAGE	OUTCOMF	TVFDC	TVDIAG
HPV	Adrenogenital syndrome, jaundice neonatal	b(6)	Female	Neonate	Unresolved	-976	1223, 1225
HPV	Bacterial sepsis, dextrocardia, facial palsy, high arched palate, low set ears, multiple congenital anomalies, talipes		Male	Neonate	Fatal		381, 343, 343, 343, 343, 343
HPV	Cerebral atrophy		Male	Neonate	Improved	-183	569
HPV	Cleft lip and palate		Male	Fetus	Fatal	-163	267
HPV	Congenital cystic kidney disease and oligohydramnios		Unknown	Fetus	Fatal	-280	413
HPV	Congenital hydrocephalus, lactic acidosis, and talipes		Female	Neonate	Fatal	-451	688
HPV	Congenital hydrocephalus, meningitis		Female	Neonate	Fatal		591, 627
HPV	Congenital laryngeal stridor		Male	Neonate	Improved	-346	695
HPV	Conjoined twins		Unknown	Fetus	Not Applicable	-899	970
HPV	Diaphragmatic hernia		Female	Neonate	Improved	-918	1191
HPV	Ectopic kidney, fetal growth retardation		Female	Neonate	Improved	-233	478
HPV	Encephalocele		Female	Fetus	Fatal	-584	860
HPV	Fetal macrosomia, ventricular hypertrophy, VSD		Female	Neonate	Resolved	-52	316
HPV	Hemangioma and talipes		Female	Neonate	Unresolved	-480	745
HPV	Hip dysplasia		Female	Neonate	Resolved	-27	258
HPV	Holoprosencephaly		Female	Fetus	Fatal		611
HPV	Hydrocephalus and meningomyelocele		Female	Neonate	Resolved with Sequelae	-211	483
HPV	Hydrocephalus		Male	Fetus	Fatal	-243	366
HPV	Hypospadias		Male	Neonate	Unresolved	-340	590
HPV	Intra-uterine death, congenital hand malformation (non serious event)		Male	Fetus	Fatal	-85	240
HPV	Klinefelter's syndrome		Male	Neonate	Fatal	-331	330
HPV	Laryngomalacia, tracheomalacia		Female	Neonate	Resolved	-43	286
HPV	Multiple congenital abnormalities		Female	Fetus	Fatal	-47	206
HPV	Multiple congenital abnormalities		Male	Neonate	Fatal	-119	262
HPV	Pulmonary hypoplasia		Male	Neonate	Fatal		343
HPV	Pulmonary valve stenosis		Male	Neonate	Fatal	-216	468
HPV	Renal aplasia and enterocolitis infectious		Female	Neonate	Improved	-44	305
HPV	Syndactyly		Male	Neonate	Unresolved		511
HPV	Talipes		Female	Neonate	Resolved with Sequelae	-17	266
HPV	Transposition of the great vessels		Female	Neonate	Improved	-222	438
HPV	Trisomy 21		Male	Neonate	Unresolved	-343	594

Source: STN 125259.48, Appendix table 003.xpt, congenital anomalies

Table 13b-Congenital anomalies in subjects who received control

TREATMNT	PTNAME	MPID	ISEX	IAGE	OUTCOMT	TVLDC	TVDIAG
HAV720	Anencephaly	b(6)	Female	Neonate	Fatal	-118	285
ALU	Anencephaly, trisomy 21		Unknown	Fetus	Fatal		99
HAV720	Ankyloglossia congenital		Male	Neonate	Resolved	-349	603
HAV720	Aortic valve stenosis, metabolic disorder, neonatal aspiration, neonatal hypoxia		Female	Neonate	Unresolved	-834	1099
HAV720	Apert's syndrome		Female	Neonate	Unresolved	-115	254
ALU	Atrioventricular septal defect		Female	Neonate	Improved	-293	568
HAV720	Cleft lip		Male	Neonate	Resolved	-40	267
HAV720	Cleft lip		Male	Neonate	Resolved	-430	574
HAV720	Cleft palate		Male	Neonate	Unresolved	-198	460
HAV720	Congenital central nervous system anomaly, fetal distress syndrome, inguinal hernia, jaundice neonatal,		Male	Neonate	Unresolved	-524	789
HAV720	Congenital eyelid malformation, hemangioma, premature baby		Female	Neonate	Unresolved	-888	1083
HAV720	Congenital hand malformation		Female	Neonate	Unresolved	-173	449
HAV720	Cystic lymphangioma, Turner's syndrome		Female	Fetus	Fatal		177
HAV720	Eyelid ptosis, neonatal hypoxia		Female	Neonate	Unresolved	-369	615
ALU	Fetal malformation		Unknown	Fetus	Fatal	-1249	1365
HAV720	Gastroschisis		Male	Neonate	Fatal	-27	276
HAV720	Heart disease congenital		Male	Neonate	Fatal	-170	444
ALU	Hip dysplasia, trisomy 21		Female	Neonate	Unresolved	-389	647
HAV720	Hypoplastic left heart syndrome		Female	Neonate	Fatal	-284	509
HAV720	Neurofibromatosis		Female	Neonate	Improved	-99	353
ALU	Patent ductus arteriosus, VSD		Female	4 Days	Resolved	-730	1086
HAV720	Polydactyly		Female	Neonate	Resolved	-266	530
HAV720	Pyloric stenosis		Male	Neonate	Resolved	-708	980
HAV720	Talipes		Male	Neonate	Unresolved	-672	923
ALU	Talipes		Male	Neonate	Resolved	-729	905
HAV720	Talipes		Male	Neonate	Improved	-390	635
HAV720	Trisomy 18		Unknown	Fetus	Not Applicable	-788	868
HAV720	Ventricular septal defect		Female	Neonate	Unresolved		924