LIST OF APPENDICES

APPENDIX 1: Protocol 015, Inclusion/Exclusion Criteria

Inclusion Criteria

- Healthy females age 16 to 23 years with intact uteri. In Singapore only, the subject would include healthy women 16-26 years of age.
- No clinical evidence of gross purulent cervicitis (otherwise postponed until after treatment or lack of laboratory confirmation of treatable cause).
- Agreed to refrain from douching or using vaginal medication or preparation for 48 hours prior to any scheduled visit that included a pelvic examination.
- Agreed to refrain from sexual intercourse (including anal and vaginal) for 48 hours prior to any scheduled visit that included a pelvic examination, in an attempt to avoid detection of viral DNA that had been deposited in the vagina or on the perineal/perianal area during sexual intercourse and was not the result of ongoing infection.
- Not pregnant on Day 1 (as determined by a serum pregnancy test or urine pregnancy test sensitive to 25 international units of human chorionic gonadotropin [IU HCG]), and agreed to use effective contraception through Month 7 of the study.
- Individuals who had sexual intercourse in the 2 weeks prior to enrollment must have been using effective contraception as defined above. (Emergency contraception was not considered effective contraception for enrollment into the study.)
- Individuals with a lifetime history of 0 to 4 male or female sexual partners (individuals with whom penetrative vaginal intercourse occurred). Women with 0 lifetime partners must have been at least 18 years of age, and if heterosexual or bisexual, must have been seeking contraception to be admitted to the study. Female subjects who were exclusively lesbian in orientation and who had 0 lifetime sexual partners may have been enrolled. In Finland only: Women 16-17 years of age who had 0 male or female sexual partners may have been enrolled, but they must have been seeking contraceptive advice at the time of enrollment or must have recently obtained contraception to enter the study. Women 16-17 years of age were enrolled in Finland regardless of the lifetime number of sexual partners. The lifetime history of 0-4 partners applied to those $\geq$ 18 years of age.
- Agreed to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes. In Finland only: This inclusion criteria was not applicable.
- No temperature $\geq$ 100°F (oral) within 24 hours prior to the first injection.

Exclusion Criteria

- Individuals with any prior abnormal Pap test showing squamous intraepithelial lesion (SIL) or biopsy showing cervical intraepithelial neoplasia (CIN).
- Individuals with genital warts or any prior history of, or treatment for genital warts.
- Individuals concurrently enrolled in clinical studies of investigational agents or studies involving collection of cervical specimens.
- History of prior HPV vaccination.
- Receipt of inactivated vaccines within 14 days prior to enrollment or receipt of live virus vaccines within 21 days prior to enrollment.
- History of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension or shock) that required medical intervention.

- Individuals allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).
- Individuals who received any immune globulin (including RhoGAM™, Ortho Clinical Diagnostics) or blood-derived products within the 6 months prior to the first injection, or planned to receive any through Month 7 of the study.
- Individuals with history of splenectomy, known immune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis), or who received immunosuppressives (e.g., radiation, administration of antimetabolites, antilymphocytic sera, systemic corticosteroids). Individuals who received periodic treatments with immunosuppressives, defined as at least 3 courses of oral corticosteroids, each lasting at least 1 week in duration for the year prior to enrollment, were excluded. Subjects using topical steroids (e.g., inhaled or nasal) were eligible for vaccination.
- Individuals who were immunocompromised or had been diagnosed as having HIV infection.
- Individuals with severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
- History of recent (within 1 year from the date of enrollment) or ongoing alcohol abuse or other drug abuse.
- Any condition that in the opinion of the investigator might have interfered with the evaluation of the study objectives.
- Any plans to permanently relocate from the area prior to the completion of the study or to leave for an extended period of time when study visits would need to be scheduled.
- Individuals with >4 lifetime male or female sexual partners. In Finland ONLY: Subjects who were 18 years or older and had >4 lifetime male or female sexual partners.
- Inability to give informed consent/assent.

APPENDIX 2: Pathology Panel

Pathology Panel

Slides of tissue specimens were prepared by the program central laboratory. The laboratory reviewed the slides and provided a diagnosis for the purpose of management of the subject. The diagnosis from the laboratory was not included in the endpoint definition because, as per the sponsor, studies have shown that pathologists who read histologic slides for the purpose of medical management tend to over-diagnose CIN 1 lesions due to medicolegal pressure. The slides prepared by the central laboratory from the cervical biopsy/definitive therapy specimens were submitted to an expert Pathology Panel.

All biopsy specimens were reviewed by a Pathology Panel, which consisted of 4 experts in the area of gynecologic pathology. After Protocol 005, all ECC and definitive therapy specimens were also reviewed by the Pathology Panel. Merck Research Laboratories and the Pathology Panel followed established guidelines for histology review. The consensus diagnoses of the Pathology Panel were used in the definition of study endpoints only. The performance of the Pathology Panel was monitored using a prespecified quality control program. Readings were assessed as being reproducible, consistent over the course of the program, and correlated with the presence of specific HPV types.

Panelists reviewed the specimen slides independently, blinded to the HPV status, central laboratory's diagnosis, other panelist's diagnosis, and other demographic and clinical data of the study subjects. If the diagnoses of the lesion by the initial 2 panelists agreed, the diagnosis was considered the final consensus diagnosis with regard to the endpoint of the clinical trials. If the 2 diagnoses were discrepant, the third pathologist was called upon for the adjudication of the diagnosis, although the third panelist was not aware that he/she was a "tie-breaker". On the rare occasion that all three diagnoses disagreed, a fourth pathologist reviewed the slides. The final diagnosis was the one rendered by 2 pathologists. If the 4 pathologists provided 4 different diagnoses for a given biopsy, a panel meeting consisting of all 4 pathologists took place to reach the final consensus. Overall, among the 12428 biopsies in the program, 76.1% achieved consensus after review by 2 pathologists, 19.3% reached consensus after review by 3 pathologists, 4% reached consensus after review by 4 pathologists, and 0.6% required a consensus meeting.

For all Phase 3 studies, this last step was required in 71 samples; one case became a primary endpoint [placebo recipient AN 32205]. There were 2 other placebo recipients [AN 44707 and AN 45516] whose lesions could have been cases based on the readings of one or more panel members, but were not cases based on the consensus diagnosis. 68 other samples were not primary efficacy endpoints.

The diagnosis of the central laboratory was used for the purposes of medical management. However, if a Pathology Panel consensus diagnosis for a given specimen was deemed more severe than the diagnosis of the central laboratory for the same

specimen, a written notification was sent to the study site informing them of the discrepancy. Study site investigators could then use this information in determining the course of patient care. This is shown below as "Safety Net Notifications".

> The panelists' classifications will also be used for providing "Safety Net notifications". The SPONSOR will notify the Principal Investigator and study site for any of the following circumstances:
>
> - Histological classification of any carcinoma, including CIN 3 (squamous cell carcinoma in-situ), adenocarcinoma in situ or adenocarcinoma, during any review stage which was NOT reported previously by the Central Laboratory pathologist;
> - Histological classification of anogenital cancer, vulvar intraepithelial neoplasia (VIN) 2/3, or vaginal intraepithelial neoplasia (VaIN) 2/3 during any review stage which was NOT reported previously by the Central Laboratory pathologist;
> - Consensus classification of CIN 2/3 or worse for any cervical specimen (cervical biopsy, ECC, or definitive therapy specimen) which is more severe than the worst diagnosis reported by the Central Laboratory pathologist for any cervical specimen from that subject-visit (see hierarchies given in Section II.E, Table 4);
> - Consensus classification for any vaginal biopsy or external genital lesion biopsy specimen of VIN 2/3, VaIN 2/3, or any more severe diagnosis which was NOT reported previously by the Central Laboratory pathologist (see hierarchies given in Section II.E, Table 5).

A well-described Standard Operating Procedure was followed for the determination of cases. (Reference 47 of BLA) In addition, a validation of the pathology panel diagnoses was included in the BLA.

Figure 3

Algorithm for Pathology Panel Review

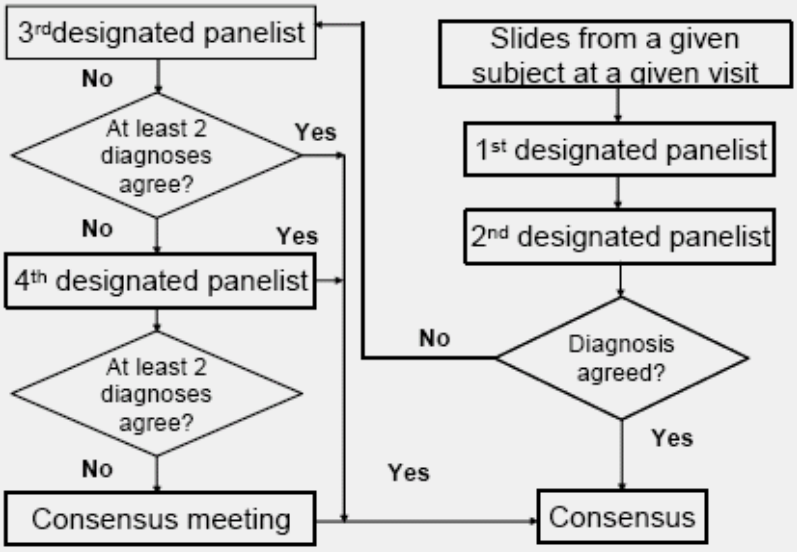

Table 1. Members of the Pathology Panel

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APPENDIX 3: Protocol 015, Colposcopy Algorithm

Mandatory Regimen for Triage of Abnormal Pap Tests to Colposcopy

ThinPrep Pap Result	Action
Negative for intraepithelial lesion or malignancy (includes reactive, reparative, inflammatory, etc.	Routine visit interval as specified by protocol.
Atypical Squamous Cells of Undetermined Significance (ASC-US)	Repeat ThinPrep Pap test 6 months later. (a)
Atypical Squamous Cells, Cannot Rule out HSIL (ASC-H)	Referral to colposcopy.
Low-grade Squamous Intraepithelial Lesions (LSIL)	Repeat ThinPrep Pap test 6 months later. (a)
High-grade Squamous Intraepithelial Lesions (HSIL)	Referral to colposcopy.
Atypical glandular cells (to include atypical endocervical, endometrial, NOS, adenocarcinoma in situ, adenocarcinoma	Referral to colposcopy.
Unsatisfactory	Repeat ThinPrep Pap test as soon as possible. The interval between the rescheduled Pap test must be at least 4 weeks from the Pap test that had the unsatisfactory finding.

For the ASC-US and LSIL Repeat Pap tests: If the repeat ThinPrep Pap test revealed ASC-H, LSIL, HSIL, or Atypical Glandular Cells, then the subject was referred to colposcopy. If the repeat Pap test was negative for squamous intraepithelial lesion, then the subject returned to routine Pap testing schedule. If the repeat Pap revealed ASC-US, then the central lab performed reflex HPV testing on residual ThinPrep material (High Risk Probe, Hybrid Capture II, DIGENE). If positive or the amount of residual ThinPrep material was insufficient to conduct the test, the subject was referred for colposcopy. If negative, then the subject returned for Pap screening at the routine visit interval.
Subjects with a diagnosis at Day 1 were referred immediately for coloscopy.

APPENDIX 4: Protocol 015, Efficacy Population Definitions

Per-Protocol Efficacy: Included subjects who: (1) received all 3 vaccinations; (2) were sero- and PCR-negative at Day 1 and PCR-negative through Month 7 to the appropriate HPV types; and (3) generally did not deviate from the protocol.

To be included in the per-protocol efficacy population for the primary efficacy analysis of HPV 16/18-related CIN 2/3 or worse, subjects were required to be seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the component being analyzed.

To be included in the per-protocol efficacy population for exploratory analyses of HPV 6- or HPV 11-related endpoints, subjects were required to be seronegative to HPV 6 and HPV 11 at Day 1 and PCR negative to HPV 6 and 11 from Day 1 through Month 7.

A list of protocol deviations that excluded subjects from the per-protocol population is given. Some of these deviations were specified in the DAP. Others were unanticipated and occurred after preparation of the DAP. An additional criterion for defining the per-protocol efficacy population was added to those outlined in the DAP. To ensure the Day 1 prevaccination serum and swab samples were appropriate for assessing baseline HPV status, day ranges were applied to the samples. The Day 1 prevaccination serum sample was required to be obtained within 14 days prior to the first vaccination or on the day of the first vaccination. The Day 1 prevaccination swab samples were required to be obtained within 14 days prior to and within 10 days after the first vaccination.
All reasons for exclusion were identified prior to unblinding.

General Protocol Violations
Incorrectly randomized
Incorrect clinical material or dose amount
Received non-study vaccination
Received immunosuppressives, IgG, or blood products
History of immune disorder
Month 7 swab sample out of acceptable day range
Vaccine temperature out of range
Vaccination not completed within 12 months
Subject has 2 cervices
Subject prematurely unblinded
Missed 2nd or 3rd vaccination
Mising Day 1 serology samples/ results
Missing Month 7 swab samples/results
Seropositive and/or PCR positive to HPV 6 or 11, HPV 16, or HPV 18 at Day 1
PCR positive to HPV 6 or 11, HPV 16, or HPV 18 at or before Month 7

Modified Intent to Treat Population 1 – (MITT-1): Included subjects who: (1) received all 3 vaccinations; (2) were sero- and PCR-negative at Day 1 and PCR-negative through Month 7 to the appropriate HPV types; (3) included protocol violators.

Modified Intent To Treat Population 2 – (**MITT-2):** Included subjects who: (1) received at least 1 vaccination; (2) were sero- and PCR-negative at Day 1 to the appropriate HPV types; and (3) had any follow-up visit after 1 month following the first injection.

Modified Intent To Treat Population 3 – (**MITT-3):** Included subjects who: (1) received at least 1 vaccination and (2) had any follow-up visit after 1 month following the first injection. These subjects could have been naïve or non-naïve to vaccine HPV type.

Modified Intent to Treat Population 4 – (MITT-4): Included subjects who (1) received at least 2 vaccinations and (2) were seronegative at Day 1 to the relevant HPV types and PCR negative Day 1 through Month 3 for the relevant HPV types. Cases were counted starting 30 days after 2nd vaccination. [Note: This was presented in Study 013 and Study 005.]

All of the vaccine-HPV-type-related exploratory endpoints were evaluated in 1 or more of these 4 populations.

An additional population, labeled the **"Restricted MITT-2" population (RMITT-2)**, was used for the evaluation of endpoints due to any HPV type. This population includes all subjects who were seronegative and PCR negative at Day 1 to all vaccine HPV types **AND** had a normal Pap test result at Day 1. As per the sponsor, the analyses performed in the restricted MITT-2 population are intended provide a "real world" estimate of the impact of the vaccine with regard to infection and clinical disease caused by vaccine HPV types among baseline HPV-naïve women. The subset of baseline HPV-naïve women cannot be completely identified without assay data for the non-vaccine HPV types. Those with negative Pap tests may still have HPV related disease, since sensitivity of Pap tests is not 100%. The sponsor, nonetheless, uses this population in the absence of such data, requiring that subjects have a normal Pap test result at baseline which would more closely serve as a proxy for assessing baseline negativity for those HPV types.

The potential therapeutic effects of the vaccine were evaluated in the following populations:

Day 1 PCR Positive and Seronegative Subjects: Included all subjects who were seronegative and PCR positive at Day 1 to the appropriate HPV type. Subjects were required to have their Day 1 serum and PCR samples collected within an acceptable day range. This population considered subjects who were infected with a vaccine HPV type, but who had not yet mounted an immune response to the HPV infection at baseline.

Day 1 PCR Negative and Seropositive Subjects: Included all subjects who were seropositive and PCR negative at Day 1 to the relevant vaccine HPV type and had serum and PCR samples collected within an acceptable day range. This population considered subjects who had mounted an immune response to natural infection with a vaccine HPV type and were not infected with the given vaccine HPV type at baseline.

Day 1 PCR Positive and Seropositive Subjects: Included all subjects who were seropositive and PCR positive at Day 1 to the relevant vaccine HPV type and had serum and PCR samples

collected within an acceptable day range. This population considered subjects who had mounted an immune response to natural infection with a vaccine HPV type and were infected with the given vaccine HPV type at baseline.

APPENDIX 5: Protocol 015, Changes in Protocol and Changes in Statistical Analyses

There were **four protocol amendments.**
Protocol Amendment 015-01 was a complete amendment finalized on 2/28/03, which included country-specific as well as overall modifications. The main purpose of the country-specific changes was to update the inclusion/exclusion and protocol requirements that may not have been applicable in all countries based on government regulations or scientific literature. They included: (1) routine screening for gonorrhea; (2) photograph identification; (3) lifetime sexual partner number; (4) alternate phone numbers or contact information; (5) age at enrollment; and (6) bimanual examination The main purpose of the overall protocol amendment modifications were to: (1) add slow-release local contraceptive as an acceptable contraception; (2) add yearly testing for Chlamydia; (3) add the requirement of the pre-LEEP/definitive therapy biopsy as a mandatory procedure; (4) add genital warts (history of or presence) as an exclusion criterion for enrollment; (5) clarify that breast-feeding is not a contraindication for vaccination and participation in protocol visits and procedures; (6) clarify that Pap testing may not be conducted during colposcopy study visits; (7) clarify that vaccination visits in pregnant subjects should be held until the pregnancy is resolved; and (8) modify the Pap test triage guidelines for the special case of women who were diagnosed with LSIL at Day 1.

Protocol Amendment 015-02 was a complete amendment finalized on 3/17/04. The main purposes of the amendment were to (1) clarify pelvic examination instructions for pregnant subjects; (2) revise the visit windows; (3) add clarification of gene-specific assay for HPV Types 6, 11, 16, 18; (4) modify instructions for the management of HSIL or AGC Pap test diagnosis; (5) add clarification on the use of steroids before or after vaccination; and (6) incorporate the formal addition of the Registry substudy as Appendix 5. Protocol Amendment 015-02 also added an exploratory objective to estimate the impact of administration of the vaccine on the incidence of the composite efficacy endpoints to include VIN, VaIN, CIN, Vaginal/Vulvar/Cervical cancer, and genital warts related to all 4 vaccine HPV Types (6, 11, 16, 18).

Protocol Amendment 015-03 was a complete amendment finalized on 6/3/04. The HPV competitive radioimmunoassay (cRIA) was replaced by HPV cLIA. The cLIA was used to identify subjects who were naïve to the relevant HPV type at baseline and to assess the vaccine-induced serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses. The decision to replace the cRIA with cLIA was based on several considerations, including the fact that the fluorescent label was preferred to a radioactive label; the kit on which the cRIA is based is being phased out; the cLIA format uses Phase III L1 VLP material, which is a more relevant measure of immunogenicity than the cRIA, which used earlier stage VLP material; the cLIA format has greater precision than the cRIA; the cLIA has a greater dynamic range compared with cRIA, so there is less variability in test results due to dilution of serum samples; the cLIA format is automated, and thus provided high volume sample processing compared with the cRIA; the cLIA format can be easily modified to provide testing of additional HPV types as the number of types are added to the vaccine in the future.

Correlation between neutralization and antibody titer as measured by cLIA was demonstrated using sera from subjects enrolled in HPV 11 L1 VLP vaccine Protocol 001. In addition, Protocol Amendment 015-03 clarified that subjects could continue study participation even if the vaccination series was not completed and also revised the Investigator Aids for the management of colposcopy and definitive therapy.

Protocol Amendment 015-04 was a complete amendment finalized on 3/2/05. The main purposes of the amendment were to (1) incorporate a secondary hypothesis to the Consistency Lot substudy related to the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3; (2) include an additional reference; (3) include revised appendices for the pregnancy and lactation reporting guidelines (4) include refined Investigator Aid Appendices for the management of colposcopy and definitive therapy. The documentation supporting the Consistency Lot hypothesis addition was previously released by the Sponsor in an independent communication to the relevant regulatory agencies.

Changes in Planned Statistical Analyses Identified Prior to Unblinding

Changes in the Planned Efficacy Analyses
Changes That Affect the Primary Efficacy Analysis

- **Additions to the PPE population:** An additional criterion for defining the per-protocol efficacy population was added to those outlined in the Data Analysis Plan (DAP). Day ranges were applied to baseline serum (within 14 days prior to the first vaccination) and PCR samples (within 14 days prior to and within 10 days after the first vaccination).

Changes That Affect the Supplementary Analyses of Primary Efficacy

- **Interaction Test Change:** The planned test of treatment-by-study-site interaction was replaced with a treatment-by-region-interaction test. This analysis was changed because the 19 (or more) cases of HPV 16/18-related CIN 2/3 or worse required for the fixed-case analysis was small relative to the number of study sites that enrolled subjects (90). Thus, study sites were grouped by region for tests of interaction. This test was not necessary based on the efficacy results.

Changes That Affect the Secondary Efficacy Analysis

- **Endpoint Deletion:** The planned secondary analysis of efficacy with respect to colposcopic biopsy and definitive excisional cervical procedures due to HPV 16/18-related disease was not performed because this analysis is identical to the HPV 16/18-related disease analyses.
- **Endpoint Additions:**
  - To obtain a more complete assessment of the impact of the vaccine on the incidence of gynecologic procedures, external genital lesion biopsies were added to the analysis of gynecologic procedures.
  - To obtain a more complete assessment of the impact of the vaccine on the incidence of all HPV related disease, an analysis of external genital lesions due to any HPV type was added. Because the population benefit of the vaccine with respect to this endpoint was of interest, this endpoint was evaluated in the restricted MITT-2 population and the MITT-3 population.

- **Endpoint Changes:** The DAP specified that an evaluation of the vaccine's impact on HPV 6/11-related external genital lesions would be performed. In a subsequent protocol amendment, an objective was added to estimate the impact of the administration of the vaccine on the incidence of the composite endpoint of HPV 6-, HPV 11-, HPV 16-, and HPV 18-related external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer. Therefore, the analysis of vaccine-HPV-type related external genital lesions focused on all 4 vaccine HPV types.
- **Population Additions:**
  - To obtain a more "real-world" estimate of the vaccine's impact with respect to HPV 16/18-related CIN, HPV 6/11/16/18-related CIN, HPV 6/11/16/18-related external genital lesions and all HPV 6/11/16/18- related lesions, summaries of these endpoints in the MITT-2 population and MITT-3 population were provided.
  - **Therapeutic Efficacy:** Analyses to assess the potential therapeutic effect of the vaccine were performed in subjects who were seropositive and PCR negative at Day 1 to the relevant vaccine HPV type in addition to the DAP-specified population of Day 1 seronegative and PCR positive subjects. This population was added to allow for an assessment of the vaccine's potential impact on the recurrence of infection and subsequent development of disease in subjects who presumably had an HPV vaccine-type infection in the past but cleared the infection.
- **Population Changes:**
  - For the endpoints of CIN due to any HPV type and any HPV-related lesion, the DAP specified that the analyses would be performed using a per-protocol approach, in a population in which subjects would be required to be naïve for a given HPV type from Day 1 through Month 7 to be eligible to be counted as a case related to that HPV type. Serology and PCR assays would be used to classify subjects as naïve through Month 7 when available. If assays were not available for a given HPV type, the subject would be required to have a normal Pap test result at Day 1 to be eligible to be a case related to that HPV type. The analyses of these 2 endpoints were performed in the restricted MITT-2 population and the MITT-3 population rather than the population specified in the DAP because: (1) the assay data for the non-vaccine HPV types were not available at the time of the preparation of this CSR, and (2) it is of interest to estimate the population benefit of these endpoints.
  - The sponsor indicated that the **restricted MITT-2** analysis allows an estimate of the impact of the vaccine on all CIN and all HPV-related disease in the target population for the vaccine (baseline HPV-naïve women).
  - The sponsor also indicated that the **MITT-3** population allows an assessment of the impact of the vaccine among all subjects.
  - Because Pap test abnormalities and gynecologic procedures such as colposcopy, biopsy, and definitive therapy are related to all HPV types and not just the vaccine HPV types, the benefit of the vaccine on a population basis is of primary interest for these endpoints. Because the restricted MITT-2 analysis allows an estimate of the impact of the vaccine in the target population for the vaccine (baseline HPV-naïve women) and the MITT-3 population allows an assessment of the impact of the vaccine among all subjects, these 2 populations were considered the most appropriate for estimating the vaccine's impact on these endpoints.

- The DAP-specified analyses of the gynecologic procedures in the PPE, MITT-1 and MITT-2 populations were not performed as they were no longer considered to be estimating the parameter of interest. The analysis of Pap test abnormalities in the population of subjects who were seronegative at Day 1 and PCR-negative from Day 1 through Month 7 for all HPV types for which assays were available and who had normal Pap test results from Day 1 through Month 7 and in a population excluding general protocol violators were not performed for the same reason.

- **Analysis Method Addition:** A more conservative method for imputing cases among subjects lost to follow-up was used in addition to the previously described method to be consistent with the Phase II studies. By this method, cases were imputed among dropouts at the rate cases were observed among non-dropouts in the placebo group, regardless of whether the vaccination series was completed.
- **Analysis Method Changes:**
  - As planned in the DAP, the analysis of the replacement of vaccine-HPV types by non-vaccine-HPV types in HPV-related disease was to be addressed by conducting the all CIN 2/3, all CIN and all HPV-related disease analyses in a population that considered endpoints on a type specific basis. However, the assay data for the non-vaccine HPV types were not available for this CSR. Therefore, the replacement of vaccine HPV types was investigated by breaking the totality of disease endpoints observed into those that had DNA evidence of vaccine HPV types (as determined by the Thinsection PCR assay) and those that did not show evidence of vaccine HPV types. Because the population benefit of the vaccine with respect to this endpoint is of interest, the analysis was conducted in the restricted MITT-2 population.

Changes in the Planned Immunogenicity Analyses
Immunogenicity Populations

- **Population Deletions:** Immunogenicity summaries were not provided in the following DAP-specified populations:
  - Subjects who were naïve to all vaccine HPV types
  - Subjects who were seropositive at Day 1 regardless of PCR status
  - Subjects who were seropositive to multiple vaccine HPV types at Day 1
  - Some analyses were deferred to an integrated analysis of data from all Phase II/III immunogenicity studies. Others were omitted because these summaries were planned to support therapeutic efficacy but were later considered not relevant, that is, they did not mimic the therapeutic efficacy populations.
- **Change to Population Definition:** An additional criterion for defining the baseline HPV status was the application of specific day ranges for serum (within 14 days prior to the first vaccination) and PCR swabs (within 14 days prior to and within 10 days after the first vaccination) in the per-protocol immunogenicity population.

Immunogenicity Analysis Methods

- The following exploratory regression analyses of the natural log of Month 7 anti-HPV titers for a given HPV type as a function of treatment group and the natural log of the baseline anti-HPV titer among subjects who are seropositive to that HPV type at baseline were not performed:

- Linear regression with the natural log anti-HPV titers at Month 7 as the response variable
- Logistic regression with an indicator of whether the subject's Month 7 cRIA anti-HPV titer is $\geq$ 200 mMU/mL as the response variable
- Linear regression model with the difference in natural log anti-HPV titer between Month 7 and Day 1 as the response variable
- The first linear regression analysis was deferred to an integrated analysis of data from all Phase II/III immunogenicity studies. The logistic regression model was not fit because cRIA was not run.

Endpoint Changes: Due to the change in the HPV serology assay from cRIA to cLIA, the endpoint of the proportion of subjects with an anti-HPV 6, anti- HPV 11, anti-HPV 16, or anti-HPV 18 cRIA $\geq$ 200 mMU/mL was not evaluated. Instead, the proportions of subjects who were seropositive to HPV 6, 11, 16, and 18 at Months 7 and 24 were summarized by vaccination group.

Changes in Planned Analyses Identified After Unblinding:

- The following changes to the analyses specified in the Protocol and DAP were identified after unblinding:
  - The risk of becoming a breakthrough case of HPV 16/18-related CIN 2/3 or worse as a function of the corresponding Postdose 3 cLIA anti-HPV titer was not performed due to an insufficient number of breakthrough cases.
  - The planned treatment-by-region-interaction test was not performed because the vaccine efficacy in the PPE population was 100% across all regions.
  - The Kaplan-Meier time-to-event analyses for HPV 16/18-related CIN 2/3 or worse were not performed in the PPE, MITT-1, and MITT-2 populations because there were too few subjects who developed a case of the endpoint in the vaccine group.
- The following analysis was conducted after unblinding:
  - An exploratory analysis of the percent reduction in the incidence of HPV 16- or HPV 18-related CIN 2/3 or AIS in the vaccine group relative to the placebo group was conducted in subjects who were seropositive and PCR positive to the relevant HPV type(s) at Day 1.

APPENDIX 6: Counting Individual Endpoints within Composite Endpoints
(Source: 5.7.5.3.2 Integrated Summary of Efficacy, p. 25-26)

Many of the efficacy endpoints in this report are composite endpoints, including more than one lesion type (i.e., pathologic diagnosis) and/or more than one HPV type. If a subject met the criteria for one or more of the components of a composite endpoint, she was counted as a case for the composite endpoint once and only once.

Many of the efficacy analysis tables for composite endpoints contain additional rows in which individual components of the composite endpoint are presented under the row for the composite endpoint itself. For the additional rows, a subject was counted once for each component of the endpoint for which she met the criteria. Because it was common for subjects to meet the criteria for more than one component of a composite endpoint, it was common for individual subjects to be counted in the rows for more than one component. Within these rows, such a subject was counted once in each row for which she meets the criteria. Thus, in most cases, the sum of the numbers of cases in the rows for the component categories almost always exceeded the number of cases in the row for the composite category.

There were 3 ways for a subject to count toward multiple component categories of a composite endpoint:

1. If a subject had distinct lesions that met the criteria for different components of a composite endpoint, she was counted once for the composite endpoint and once for each relevant component displayed in the rows underneath the composite endpoint.
2. If a subject had a single lesion which contained more than one vaccine HPV type, she was counted once for the composite endpoint and once for each HPV type that was detected in the lesion.
3. If a subject had an infection that progressed to a lesion which, at different time points, met the criteria for different components of a composite endpoint, she was counted separately for each component.

The following example illustrates the counting. It applies to the composite endpoint of HPV 6/11/16/18-related CIN (i.e., CIN or worse).
Subject X was in the analysis population for endpoints related to all 4 vaccine HPV types. She had a CIN 2 lesion at Month 12, containing HPV 18. At Month 17, she had a CIN 3 lesion containing HPV 18 (most likely related to the same infection as was detected at Month 12). At Month 20, she had a CIN 1 lesion containing HPV 6 and 16. Subject X would have been counted a single time toward the composite endpoint of HPV 6/11/16/18-related CIN. She would also have been counted once toward each of the following individual component categories:
A. Categories presenting the composite endpoint by HPV type:
– HPV 6/11-related CIN;
– HPV 16-related CIN;
– HPV 18-related CIN.

B. Categories presenting the composite endpoint by lesion type:
- HPV 6/11/16/18-related CIN 1;
- HPV 6/11/16/18-related CIN 2;
- HPV 6/11/16/18-related CIN 2 or Worse;
- HPV 6/11/16/18-related CIN 3 or Worse.

APPENDIX 7: Protocol 015 Consistency Lot Substudy, Changes in Statistical Analyses

Changes in Statistical Analyses: The statistical analyses performed for this study differed from those stated in the Protocol as follows:

- The secondary immunogenicity objective regarding persistence of responses will be addressed in the final efficacy CSR because the complete post-Month 7 immunogenicity data was not available at the time data for consistency lot substudy was unblinded.
- Exploratory immunogenicity analyses were to be deferred to the integrated summary of immunogenicity.
- Because the numbers of subjects enrolled in some of the study sites were very small, the study sites were pooled into four regions (North America, Latin America, Asia-Pacific, and Europe) in lieu of "study center" to compute the overall GMT ratio and the difference of proportions of subjects seroconverted by Month 7.
- The GMT ratio in the primary analysis was calculated using the average of those across geographic regions instead of the average weighted by sample size of the study center. The GMT ratios were fairly comparable across geographic regions and no interaction between consistency lot and geographic region was found to be significant ($p>0.1$) in modeling the natural log of anti- HPV cLIA responses.
- Because almost every subject in the per-protocol immunogenicity population seroconverted by Month 7 for the relative vaccine HPV type, the planned analysis to assess the interaction of treatment by geographic region with respect to difference of Month 7 seroconversion rate was not performed.

APPENDIX 8: Protocol 013, Colposcopy Algorithm

Protocol 013: Mandatory Regimen for Triage of Abnormal Pap Tests to Colposcopy

Mandatory Regimen for Triage of Abnormal Pap Tests to Colposcopy

ThinPrep Pap Result	Action
Negative for intraepithelial lesion or malignancy (includes reactive, reparative, inflammatory, etc.	Routine visit interval as specified by protocol.
Atypical Squamous Cells of Undetermined Significance (ASC-US)	Central laboratory performed reflex HPV testing on residual ThinPrep material (High-Risk and Low-Risk Probe, Hybrid Capture II, DIGENE). If at least 1 probe was positive, the subject was to be referred for colposcopy. If both probes were negative, then the subject returned for Pap screening at the routine visit interval.
Atypical Squamous Cells, Cannot Rule out HSIL (ASC-H)	Referral to colposcopy.
Low-grade Squamous Intraepithelial Lesions (LSIL)	Referral to colposcopy.
High-grade Squamous Intraepithelial Lesions (HSIL)	Referral to colposcopy.
Atypical glandular cells (to include atypical endocervical, endometrial, NOS, adenocarcinoma in situ, adenocarcinoma	Referral to colposcopy.
Unsatisfactory	Repeat ThinPrep Pap test as soon as possible. The interval between the rescheduled Pap test must be at least 4 weeks from the Pap test that had the unsatisfactory finding.

Subjects with any abnormal Pap test result at Month 48 were referred immediately for colposcopy. This colposcopy must have been performed within 2 months of the Month 48 visit. All specimens collected during this colposcopy were handled through the Sponsor central laboratory.

A diagnosis of an HPV-related external genital lesion (e.g., VIN, VaIN, and genital warts), as confirmed by the Sponsor central laboratory ALSO constituted a reason for referral to colposcopy. If a histologically confirmed HPV-related vaginal lesion was diagnosed as a consequence of a colposcopic examination of the cervix, then the subject did not require another referral to colposcopy. Any cervical/vaginal lesion suspected to be HPV-related (e.g., CIN, VaIN, cancer, or condylomata) was to be biopsied.

Colposcopy should have only been performed according to the guidelines in this table.

Source: CSR 013v1, Table 5-3, p. 81

APPENDIX 9: Protocol 013, Changes in Protocol and Changes in Statistical Analyses

There were **three protocol amendments.**

Changes in Conduct of Protocol 011:

- **Protocol Amendment 011-01:** The principal change was the removal of the consistency lot evaluation.
- **Protocol Amendment 011-02:** The principal change was the description of unblinding the Hepatitis B placebo recipients at Month 18 so that these subjects could be given Hepatitis B vaccine in a timely manner.
- **Protocol Amendment 011-03:** The principal change was to change the assay from cRIA to cLIA.

Changes in Conduct of Protocol 012: The changes were as noted for Protocol 011, and included change of efficacy endpoints as noted in Protocol 011.

Changes in the Planned Statistical Analyses Identified Prior to Unblinding: Prior to unblinding the study, the following changes and additions to analyses specified in the Protocol and the DAP were planned.

Changes to the Planned Efficacy Analyses

- **Changes That Affect the Primary Efficacy Analyses**
  - **Additions to the PPE population:** Two (2) criteria for defining the per protocol efficacy population were added to those outlined in the DAP. They were: (1) All 3 vaccinations must have been received within 12 months of enrollment; (2) To ensure the Day 1 prevaccination serum and swab samples were appropriate for assessing baseline HPV status, day ranges were applied to the samples. The Day 1 prevaccination serum sample was required to be obtained within 14 days prior to the first vaccination or on the day of the first vaccination. The Day 1 prevaccination swab samples were required to be obtained within 14 days prior to and within 10 days after the first vaccination.
  - **Changes to the Naming of the MITT populations:** To be consistent with the Phase II studies and Protocol 015, the MITT-2 population which was unique to this protocol, was renamed as MITT-4; the MITT-3 population was renamed as MITT-2; and the MITT-4 population was renamed as MITT-3.
- **Changes That Affect the Exploratory Efficacy Analyses**
  - **Endpoint Additions:**
    - To evaluate the impact of the vaccine on the overall burden of vaccine- HPV-type-related disease (cervical and external genital), the efficacy of the vaccine against HPV 6/11/16/18-related disease was summarized. This summary was performed in the per-protocol efficacy, MITT-2, MITT-3, and MITT-4 populations.
    - The number of cases of HPV 16-related CIN 1 or worse and HPV 16- related external genital lesions in the Monovalent HPV 16 vaccine group of Protocol 012 were presented for completeness.
    - To evaluate the population benefit of the vaccine with respect to the overall burden of HPV-related disease (cervical and external genital), the efficacy of the

vaccine against all HPV-related disease was summarized. This summary was performed in the restricted MITT-2 and MITT-3 populations.

- Analyses to assess the potential therapeutic effect of the vaccine against HPV 16/18-related CIN 2/3 or worse were performed in addition to the analyses to assess the potential therapeutic effect of the vaccine against the co-primary endpoints.

- **Population Changes:**
  - For the endpoints of CIN and EGL due to any HPV type, and disease (cervical and/or external genital) due to any HPV type, the Data Analysis Plan (DAP) specified that the analyses would be performed in a population similar to the per-protocol efficacy population in which subjects would be required to be naïve for a given HPV type from Day 1 through Month 7 to be eligible to be counted as a case related to that HPV type. If available, serology and PCR assays were to be used to classify subjects as naïve through Month 7. If assays were not available for a given HPV type, the subject was required to have normal Pap test results Day 1 through Month 7 to be eligible to be a case related to that HPV type. The analyses of these endpoints were performed in the restricted MITT-2 population and the MITT-3 population rather than the population specified in the DAP because: (1) the assay data for the non-vaccine HPV types were not available at the time of this CSR, and (2) it was of interest to estimate the population benefit of these endpoints. The sponsor notes that the restricted MITT-2 analysis allows an estimate of the impact of the vaccine on all CIN, all EGL, and all HPV-related disease in the target population for the vaccine (baseline HPV-naïve women). The MITT-3 population allows an assessment of the impact of the vaccine among all subjects, and included all cervical biopsies, regardless of the reason for colposcopy, and biopsies outside the context of the study. The Day 1 normal Pap test criterion was added to the DAP-specified population because it was considered by the sponsor to be a surrogate for infection with other non-vaccine HPV types.
  - **Therapeutic Efficacy:** An analysis to assess the potential therapeutic effect of the vaccine with respect to development of disease was performed in subjects who were seropositive and PCR negative at Day 1 to the relevant vaccine HPV type in addition to the DAP-specified population of Day 1 seronegative and PCR positive subjects. This population was added to allow for an assessment of the vaccine's potential impact on the development of disease in subjects who presumably had an HPV vaccine-type infection in the past but cleared the infection.
- **Analysis Method Deletions:**
  - HPV PCR assays for the vaccine HPV types were not performed on swab samples. Therefore, an analysis of vaccine efficacy against vaccine-HPV type-related infection was not performed. For the same reason, evaluations of whether the vaccine provides protection against re-infection and whether the vaccine clears pre-existing infections were not performed.
- **Analysis Method Additions:**
  - A more conservative method for imputing case status among subjects lost to follow-up was used in addition to be consistent with the Phase II studies. By this

method, case status was imputed among dropouts at the rate cases were observed among non-dropouts in the placebo group, regardless of whether the vaccination series was completed.

- To provide an assessment of the vaccine's potential impact on the time to development of CIN due to any HPV type and external genital lesions due to any HPV type, time to event distributions were compared between the vaccination groups for the endpoints of CIN due to any HPV type and external genital lesions due to any HPV type.

- **Analysis Method Changes:**
  - An exact test of homogeneity of relative risks across regions was performed based on the method of Martin and Austin instead of a logistic regression analysis, to evaluate the presence of vaccination-group by-region interaction. The exact method was used because the primary analysis of vaccine efficacy used an exact conditional procedure. Due to sample size limitations, vaccination-group-by-region interaction was assessed instead of vaccination-group-by-study-site interaction.
  - Since PCR results for the non-vaccine HPV types were not available for this CSR, the incidence of non-vaccine-HPV-type-related CIN was observationally compared between the vaccine group and the placebo group in the MITT- 3 population.
  - The analysis of the replacement of vaccine- HPV-types by non-vaccine-HPV types in HPV-related disease was to be addressed by conducting the all CIN, all EGL, and all HPV-related disease analyses in a population that considered endpoints on a type-specific basis. However, the assay data for the non-vaccine HPV types were not available for this CSR. Therefore, the replacement of vaccine HPV types was investigated by breaking the totality of disease endpoints observed into those that had DNA evidence of vaccine HPV types (as determined by the Thinsection PCR assay) and those that did not show evidence of vaccine HPV types. These analyses were conducted in the restricted MITT-2 population.

Changes in the Planned Immunogenicity Analyses

- **Addition to the Per-Protocol Immunogenicity population:** Day ranges were applied to serum and swab samples for defining the per-protocol immunogenicity population was added to ensure the Day 1 prevaccination these samples were appropriate for assessing baseline HPV status.
- **Population Additions:** Immunogenicity summaries were provided in the "all type-specific HPV-naïve subjects with serology data" population.
- **Population Changes:** The populations used to assess immunogenicity in baseline positive subjects were revised to facilitate the clinical interpretation of the results. For each vaccine HPV type, immune responses were summarized in subjects who were: (1) seropositive and PCR negative at Day 1 to that HPV type, (2) seronegative and PCR positive at Day 1 to that HPV type, and (3) seropositive and PCR positive at Day 1 to that HPV type. Subjects in the pre-positive summaries were also required to have their Day 1 serology and PCR samples collected within acceptable day ranges, to have a Month 7 serology sample collected within an acceptable day range, to have received the correct clinical material, and to have received all 3 vaccinations.

- **Analysis Method Changes:** Due to the change in the HPV serology assay from cRIA to cLIA, the endpoint of the proportion of subjects achieving an anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18 cRIA $\geq$ 200 mMU/mL was not evaluated. Instead, the proportion of subjects who were seropositive by Week 4 Postdose 3 based on anti-HPV 6, anti-HPV11, anti-HPV16, anti- HPV 18 cLIA was summarized by vaccination group. This change is documented in a memo sent to CBER.

APPENDIX 10: Protocol 007, Inclusion/Exclusion Criteria

- **Protocol 007: Inclusion Criteria**
  - Healthy, females 16 to 23 years of age with intact uteri.
  - No clinical evidence of gross purulent cervicitis (otherwise postponed until after treatment or lack of laboratory confirmation of treatable cause).
  - Must have agreed to refrain from douching or using vaginal medication or preparation for 48 hours prior to any scheduled visit that included a pelvic examination.
  - Must have agreed to refrain from sexual intercourse for 48 hours prior to any scheduled visit that included a pelvic examination.
  - Not pregnant now and must have agreed to use effective contraception through Month 7 of the study.
  - Individuals who had sexual intercourse in the 2 weeks prior to enrollment must have been using effective contraception as defined above.
  - Individuals with a lifetime history of 0 to 4 male sexual partners, and women with 0 lifetime male sexual partners must have been at least 18 years of age and seeking contraception at the time of enrollment or have recently obtained contraception to be permitted to enter the study.
  - Must have agreed to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes.
  - No temperature ≥100°F (≥37.8°C [oral]) within 24 hours prior to the first injection.
- **Exclusion Criteria**
  - Individuals concurrently enrolled in clinical studies of investigational agents or studies involving collection of cervical specimens.
  - History of known prior vaccination with an HPV vaccine.
  - Receipt of inactivated or recombinant vaccines within 14 days prior to enrollment or receipt of live vaccines within 21 days prior to enrollment.
  - Individuals with any prior abnormal Pap test showing squamous intraepithelial lesion (SIL) or biopsy showing CIN.
  - Individuals with any prior history of genital warts or treatment for genital warts.
  - History of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention.
  - Individuals allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).
  - Individuals who had received any immune globulin or blood derived products within the 6 months prior to the first injection, or planned to receive any through Month 7 of the study.
  - Individuals with history of splenectomy, known immune disorders, or receiving immunosuppressives Individuals who had received periodic treatments with immunosuppressives, defined as at least 3 courses of oral corticosteroids each lasting at least 1 week in duration for the year prior to enrollment, were to be excluded. Subjects using topical steroids were eligible for vaccination.

- Individuals with known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
- Any condition that, in the opinion of the investigator, might have interfered with the evaluation of the study objectives
- Any plans to permanently relocate from the area prior to the completion of the study or to leave for an extended period of time when study visits would need to be scheduled.
- Individuals with >4 lifetime male sexual partners.

APPENDIX 11: Protocol 007, Colposcopy Algorithm

Protocol 007: Guidelines for Triage of Abnormal Pap Tests to Colposcopy

ThinPrep Pap Result	Action
Negative for intraepithelial lesion or malignancy (includes reactive, reparative, inflammatory, etc.	Routine visit interval as specified by protocol.
Atypical Squamous Cells of Undetermined Significance (ASC-US)	Central laboratory performed reflex HPV testing on residual ThinPrep material (High-Risk and Low-Risk Probe, Hybrid Capture II, DIGENE). If at least 1 probe was positive, the subject was to be referred for colposcopy. If both probes were negative, then the subject returned for Pap screening at the routine visit interval.
Atypical Squamous Cells, Cannot Rule out HSIL (ASC-H)	Referral to colposcopy.
Low-grade Squamous Intraepithelial Lesions (LSIL)	Referral to colposcopy.
High-grade Squamous Intraepithelial Lesions (HSIL)	Referral to colposcopy.
Atypical glandular cells (to include atypical endocervical, endometrial, NOS, adenocarcinoma in situ, adenocarcinoma	Referral to colposcopy.
Unsatisfactory	Repeat ThinPrep Pap test as soon as possible. The interval between the rescheduled Pap test must be at least 4 weeks from the Pap test that had the unsatisfactory finding.

A diagnosis of HPV related genital lesion (e.g., VIN, VaIN, and genital warts) as confirmed by the sponsor central lab also constituted a reason for referral to colposcopy. Any cervical lesion suspected to be HPV related was to be biopsied.
Source: Table 5-2, CSR 007, p. 80

APPENDIX 12: Protocol 007, Changes in Protocol and Changes in Statistical Analyses

There were **six protocol amendments.**

- **Protocol Amendment 007-01** was a complete amendment finalized on 3/1/00. The purpose of the amendment was to: (1) submit the Day 1 and End of Study questionnaires; (2) revise the study procedures to allow vaginal pH, wet mount, whiff test, and KOH testing to be performed at the investigator's discretion; (3) clarify that slides from biopsy specimens were prepared by a central laboratory; (4) revise the procedures for Pap test specimen collection, using the spatula and cytobrush; (5) include collection of serum for antibody measurements at Month 6; (6) revise the procedure for wart biopsy to exclude Day 1; and (7) add ---------- swab for PCR testing.
- **Protocol Amendment 007-02** was a complete amendment finalized on 7/26/00. The purpose of the amendment was to: (1) change the statistical criterion for success for the HPV 11 component in the primary hypothesis to account for potential interference; (2) add an objective to investigate response rates defined as ≥100 mMU/mL for each component; (3) move the neutralization endpoint from secondary to exploratory; (4) move the tertiary hypotheses to secondary; and (5) add a confirmatory analysis at the interim time point with 100% of Postdose 2 data.
- **Protocol Amendment 007-03** was a complete amendment finalized on 6/8/01. The purpose of the amendment was to: (1) revise the assay method used to measure serum antibody responses to HPV 6, 11, 16, and 18 from enzyme immunoassay (EIA) to cRIA; (2) increase the total number of subjects enrolled in the study due to a higher than expected baseline rate of HPV 6/11 seropositivity based on nonvalidated HPV 6 and HPV 11 cRIA; (3) include review of cervical biopsy slides by the Pathology Panel; and (4) revise procedures for subjects who became pregnant, allowing subjects who became pregnant prior to Month 6 to remain in the study without receiving further vaccinations.
- **Protocol Amendment 007-04** was a complete amendment finalized on 4/12/02. The purpose of the amendment was to evaluate the efficacy of the quadrivalent HPV VLP vaccine with regard to persistent HPV infection and clinical HPV disease caused by vaccine HPV types. An objective, corresponding hypothesis, and efficacy endpoint definitions were included in the amendment. Protocol amendment 007-04 also: (1) provided subjects who were randomized to receive placebo with the opportunity to receive active quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine if vaccine efficacy was demonstrated in Phase III efficacy studies; (2) added a colposcopy at the final study visit; (3) added a table containing guidelines for triage of abnormal Pap tests to colposcopy; and (4) included detailed procedures for external genital inspection to be performed at routine visit intervals.
- **Protocol Amendment 007-05** was a complete amendment finalized on 4/22/03. The purpose of the amendment was to add the collection of an additional -- mL of blood (for a total of -- mL) at Month -- for use in the development of human standards for the serologic assays used in the HPV vaccine program. In addition, the Guidelines for Triage of Abnormal Pap Tests to Colposcopy were clarified for inadequate/unsatisfactory specimens to include repeat Pap test as soon as possible.

- **Protocol Amendment 007-06** was a complete amendment finalized on 1/30/04. The purpose of the amendment was to revise the assay method for serum samples from cRIA to cLIA and remove the neutralization assay. The hypotheses and statistical analyses were revised to reflect the role of this protocol in evaluating the performance of the cLIA. In addition, clarifications to endpoint definitions were included.

Changes in Statistical Analyses

- To be consistent with the terminology used in Phase III studies, "Day 0" in the study Protocol and DAP was referred to as "Day 1" throughout the CSR for this protocol.
- During the safety assessment of quadrivalent HPV vaccine, the 225 mcg and 450 mcg aluminum adjuvant placebo groups were not combined into one group for comparison with each of the 3 quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine groups because current comparisons provided sufficient evidence of the overall safety and general tolerability of the quadrivalent HPV vaccine.
- Inclusion of subjects who were positive for vaccine-type HPV DNA at the last visit without observed persistence in the study's primary endpoint represented the study's conservative approach of imputing for missing data. To assess the impact of this method, secondary analyses were performed among the per-protocol and MITT populations excluding such cases.
- Due to the small number of cases observed among vaccine recipients in the study, treatment-by-center interaction was not assessable using the modeling approach. Instead, the interaction was assessed observationally by investigating the incidence of HPV 6-, 11-, 16-, or 18-related persistent infection or disease by region in the quadrivalent HPV vaccine 20/40/40/20-mcg dose and placebo groups among subjects enrolled in the dose-ranging phase.
- Sensitivity analyses were conducted in the per-protocol population to evaluate the robustness of our vaccine efficacy estimates. The additional efficacy endpoints explored in these analyses included: (1) HPV (Types 6, 11, 16, 18) DNA detection at ≥1 time point; (2) HPV 6-, 11-, 16-, or 18-related disease or infection at ≥2 time points that were not necessarily consecutive but were ≥4 months apart; and (3) HPV 6-, 11-, 16-, or 18-related disease or infection at ≥2 consecutive time points that were not necessarily 4 months apart.
- The planned analysis to assess the ascertainment bias was not conducted because the number of CIN cases observed in this study was very small.
- To evaluate the impact of the 20/40/40/20-mcg dose of the quadrivalent HPV vaccine on a woman's overall risk for development of new cervicovaginal diseases and cervical cancer lesions, exploratory analyses were performed for CIN or EGL diseases due to any HPV type among the following subjects: (1) per-protocol subjects who were negative to all vaccine HPV types and had normal Pap tests from Day 1 through Month 7; and (2) subjects in the MITT-2 population who were naïve to all vaccine HPV type(s) and had normal Pap test at Day 1. In addition, analysis of all CIN and EGL, regardless of HPV type, was performed among the MITT-3 population.
- An exploratory analysis to evaluate potential risk factors associated with a subject becoming a HPV 6-, 11-, 16-, 18-related infection or disease case was performed in the per-protocol efficacy analysis population.

- Exploratory analyses were performed to evaluate the impact of baseline subject characteristics on the type-specific Month 7 anti-HPV serum cLIA responses.
- An exploratory analysis of vaccine efficacy was performed by pooling together the 3 quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine dose groups and comparing the vaccine's efficacy with the pooled placebo group.
- In order to assess the potential impact of contraceptive use on the vaccine's efficacy estimate, summaries of contraceptive use during the follow-up period were performed with respect to the percentages of subjects using each contraceptive method and the total person-years exposed to hormonal contraception.
- To assess the potential impact of sexual behavior on vaccine's efficacy estimate, a summary of new sexual partners during the efficacy follow-up period was provided in both the quadrivalent HPV vaccine 20/40/40/20-mcg dose and placebo groups. In addition, incidences of non-HPV cervicovaginal infections and sexually transmitted diseases during the efficacy follow-up period were provided for these 2 groups.
- A secondary objective to investigate whether there was a dose response to HPV 6, 11, and 18 as measured by serum cRIA was not addressed due to the assay change from cRIA to cLIA.
- Another secondary objective was to evaluate the kinetics of the antibody responses to the vaccine as measured by anti-HPV 6, 11, 16 and 18 serum cRIA levels up to 2.5 years following the completion of the vaccination regimen in subjects who were seronegative at Day 1 and PCR-negative Day 1 through Month 7 to at least 1 of the 4 vaccine HPV types. This objective was not addressed due to the assay change from cRIA to cLIA.
- The last secondary immunogenicity objective was to estimate the proportion of subjects responding to the quadrivalent HPV vaccine with ≥100 mMU/mL for each component. This objective was not addressed due to the change of assay from cRIA to cLIA.
- The planned comparison of reverse cumulative distribution function plots of Month 7 anti-HPV serum cLIA responses between the quadrivalent HPV vaccine 20/40/40/20-mcg group and pooled placebo group was not provided because the difference was apparent. Instead, reverse cumulative distribution function plots of the Month 7 anti-HPV serum cLIA responses for the recipients of the quadrivalent HPV vaccine 20/40/40/20-mcg dose are provided for the per-protocol immunogenicity population, baseline PCR-positive and seronegative population and baseline PCR-negative and seropositive population, respectively.
- A summary of anti-HPV serum cLIA responses is also provided by region (U.S., Brazil, and Nordic Countries) in the per-protocol immunogenicity population.
- In the case definitions of disease (external genital and cervical disease) when the Thinsection PCR result was not available, the case definition required that the same HPV type be detected in a routine visit swab that immediately preceded the date of the biopsy. This was different from what is specified in Protocol Amendment 007-06. In the protocol amendment, the definition required that the same HPV type be detected in a routine visit swab that immediately preceded or immediately followed the date of the biopsy. The definition was changed here to match the definition of a disease endpoint in Protocol 005. A sensitivity analysis that included the routine visit swab that immediately followed the date of the biopsy was also performed.

APPENDIX 13: Protocol 005, Inclusion/Exclusion Criteria

Inclusion Criteria:

- Healthy, unmarried females 16-23 years of age
- Informed consent
- No clinical evidence of gross purulent cervicitis (in subjects with evidence of cervicitis, the visit was postponed until after treatment or until a full laboratory evaluation demonstrated lack of laboratory confirmation of treatable cause).
- Required to refrain from douching or using vaginal medication or preparation for 48 hours prior to any scheduled visit that included a pelvic exam.
- Required to refrain from sexual intercourse (including anal and vaginal) for 48 hours prior to any scheduled visit that included a pelvic examination
- Was not pregnant at enrollment and using effective contraception through Month 7 of the study.
- Individuals with a lifetime history of 0 to 5 male sexual partners. Women who reported 0 lifetime male sexual partners at enrollment were required to be at least 18 years of age and to be seeking contraception at the time of enrollment or to have recently obtained contraception to be permitted to enter the study.
- Required to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes.
- Reported no temperature 100°F (37.8°C) oral within 24 hours prior to each injection.

Exclusion Criteria

- Individuals concurrently enrolled in clinical studies of investigational agents or studies involving collection of cervical specimens.
- History of prior HPV vaccination.
- Receipt of any other vaccination within 1 month prior to enrollment or having planned to receive any other vaccination within 1 month prior to or after any dose of study vaccine.
- Individuals with any prior abnormal Pap test showing SIL or biopsy showing CIN.
- History of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention.
- Individuals allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).
- Individuals who had received any immune globulin (including RhoGAM™) or blood derived products within the 6 months prior to the first injection, or had planned to receive any through Month 7 of the study.
- Individuals with history of splenectomy, known immune disorders, or receiving immunosuppressives. Subjects using topical steroids (i.e., inhaled or nasal) were eligible for enrollment.
- Individuals who received DEPO-PROVERA™ (sterile medroxyprogesterone acetate suspension, USP, Pharmacia and Upjohn) into both arms within the 9 months prior to enrollment.
- Individuals diagnosed with severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

- Any condition that, in the opinion of the investigator, had the potential to interfere with the evaluation of the study objectives.
- Any plans to permanently relocate from the area prior to the completion of the study or to leave for an extended period of time when study visits would need to be scheduled.

APPENDIX 14: Protocol 005, Colposcopy Algorithm

Protocol 005: Colposcopy Algorithm

ThinPrep Pap Result	Action
Negative for intraepithelial lesion or malignancy (includes reactive, reparative, inflammatory, etc.	Routine visit interval as specified by protocol.
Atypical Squamous Cells of Undetermined Significance (ASC-US)	--- tests ThinPrep material using HC 2 High Risk DNA test (high risk probe). If the test was positive, the subject had colposcopy. If the test was negative, then the subject returned for Pap testing at the routine visit interval.
Atypical Squamous Cells, Cannot Rule out HSIL (ASC-H)	Referral to colposcopy.
Low-grade Squamous Intraepithelial Lesions (LSIL)	Referral to colposcopy.
High-grade Squamous Intraepithelial Lesions (HSIL)	Referral to colposcopy.
Atypical glandular cells (to include atypical endocervical, endometrial, NOS, adenocarcinoma in situ, adenocarcinoma	Referral to colposcopy.
Unsatisfactory	Repeat ThinPrep Pap test as soon as possible.

A central laboratory pathology diagnosis of VIN, VaIN, or genital warts constituted a reason for referral to colposcopy.
Source: Table 5-1, CSR 005, p. 64

APPENDIX 15: Protocol 005, Changes in Protocol and Changes in Statistical Analyses

There were **five protocol amendments**.

- **Protocol 005-01** (10/14/98): changed the questionnaire at end of study, and time for cytology lab to process samples.
- **Protocol 005-02** (10/1/99): increased the sample size because of a higher than expected rate of baseline HPV 16 positivity; made cervicovaginal ------ testing optional; revised universal PCR test to swabs from external genitalia and cervix and cervicovaginal ------ optional; revised procedure for cervical biopsy so that adjacent area should be biopsied for HPV PCR and to include a swab of the biopsy site for optional PCR analysis (changed definition of primary endpoint); redefined the follow-up period for the primary analysis in those subjects who undergo a cervical biopsy during the study.
- **Protocol 005-03** (9/19/00): mandated follow-up of all subjects regardless of HPV 16 PCR status through Month 30; include LEEP as definitive treatment for CIN2/3; follow subjects who had definitive treatment through end of study; optionally test all subjects for HPV 16 neutralizing antibody; reword sections to reflect change in purpose of interim analysis [formerly, they would stop for effectiveness, and then changed to no stopping, but just conducted for administrative purposes]; add optional thin-section PCR test for cervical biopsy (exploratory assay) and wart specimens; modify the secondary objective to include composite incidence of HPV 16 related CIN 1, 2, or 3 or the composite incidence of HPV 16 related CIN 2/3 relative to placebo; modify time points, variables and statistical methods in the Data Analysis Plan.
- **Protocol 005-04 (**6/5/01): extend study follow-up for all subjects until Month 42; require a colposcopy (and biopsy if there was a lesion) for all Month 48 subjects.
- **Protocol 005-05** (4/25/02): extend the study follow-up for all subjects until Month 48; revise the colposcopy triage strategy guidelines to align them with the Bethesda 2001 Pap reporting categories; offer active quadrivalent HPV L1 VLP vaccine to all subjects if vaccine efficacy is demonstrated at the completion of the Phase III efficacy studies; revise procedures for notification of type specific HPV 16 PCR status.

Changes in Planned Analysis

- **Changes in Populations Analyzed:** The populations analyzed were as follows:
  - **Per-Protocol:** Unchanged, and efficacy cases were counted starting after Month
  - **MITT-1**: Unchanged and efficacy cases were counted starting after Month 7
  - **MITT-2**: Included subjects who (1) received at least 1 vaccination, and (2) were HPV 16 sero- and PCR-negative at Day 1, and efficacy cases were counted starting 30 days after Day 1
  - **MITT-3**: Included subjects who received at least 1 vaccination, and efficacy cases were counted starting 30 days after Day 1. [Note: MITT-2 and MITT-3 were changed to coordinate efficacy populations of this Phase II trial with the Phase III trials.]
  - **MITT-4**: Same as the MITT-2 described earlier (i.e., included subjects who (1) received all 3 vaccinations and (2) were HPV 16 sero- and PCR-negative at Day 1

and PCR-negative at Month 7) and efficacy cases were counted starting after Month 7

- **Changes in Planned Analyses**
  - Planned vaccination group by study site interaction on incidence rate of persistent HPV 16 infection not does (spare numbers of vaccine cases)
  - Planned sensitivity analyses not conducted
  - Statistical tests comparing anti-HPV 16 GMTs in vaccine vs. placebo not conducted because placebo titers were < level of detection.
  - Month 6 cRIA GMTs not performed, so fold rise from Month 2 to Month 3 not done.
  - All immunogenicity analyses were conducted with cRIA (and ---------- test not done after Day 1)
  - Unable to determine correlate of protection (sparse cases in vaccine group)
  - Unable to do breakthrough cases analysis as no HPV 16 CIN in vaccine group
  - Assays to measure Viral Load and neutralization were not performed.
  - ---------- not performed.
  - **CIN 1 or worse preceded by HPV 6, 11, or 18 positivity were treated as disease cases.**
  - Estimate of VE by age and HPV type (other than HPV 16) infection status at Day 1 not performed.
  - Comparisons of results of Thinsection PCR and frozen biopsy PCR assays are to be provided in a separate report.
  - The planned correlation/epidemiological analysis between clinical disease endpoints and measures of HPV 16 positivity was not performed. This analysis was superceded by a more formal review of the performance of the pathology panel.
  - Analysis of incidence of pap abnormalities and gynecologic procedures was added.
  - To be consistent with the Phase III studies of the HPV program, section VII.E.1.c.3 of the DAP was changed from: "*Subjects who received any nonstudy inactivated vaccine within 14 days of a study vaccine shall be excluded as well as subjects who receive any nonstudy live virus within 21 days of a study vaccine"* to "*Subjects who received any nonstudy inactivated vaccine within 14 days of a study vaccine shall be excluded as well as subjects who receive any nonstudy live virus 21 days before or 14 days after a study vaccine"*.
- **Changes in Planned Covariate Adjusted Analyses:**
  - Logistic regression models were used to model the odds of becoming a case of persistent HPV 16 infection as a function of: (1) age; (2) number of lifetime male sexual partners; (3) ethnicity; (4) hormonal contraception use at Day 1; (5) HPV 6, 11, and 18 infection status at baseline; (6) history of chlamydia, gonorrhea; (7) history of pregnancy; (8) history of smoking; and (9) history of alcohol use. Only cases of verifiable persistent infection were used in the model (i.e., cases of HPV 16 DNA detection at the last visit prior to dropout or lost to follow-up were excluded). The models were not adjusted for vaccination group. Rather, only the placebo group was used in modeling the odds of becoming a case of persistent

infection, because no cases of verifiable persistent infection were observed in the vaccination group.

- The natural logarithm of anti-HPV 16 cRIA levels in the vaccine group were modeled as a function of: (1) race; (2) age; (3) study site; (4) smoking status; (5) pregnancy status; (6) number of lifetime male sexual partners; (7) number of new male sexual partners in the last 6 months; (8) history of chlamydia, gonorrhea; (9) hormonal contraception use at Day 1; and (10) HPV 6, 11, and 18 infection status at baseline. The added baseline covariates represent possible risk factors that may potentially influence the efficacy of the HPV 16 L1 VLP vaccine in preventing persistent HPV 16 infection or inducing an immune response.

APPENDIX 16: Protocol 016, Changes in Protocol and Changes in Statistical Analysis

There were **three protocol amendments.**
Protocol Amendment 016-01: This amendment was a complete amendment finalized on 8/11/03. Some administrative changes were included. The main purpose for this amendment was to describe the process for reporting the positive or indeterminate Day 1 cRIA results for subjects 10 to 15 years of age to the primary investigator, the subject, and his or her parent/guardian.

Other administrative changes/clarifications included in this amendment are listed as follows:

- Text was added describing that subjects were to be offered revaccination after the study is over if they have not achieved the desired immune response.
- Text was added describing that Month 12 follow-up calls were to be conducted to collect AE information for subjects 10 to 15 years of age.
- Text was added indicating that subjects must not have received a course of systemic corticosteroids or any other immunosuppressive agent before a vaccination.
- Text was added describing the unblinding of serious adverse experiences.
- Text was added describing the reporting of lactation during the study.
- Text was added describing the use of an independent safety monitor.
- Text was added describing the minimum serum required for cRIA testing.
- Text was added describing the addition of a ---mL blood draw to obtain serum for development of human standards from the 16- to 23-year-old subjects.
- Text was added describing the use of ---------- only for lubrication of the speculum.
- Text was added to description of collection of Pap test.
- Text was added indicating that external genital biopsy, colposcopy, cervical biopsy, and endocervical curettage procedures were to be performed if indicated, and not optionally.
- Text was added describing content of labels for clinical material for injection.
- Text was added indicating the change of “confidence interval” to “multiplicity-adjusted 95% confidence interval” in hypotheses and discussion of primary analysis.
- Text was added clarifying what safety summaries were to be performed during the study.

Protocol Amendment 016-02: This amendment was a complete amendment finalized on 1/4/04. The HPV cRIA was replaced by HPV cLIA. The cLIA was used to identify subjects who were naïve to the relevant HPV type at baseline and to assess the vaccine-induced serum anti-HPV 6, 11, 16, and 18 responses. The decision to replace the cRIA with cLIA was based on the following considerations:

- Substitution of a radioactive label with a fluorescent label was reported by the sponsor to have important advantages. The use of radioactive material is more hazardous than the use of a fluorescent label. Also, most companies who manufacture detection kits are moving away from radioactivity due to increasingly stringent regulations regarding shipping, storage, and accounting for the use of these products.

- The kit on which the cRIA was based is being phased out. The use of a new kit would have required requalification of the assay.
- The cLIA format uses Phase III L1 VLP material. The use of Phase III L1 VLP material as the target antigen provides a more relevant measure of immunogenicity than the cRIA, which used earlier stage VLP material.
- The cLIA format has greater precision than the cRIA; there are 50 replicates per test result compared with only 2 when using cRIA.
- The cLIA has a greater dynamic range compared with cRIA, so there is less variability in test results due to dilution of serum samples.
- The cLIA format is automated, and thus provided high volume sample processing compared with the cRIA.
- The cLIA format can be easily modified to provide testing of additional HPV types as the number of types are added to the vaccine in the future.
- Correlation between neutralization and antibody titer as measured by cLIA was demonstrated using sera from subjects enrolled in HPV 11 L1 VLP vaccine Protocol 001.

As a result of the removal of cRIA testing, the hypothesis regarding immune responses $\geq$200 mMU/mL at Week 4 Postdose 3 was deleted.
Additionally, a definition of overdose was added to the protocol.

Protocol Amendment 016-03: This amendment was a complete country-specific amendment for Sweden finalized on 1/27/05. Because of the laws in effect in that country, Day 1 positive and indeterminate serology responses in 10- to 15-year-old subjects cannot be reported to the investigator or to the subjects or the subjects' parents/guardians. Therefore, Sweden was not able to approve amendments 016- 01 and 016-02, which included the requirement for such reporting. With amendment 016-03, all changes from amendments 016-01 and 016-02 were incorporated, with the exception that Day 1 positive and indeterminate serology results in 10- to 15-year old subjects enrolled in Sweden are not to be reported to the investigator or to the subjects or the subjects' parents/guardians.

Biopsies Outside of the Context of the Study
Protocol 016 states that biopsies obtained outside the study should be strongly discouraged. If a subject did undergo a biopsy outside of the study, all efforts were to be made to obtain the diagnostic slides, local pathology diagnosis, and tissue block for HPV analysis. However, because HPV disease was not an endpoint for this study, it was decided that only the pathology reports for the biopsies which were obtained outside of the study from female subjects in the 16- to 23-year-old group would be sent to --- for transcription to a Merck preferred diagnosis.

Independent Safety Monitor Monitoring Guidelines
Safety data summaries were to be prepared and provided to the independent Safety Monitor by the unblinded Statistician at 3 time points. The first time point was when approximately half of the Postdose 1 safety data for the 10- to 15-year old subjects were available in the Clinical Trial System (CTS) database. However, at the time that half of

the Postdose 1 safety data for the 10- to 15-yea old subjects were available in the CTS database the study had passed its midpoint.
Therefore, the decision was made to omit the first time point and wait until all of summary was prepared and provided to the independent Safety Monitor at approximately the time that all of the Postdose 1 safety data for the 10- to 15-year-old subjects were available in the CTS database. The time point for the final safety summary was to be at the time that all of the Postdose 2 safety data for the 10- to 15-year-old subjects were available in the CTS database. However, most of the Postdose 2 safety data were being entered into the CTS database at approximately the same time frame as the Postdose 3 safety data. Therefore, the final summary was completed and submitted at the time that all Postdose 3 safety data were available in CTS. As a result, only 2 safety data summaries were submitted to the independent Safety Monitor. The change to the time points for the safety data summaries was communicated verbally to the independent Safety Monitor.

Other Changes:
Because HPV disease was not an endpoint for this study, it was decided that only the pathology reports for the biopsies obtained outside of the study in 16-23 year old women would be sent to --- for transcription to a Merck preferred diagnosis.

Independent Safety Monitoring Guidelines: the first safety data summary was prepared and provided to the Independent Safety Monitor at app. the time that all Postdose 1 safety data for 10-15 year old subject were available (instead of the planned 50%). In addition, the second summary was provided when all postdose 3 safety data were available, instead of postdose 2 and postdose 3.

Changes in Statistical Analyses
Exploratory immunogenicity summaries were provided for 16- to 23-year-old females who were HPV PCR positive and anti-HPV seropositive at Day 1. Additional Safety summaries were provided for subgroups of the overall study cohort based on Day 1 HPV status.

APPENDIX 17: Protocol 018, Inclusion/Exclusion Criteria

Inclusion Criteria

- Healthy preadolescents or adolescents between the ages 9 years and 0 daysand 15 years and 364 days.
- Must not yet have had coitarche and did not plan on becoming sexually active through the course of the study.
- Must have agreed to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes.
- No temperature 100°F or 37.8°C (oral) within 24 hours prior to the first injection.
- Not pregnant at study entry (as determined by a serum pregnancy test or urine pregnancy test sensitive to 25 IU hCG) or was a male.

Exclusion Criteria

- Individuals concurrently enrolled in clinical studies of investigational agents or studies involving collection of cervical specimens.
- History of known prior vaccination with a HPV vaccine.
- Receipt of inactivated vaccines within 14 days prior to enrollment or receipt of live virus vaccines within 21 days prior to enrollment.
- History of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention.
- Individuals allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).
- Individuals who had received any immune globulin preparation (including RhoGAM™ [Ortho-Clinical Diagnostics]) or blood-derived products within the 6 months prior to the first injection, or planned to receive any through the completion of the study.
- Individuals with a history of splenectomy, known immune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis), or receiving immunosuppressives. Individuals who had received periodic treatments with immunosuppressives, defined as at least 3 courses of systemic corticosteroids each lasting at least 1 week in duration for the year prior to enrollment, were excluded. Subjects using topical steroids (i.e., inhaled or nasal) were eligible for vaccination.
- Individuals with known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
- Any condition that, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.
- Any plan to permanently relocate from the area prior to the completion of the study or to leave for an extended period of time when study visits needed to be scheduled.
- Individuals who were immunocompromised or had been diagnosed as having HIV infection.
- History of recent or ongoing alcohol or other drug abuse.
- Inability to give consent/assent.

APPENDIX 18: Protocol 018, Changes in Protocol and Changes in Statistical Analyses

Protocol 018 Amendments

Amendment 018-01 was a partial amendment for Canada. However, there were no subjects enrolled in Canada.

Amendment 018-02 was a partial amendment to include ----------
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Amendment 018-03 was a complete amendment implemented in all participating countries. The main purpose of the amendment was to include a comparison of the immunogenicity profile of Gardasil between male and female adolescents. The revised immunogenicity objectives were as follows: (1) To demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses induced by a 3-dose regimen of Gardasil in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls; and (2) To describe the persistence of immune response to the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, when given in a 3-dose regimen. The statistical criterion for noninferiority requires that the lower bounds of the 95% confidence intervals for the fold difference in GMTs (boys/girls) exclude a decrease of 2-fold or more).

In addition, the procedures for unblinding were provided in further detail.

Amendment 018-04 included all the changes in 018-03 and 018-02. The amendment only applied to the subjects enrolled in Spain.

An **Informational Amendment**, submitted in a letter dated 11/17/04 to the U.S. FDA CBER documented the addition of a secondary immunogenicity hypothesis and additional immunogenicity endpoint that Gardasil induces similar immune responses, as measured by the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3, in preadolescent/adolescent boys and preadolescent/adolescent girls. The statistical criterion for noninferiority requires that the lower bound of the 95% confidence interval for the difference in proportions between the 2 groups (boys-girls) exclude a decrease of 5 percentage points or more for each HPV type.)

Changes in Statistical Analyses

Observational comparison to other Phase II/III studies in which efficacy has been shown were not included in this CSR, because the Phase III studies were yet to be unblinded, but will be made based on integrated immunogenicity data presented in the Biologics License Application for the quadrivalent HPV vaccine.

Data collected after Month 7 will not be included in this CSR, but will be summarized separately, as the data become available.

Due to the large number of study sites, the statistical models used to estimate Week 4 Postdose 3 GMTs were adjusted for geographic region (and age at enrollment), rather than individual study site.