Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Vaccines and Related Product Applications

Subject: Clinical Review of Biologics License Application Supplement STN# 125126/773 – mid-adult women indication for GARDASIL

Product: GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]

Date of submitted application: January 11, 2008
Date of completed review: August 8, 2010

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1 General Information

1.1 Medical Officer's (MO) Review Identifiers and Dates

1.1.1 sBLA

125126/773.0

1.1.2 Related IND #(s)

Gardasil IND#: 9030
Original Gardasil BLA#: 125126

1.1.3 Reviewer Name, Division and Mail Code (HFM Number)

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1.1.4 Submission Received by FDA

January 11, 2008

1.1.5 Review Completed

August 8, 2010

1.2 Product

1.2.1 Proper Name or Established Name

Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant

1.2.2 Trade Name

Gardasil

> **Clinical Reviewer Note:** In this review, the product may be referred to by its proper name, by the trade name, Gardasil, or as qHPV vaccine.

1.2.3 Abbreviations Used in This Review

Abbreviation	Definition
AAHS	Amorphous aluminum hydroxyphosphate sulfate
CBER	FDA's Center for Biologics Evaluation and Research
CIN	cervical intraepithelial neoplasia
cLIA	competitive luminex immunoassay

CR letter	complete response letter
EGL	external genital lesion
FAS	full analysis set analysis population
GHN	generally HPV naïve analysis population
hrHPV	high risk Human Papillomavirus
MAW	mid-adult women
OBE	CBER's Office of Biostatistics and Epidemiology
PI	persistent infection
PPE	per protocol efficacy analysis population
qHPV	Quadrivalent HPV vaccine, or Gardasil
sBLA	Biologics License Application Supplement
VLP	Virus-like particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee
YAW	young-adult women

1.2.4 Product Formulation(s) Including Adjuvants, Preservatives, etc.

GARDASIL is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The VLPs are adsorbed on preformed aluminum-containing adjuvant, Amorphous Aluminum Hydroxyphosphate Sulfate (AAHS). The contents of each 0.5mL dose are listed in Table 1.

The product does not contain a preservative or antibiotics.

Table 1: Contents of Each 0.5mL Dose of Gardasil

Material *	**Amount**
HPV Type 6 L1 protein	20 ug
HPV Type 11 L1 protein	40 ug
HPV Type 16 L1 protein	40 ug
HPV Type 18 L1 protein	20 ug
Aluminum hydroxyphosphate sulfate adjuvant	225 ug
Sodium chloride	9.56 mg
Sodium borate	35 ug
L-histidine	0.78 mg
Polysorbate 80	50 ug
Yeast protein	<7 ug

* Prepared in water for injection

1.3 Applicant

Merck Research Laboratories

1.4 Indication(s)

1.4.1 Current Indications for Gardasil

GARDASIL is a vaccine indicated in **girls and women 9 through 26 years** of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

GARDASIL is indicated in **boys and men 9 through 26 years** of age for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11.

1.4.2 Indication for Gardasil Proposed Under This sBLA

The BLA supplement is submitted in support of extending the current indications for Gardasil to women 27-45 years of age.

1.5 Dosage Form(s) and Route(s) of Administration

Gardasil is a 0.5mL suspension for intramuscular injection supplied as a single dose vial or pre-filled syringe.

2 Table of Contents

1 GENERAL INFORMATION 2

1.1 MEDICAL OFFICER'S (MO) REVIEW IDENTIFIERS AND DATES 2
1.1.1 sBLA # *2*
1.1.2 Related IND #(s) *2*
1.1.3 Reviewer Name, Division and Mail Code (HFM Number) *2*
1.1.4 Submission Received by FDA *2*
1.1.5 Review Completed *2*
1.2 PRODUCT 2
1.2.1 Proper Name or Established Name *2*
1.2.2 Trade Name *2*
1.2.3 Abbreviations Used in This Review *2*
1.2.4 Product Formulation(s) Including Adjuvants, Preservatives, etc. *3*
1.3 APPLICANT 3
1.4 INDICATION(S) 4
1.4.1 Current Indications for Gardasil *4*
1.4.2 Indication for Gardasil Proposed Under This sBLA *4*
1.5 DOSAGE FORM(S) AND ROUTE(S) OF ADMINISTRATION 4

2 TABLE OF CONTENTS 4

3 EXECUTIVE SUMMARY 6

4 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 7

4.1 CHEMISTRY, MANUFACTURING AND CONTROLS (CMC) 7
4.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 7
4.3 STATISTICS 7

5 CLINICAL AND REGULATORY BACKGROUND 7

5.1 DISEASE OR HEALTH-RELATED CONDITION(S) STUDIED AND AVAILABLE INTERVENTIONS 7
5.2 IMPORTANT INFORMATION FROM PHARMACOLOGICALLY RELATED PRODUCTS, INCLUDING MARKETED PRODUCTS 8
5.3 PREVIOUS HUMAN EXPERIENCE WITH THE PRODUCT 8
5.4 REGULATORY BACKGROUND INFORMATION 8

6 CLINICAL DATA SOURCES (BOTH IND AND NON-IND), REVIEW STRATEGY AND DATA INTEGRITY 9

6.1 MATERIAL REVIEWED 9
6.1.1 BLA Supplement 125126/773 - Files Reviewed *9*
6.1.2 Literature *10*
6.1.3 Post-Marketing Experience *10*
6.2 CLINICAL STUDIES 10
6.3 REVIEW STRATEGY 10
6.4 GOOD CLINICAL PRACTICES (GCP) AND DATA INTEGRITY 10

7 HUMAN PHARMACOLOGY 10

8 CLINICAL STUDIES 11

8.1 STUDY V501-019 – GARDASIL IN MID-ADULT WOMEN 11
8.1.1 Design Overview *11*
8.1.2 Objectives *11*
8.1.3 Eligibility Criteria *12*
8.1.4 Products Mandated by the Protocol *14*
8.1.5 Endpoints *15*
8.1.5.1 Efficacy Endpoints 15
8.1.6 Surveillance/Monitoring *15*
8.1.7 Statistical Considerations *17*
8.1.8 Results *17*
8.1.8.1 Analysis Populations 17
8.1.8.2 Populations Enrolled/Analyzed 18
8.1.8.3 Subject Demographics/Characteristics 18
8.1.8.4 Efficacy Endpoints/Outcomes 19
8.1.8.4.1 Primary Endpoint 19
8.1.8.4.2 Estimates of Efficacy in the General Population – Full Analysis Set (FAS) Analyses 22
8.1.8.4.3 Estimates of Efficacy in Naive Population – Generally HPV Naïve (GHN) Analyses 25
8.1.8.4.4 Estimates of Efficacy in Prevention of Other Clinically Important Endpoints (e.g., Pap diagnoses) 25
8.1.8.5 Immunogenicity 26
8.1.8.6 Safety 29
8.1.8.6.1 Systemic Adverse Events 30
8.1.8.6.2 Injection Site Adverse Events 32
8.1.8.6.3 Pregnancy Outcomes 32
8.1.8.6.4 Serious Adverse Events 34
8.1.8.6.5 Deaths 34

9 ADDITIONAL CLINICAL ISSUES 36

9.1 SPECIAL POPULATIONS 36
9.1.1 Pregnancy *36*
9.1.2 Geriatric Use *36*
9.1.3 Immunocompromised Patients *36*
9.1.4 Pediatrics *36*
10 CONCLUSIONS - OVERALL 36
11 RECOMMENDATIONS 37
11.1 APPROVAL RECOMMENDATIONS 37
11.2 RECOMMENDATIONS ON POSTMARKETING ACTIONS 37
11.3 LABELING 37

3 Executive Summary

Gardasil is currently licensed for prevention of cervical, vulvar and vaginal cancer and the associated precancerous lesions in females 9 to 26 years of age, and for the prevention of genital warts in males and females 9 to 26 years of age. With this Biologics License Application supplement (sBLA), the applicant sought approval for extension of all indications to women 27 to 45 years of age.

Clinical data from a single clinical trial were submitted in support of the expanded indication. The study was conducted in ~3800 subjects (women aged 24 to 45 years), who were randomized 1:1 to receive Gardasil or AAHS control. Efficacy was demonstrated on the primary endpoint, which was a composite of peristent infection, any grade of cervical or vulvovaginal dysplasia, and genital warts. However, the vast majority of cases on the primary endpoint were persistent infection (PCR positive for one HPV type on two consecutive visits at least 6 months apart) or low grade cervical disease. Efficacy in the prevention of high grade cervical disease was not established. In addition, for a number of other outcomes, including prevention of genital warts, prevention of abnormal Paps, and prevention of definitive cervical or genital therapy, the data did not establish a substantial benefit in a population of women 27-45 years of age unscreened for past or current HPV infection.

Over the course of the BLA supplement review, CBER issued two complete response (CR) letters. Both letters focused on the fact that the analyses in which efficacy was clearly demonstrated were driven primarily by cases of persistent infection, a correlate for protection against advanced dysplasia and cancer about which there is more uncertainty in older compared with younger women. Concern was expressed about the lack of efficacy in the prevention of advanced dysplasia due to vaccine HPV types and about the reverse case splits on advanced dysplasia (more cases of CIN2+ in the Gardasil group compared with the control group) due to any HPV type in the full analysis set (FAS) population analyses. While the applicant's responses never adequately addressed the lack of efficacy in preventing advanced dysplasia due to vaccine HPV types, the reverse case splits likely were due to imbalances in the initial randomization and other factors.

The safety profile of Gardasil in women 27-45 years of age is comparable to that observed in younger females. No safety signals were identified in this population.

The clinical reviewer concluded that the data submitted do not support a recommendation for approval of the request to extend the current indications for Gardasil to the population of women 27-45 years of age. However, the reviewer recommended approval of the BLA supplement for the display in the package insert of safety, immunogenicity and certain key efficacy data in women 27-45 years of age in order to inform patients and physicians of these results.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)

All lots of vaccine used in this study were reviewed and released for distribution by CBER.

In addition, the immunogenicity assay, Merck's competitive Luminex immunoassay (cLIA) version 2.0, that was utilized in the pivotal study submitted to this file, has been reviewed by CBER in previous Gardasil supplements.

Because this supplement contains no new assays or other product issues, CBER did not perform a comprehensive CMC review.

4.2 Animal Pharmacology/Toxicology

No new pharmacology or toxicology data were required or submitted for this sBLA.

4.3 Statistics

The statistical reviewer concluded that the data submitted to the BLA demonstrated efficacy of the vaccine in prevention of the composite endpoint (persistent infection, CIN, and EGL). However, the reviewer also concluded that none of the data submitted adequately addressed the issues raised in CBER's CR letters, namely that efficacy on the composite endpoint was driven primarily by persistent infection and that a higher number of any-HPV-type cases of CIN 2+ was observed in the qHPV vaccine group compared to placebo.

5 Clinical and Regulatory Background

5.1 Disease or Health-Related Condition(s) Studied and Available Interventions

A large majority of individuals acquire HPV soon after becoming sexually active. Mild cervical dysplasia caused by infection with oncogenic HPV is common in young women. Most of these lesions regress and resolve spontaneously, but those that persist can develop into severe dysplasia and ultimately cervical cancer. A similar process occurs less commonly at other anogenital sites, such as vagina, vulva, perineum, and anus. Certain low risk HPV types, particularly HPV 6 and 11, can cause anogenital warts.

Available interventions for HPV associated diseases consist of treatment (mostly ablative or excisional) of established lesions. Aside from vaccination, no intervention, including condom use, has been shown consistently to prevent HPV infection or disease.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

At the time of submission of the sBLA, Cervarix (manufactured by GSK Biologicals) was the only other HPV vaccine licensed in the U.S. The upper age limit for the Cervarix indication is the same as for the Gardasil indication: 26 years of age. Cervarix is indicated for prevention of disease caused by HPV types 16 and 18 but not for prevention of genital warts.

5.3 Previous Human Experience with the Product

Gardasil was licensed in the U.S. in June of 2006. The FDA/CBER clinical review of the safety and efficacy data submitted to the original BLA is available at: http://www.fda.gov/cber/products/gardasil.htm.

5.4 Regulatory Background Information

2001 November: The Vaccines and Related Biological Products Advisory Committee (VRBPAC) deliberated on the design of phase III development programs for vaccines for prevention of cervical cancer. The VRBPAC committee members discussed different endpoints and ultimately concurred with the use of CIN 2/3, AIS, or cervical cancer (i.e., CIN 2/3 or worse, also referred to as CIN2+).

2004 December: CBER issued a letter to Merck commenting on the proposed protocol for Study 019 to evaluate Gardasil in "mid-adult women". In the letter, CBER made several suggestions for revisions to the protocol but essentially agreed to the proposed composite primary endpoint of vaccine type persistent infection and the associated disease outcomes. Relevant language from CBER's letter:

> *"If efficacy can be demonstrated in the ongoing studies designed to assess prevention of advanced dysplasia caused by serotypes 16 and 18 in a younger population of women (16-23 years old), CBER would consider virologic and less advanced histopathologic lesions as data supportive of efficacy in the older population of women (24–45 years old)."*

2008 January: Merck submitted sBLA #125126/773 with analysis of data from Study 019, triggered by fixed event analysis design.

2008 June: CBER issued the first of two CR letters. The letter made note of the fact that not all subjects had completed the 48 month study at the time of the pre-specified analysis. Attention was drawn to the lack of efficacy against CIN2+ lesions, particularly in the analyses that included any HPV type.

2008 July: Merck responded to CR #1, pointing out that CBER agreed to the composite endpoint and that the study was not powered to evaluate an advanced disease endpoint.

2008 December: CBER issued CR #2, calling attention again to the lack of efficacy

against vaccine type associated CIN2+. CBER stated particular concern about the substantial reverse case split (more disease in the vaccinated versus the placebo arm) in the analysis of CIN2+ due to any HPV type in the full analysis set population. CBER recommended responding when Study 019 is complete and the close-out data are available.

2009 November: Merck responded to CR #2 with the completed Study 019 clinical study report, which included the close-out data.

2010 February: After preliminary review of the Study 019 close-out data, CBER informed Merck that the unfavorable results on the CIN2+ endpoint remain problematic, and CBER proposed convening a VRBPAC to discuss the application. Merck subsequently withdrew the request for expansion of the indication to include mid-adult women, proposing instead that the body of label be revised to communicate some of the data from Study 019 in order to inform practitioners about use of the vaccine in mid-adult women.

2010 April: CBER issues a major amendment letter in order to adequately review major revisions to the label that included data from the mid-adult women study.

6 Clinical Data Sources (both IND and non-IND), Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 BLA Supplement 125126/773 - Files Reviewed

V501-019v1 – Interim Clinical Study Report
V501-019 – Final Clinical Study Report
Reference 2047 – Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine Protocol 007-10: A Placebo-Controlled, Dose-Ranging Study of Quadrivalent HPV Virus-Like Particle (VLP) Vaccine in 16- to 23-Year-Old Women Reference 2155 - MRL Statistical Report: Update of the integrated summary of efficacy of Merck's quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine
Reference 2154 – Special Report: Updated and additional analyses on the impact of quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine on the incidence of cervical or external genital disease related to HPV types not included in the vaccine in young women (evaluation of cross-protection and HPV type replacement) (Protocols 013 and 015), 2007
Reference 2157 – Genital Human Papillomavirus (HPV) infection in mid-adult (24-to 45-year-old) women: natural history and disease burden
Reference 2158 – Updated evaluation of congenital anomalies in pregnancy outcomes of subjects enrolled in the clinical development program for qHPV vaccine (quadrivalent HPV [types 6, 11, 16, 18] L1 VLP Vaccines), 2007
Reference P015 – A Randomized Worldwide, Placebo-Controlled, Double-Blind Study to Investigate the Safety, Immunogenicity, and Efficacy on the Incidence of HPV 16-/18-Related CIN 2/3 or Worse of the Quadrivalent HPV (Types 6, 11, 16, 18] L1 Virus-Like Particle (VLP) Vaccine in 16- to 23-Year-Old Women - The FUTURE II Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease)

6.1.2 Literature

Bosch et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine. 2008 Aug 19;26 Suppl 10:K1-16.

Khan et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst. 2005 Jul 20;97(14):1072-9.

Rodríguez el al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst. 2008 Apr 2;100(7):513-7.

Rodríguez et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. J Natl Cancer Inst. 2010 Mar 3;102(5):315-24.

6.1.3 Post-Marketing Experience

In accordance with the terms of initial licensure in June 2006, the applicant has conducted a postmarketing safety study in females. The final study report has been submitted to CBER and is currently under review. The status of other postmarketing studies to which the applicant has committed can found at http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

6.2 Clinical Studies

The only study submitted to the sBLA was the end of study report for Protocol 019, which presents the close-out data for mid-adult women.

6.3 Review Strategy

6.4 Good Clinical Practices (GCP) and Data Integrity

----------Removed Per the Privacy Act----------

7 Human Pharmacology

See Section 8.

8 Clinical Studies

8.1 Study V501-019 – Gardasil in Mid-Adult Women

Title: Safety, Immunogenicity, and Efficacy of GARDASIL™ (Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine) in Mid-Adult Women - The FUTURE III (Females United to Unilaterally Reduce Endo/Ecto Cervical Cancer) Study

8.1.1 Design Overview

This was a randomized, double-blind, placebo-controlled, multicenter study. Women 24-45 years of age were screened on Day 1 and randomized 1:1 to receive qHPV (VLPs plus aluminum adjuvant) or placebo (aluminum adjuvant) on Day 1, Month 2 and Month 6.

Each subject underwent a gynecologic exam and had specimens collected for HPV PCR and Pap testing at Months 0, 7, 12, 18, 24, 30, 36, 42, and 48. Sera were collected for immunogenicity at screening and at Months 7, 12, 24, 36, and 48. Each subject was instructed to complete a Vaccination Report Card (VRC), recording temperatures for 4 days post-vaccination and injection site and systemic AEs for 14 days post-vaccination. Safety assessments were performed at each visit.

> **Clinical Reviewer Note:** CBER noted that the study included a substantial number of subjects 24-26 years of age (n = 563, which is ~15% of the total study population). Because the requested expansion of the indication was to women 27-45 years of age, CBER requested that the key efficacy analyses be re-calculated, excluding the subjects younger than 27 years of age. These analyses were submitted, and they were evaluated by CBER reviewers. The differences from the overall analyses were insubstantial and were judged to be of negligible clinical significance.

8.1.2 Objectives

Primary Efficacy Objectives:

1. To demonstrate that administration of qHPV vaccine reduces the combined incidence of HPV 6/11/16/18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS, and cervical cancer, compared with placebo in women 24 to 45 years of age who are naïve to the relevant HPV type.

2. To demonstrate that administration of qHPV vaccine reduces the combined incidence of HPV 16/18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS, and cervical cancer, compared with placebo in women 24 to 45 years of age who are naïve to the relevant HPV type.

Secondary Efficacy Objectives:

1. To demonstrate that administration of qHPV vaccine reduces the combined incidence of HPV 6/11-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS, and cervical cancer, compared with placebo in women 24 to 45 years of age who are naïve to the relevant HPV type.

2. To demonstrate that administration of qHPV vaccine reduces the combined incidence of HPV 31/33/35/52/58-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS, and cervical cancer, compared with placebo in women 24 to 45 years of age who are generally HPV naive.

Tertiary Efficacy Objective:
To demonstrate that administration of qHPV vaccine reduces the combined incidence of the following Pap diagnoses related to HPV 16 and/or 18 compared with placebo in women 24 to 45 years of age who are naïve to the relevant HPV type: ASC-US with positive high-risk probe, LSIL, HSIL, ASC-H, AGC, and cancer.

Immunogenicity Objectives:
1. To evaluate the kinetics and age dependence of anti-HPV 6, 11, 16, and 18 responses following administration of a 3-dose regimen of qHPV vaccine.

2. To observationally compare anti-HPV 6, 11, 16, and 18 responses following administration of a 3-dose regimen of qHPV vaccine among HPV-naïve women 24 to 45 years of age enrolled in this protocol and HPV-naïve women 16 to 23 years of age from Protocols 011, 012, and the Consistency Lots substudy of Protocol 015.

Primary Safety Objective: To demonstrate that a 3-dose regimen of qHPV, when administered at 0, 2, and 6 months, is generally well tolerated in women 24 to 45 years of age.

8.1.3 Eligibility Criteria

Clinical Reviewer Note: Compared with the studies in females aged 16-26 years, the sponsor made notable modifications to the eligibility criteria. The justification provided is as follows: in women aged 16 to 23, it is possible to use the lifetime number of sexual partners to select a cohort that is relatively HPV-naïve at enrollment but is at high risk of subsequent HPV infections. In women who are 24 to 45 years of age, such a defining marker is not as useful, but screening out women with the most significant history of HPV exposure and disease is still desirable.

Therefore, in contrast to the young adult women studies (in which women were eligible only if they had a lifetime number of sexual partners below a certain number), in the mid-adult women study, women with an intact cervix (i.e., those without hysterectomy) were eligible for further evaluation based on the algorithm cited below, which screens out women with history of treatment for dysplasia.

Algorithm for screening potential study subjects before application of inclusion/exclusion criteria:

Has the subject ever had a surgical procedure (either treatment or biopsy) to the cervix?
If **no**, subject is eligible for further evaluation for recruitment.

If **yes** to having had a surgical procedure,
1. Was the procedure treatment to the cervix in an outpatient surgery setting (such as conization, LEEP, laser, cervical cryotherapy, etc.) or was subject hospitalized for surgery to the cervix? If **yes** to any treatment-related procedure, the subject is not

eligible for recruitment.

2. Was the procedure exclusively a biopsy of the cervix, i.e., no surgical treatment to the cervix?

   If **yes**, when was the biopsy taken?

   - If the biopsy occurred 5 or more years ago, the subject is eligible for further evaluation for recruitment
   - If the biopsy occurred <5 years ago, the subject is not eligible for further evaluation.

   If **no,** subject is not eligible for further evaluation.

Inclusion Criteria

1. Subject is between the ages 24 years and 0 days and 45 years and 364 days as of visit 1.
2. Subject is judged to be in good physical health on the basis of medical history, physical examination, and laboratory testing.
3. Subject is able to understand study procedures and agrees to participate in the study by giving written informed consent.
4. Subject has no clinical evidence of gross purulent cervicitis (otherwise postpone until after treatment or laboratory tests indicate no specific etiology for the condition).
5. Subject agrees to refrain from douching/vaginal cleansing or using vaginal medication or preparation for 48 hours prior to any scheduled visit that includes specimen collection. (If the subject has not met this inclusion criterion at the time of the enrollment visit, enrollment must be delayed until the 48 hour requirement is met.)
6. Subject agrees to refrain from sexual activity (including anal, vaginal, or genital/genital contact whether same sex or opposite sex) for 48 hours prior to any visit (scheduled or unscheduled) that includes specimen collection, in an attempt to avoid detection of viral DNA which has been deposited in the vagina or on the perineal/perianal area during sexual intercourse and is not the result of ongoing infection. (If the subject has not met this inclusion criterion at the time of the enrollment visit, enrollment must be delayed until the 48 hour requirement is met.)
7. Subject is not pregnant now (as determined by a serum pregnancy test or urine pregnancy test sensitive to 25 IU -hCG) and agrees to use effective contraception through Month 7 of the study. Effective contraception will be considered: oral contraceptives, injection or implant contraception *such as* DEPO-PROVERA™ (sterile medroxyprogesterone acetate suspension, USP, Pharmacia and Upjohn), NORPLANT™ (levonorgestrel implants, Wyeth-Ayerst), slow-release local contraceptive *such as* NuvaRing™ (etonogestrel/ethinyl estradiol vaginal ring, Organon Inc.), hormonal patch, IUD, sterilization, abstinence, condom (male), diaphragm, cervical cap.
8. Subject has used effective contraception as defined above for 2 weeks prior to enrollment. (Emergency contraception is not considered effective contraception for enrollment into the study.)
9. Subject has had no temperature 100 F or 37.8 C (oral) within 24 hours prior to the first injection.
10. Subject is sexually active.
11. Subject has no history of genital warts.
12. Subject has intact cervix.
13. Subject meets criteria of surgical procedure to the cervix algorithm.

Exclusion Criteria

All candidate subjects who manifest any of the following exclusion criteria at the time of randomization will not be eligible for the study:

1. Subject is pregnant.
2. Subject has a history of any disease, which, in the investigator's opinion, may confound the results of the study or pose an additional risk to the Subject.
3. Subject is concurrently enrolled in clinical studies of investigational agents or studies involving collection of cervical specimens.
4. Subject has a history of known prior vaccination with an HPV vaccine.
5. Subject has a history of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension or shock) that required medical intervention.
6. Subject is allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]). For the purpose of this exclusion criterion, an allergy to vaccine components is defined as an allergic reaction that met the criteria for serious adverse experiences.
7. Subject has received any immune globulin (including RhoGAM™ [Ortho-Clinical Diagnostics]) or blood derived products within the 3 months prior to the first injection, or plans to receive any through Month 7 of the study.
8. Subject has a history of splenectomy, known immune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis), or receiving immunosuppressives (e.g., substances or treatments known to diminish the immune response such as radiation therapy, administration of antimetabolites, antilymphocytic sera, systemic corticosteroids). Individuals who have 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, will be excluded. Subjects using topical steroids (i.e., inhaled, nasal, or topical) will be eligible for vaccination.
9. Subject is immunocompromised or has been diagnosed as having HIV infection.
10. Subject has a known thrombocytopenia or other coagulation disorder that would contraindicate intramuscular injections.
11. Subject has a history of recent (within 1 year from the date of enrollment) or ongoing alcohol abuse or other drug abuse.
12. Subject has any condition which in the opinion of the investigator might interfere with the evaluation of the study objectives.
13. Subject 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.
14. Subject is unable to give informed consent.
15. Subject has any prior history of genital warts or any prior treatment for genital warts.
16. Subject has active cervical disease or a significant history of cervical disease (i.e., surgical treatment for cervical lesions).
17. Subject has undergone hysterectomy (either vaginal or total abdominal hysterectomy).

8.1.4 Products Mandated by the Protocol

Subjects were randomized 1:1 to receive qHPV vaccine or placebo at Day 1, Month 2 (±3 weeks), and Month 6 (±4 weeks). Vaccine or placebo was administered as a 0.5mL intramuscular injection in the deltoid muscle of the nondominant arm.

The placebo was normal saline with adjuvant; each 0.5mL dose of placebo contained 225 mcg of AAHS adjuvant, the same amount contained in each dose of Gardasil.

8.1.5 Endpoints

8.1.5.1 Efficacy Endpoints

Primary Efficacy Endpoint
There were two co-primary efficacy endpoints that were a composite of multiple HPV-related clinical endpoints. They are as follows:

- persistent infection, condyloma acuminata, VIN 1, VIN 2/3, VaIN 1, VaIN 2/3, vulvar cancer, vaginal cancer, CIN 1, CIN 2, CIN 3, AIS, or cervical cancer, caused by HPV type 6 and/or 11 and/or 16 and/or 18.
- persistent infection, condyloma acuminata, VIN 1, VIN 2/3, VaIN 1, VaIN 2/3, vulvar cancer, vaginal cancer, CIN 1, CIN 2, CIN 3, AIS, or cervical cancer, caused by HPV type 16 and/or 18.

Secondary Efficacy Endpoints
- Cervical dysplasia (any grade CIN) due to any HPV type.
- Cervical dysplasia (CIN 2/3 or worse) due to any HPV type.
- Cervical dysplasia (any grade CIN) or worse due to HPV types 31/33/35/52/58.
- External genital HPV-related lesions (e.g., genital warts) due to HPV types 31/33/35/52/58.

Tertiary Efficacy Endpoints
- Pap diagnoses related to HPV 16 and/or 18: ASC-US with positive high-risk probe, LSIL, HSIL, ASC-H, AGC, and cancer

8.1.6 Surveillance/Monitoring

The surveillance and monitoring for Protocol 019 is listed in Table 2.

In addition to what is listed in Table 2, subjects were given a VRC (vaccine report card) on which to record oral temperatures 4 hours following vaccination and daily for the next 4 days; any systemic or local adverse experiences that occurred on Day of vaccination or within 14 calendar days following vaccination; and medications received on Day of vaccination or during the 14 days following vaccination.

Table 2: Study Procedures for Protocol 019

Event/Test	Randomization Day 1	Months 2	6	7	12	18	24	30	36	42	48
Obtain informed consent	+										
Physical examination	+					+			+		+
Gynecologic/medical history[a]	+			+	+	+	+	+	+	+	+
Gynecologic physical examination	+			+	+		+		+		+
External genital inspection	+			+	+	+	+	+	+	+	+
Specimen collection/laboratory measurements (in serial order):											
Pregnancy test[b]	+	+	+								
Serum for anti-HPV 6, 11, 16, and 18 cLIA and retention[c]	+			+	+		+		+		+
Labial/vulvar/perineal/and perianal swabs for HPV PCR[d]	+			+	+	+	+	+	+	+	+
Swab for HSV culture[e]	(+)				(+)		(+)		(+)		(+)
pH of vaginal fluid[e]	(+)				(+)		(+)		(+)		(+)
Wet mount for trichomonas and be	(+)				(+)		(+)		(+)		(+)
Whiff test for be	(+)				(+)		(+)		(+)		(+)
KOH for yeast[e]	(+)				(+)		(+)		(+)		(+)
Endo/ectocervical swab for HPV PCR[d]	+			+	+	+	+	+	+	+	+
Pap test (**ThinPrep**™) for cytology[f]	+			+	+	+	+	+	+	+	+
Vaccination[g]	+	+	+								
Clinical follow-up for safety[h]	+	+	+	+							

Note: Any test may be repeated if medically indicated.

The Month 2 visit can be performed with ±3 weeks. The Month 6 visit and all scheduled visits from Month 12 through Month 48 can be performed within ±4 weeks. The interval between the Month 6 and Month 7 visits should be a minimum of 3 weeks and a maximum of 7 weeks. Any visit for pelvic specimen collection should be performed at least 2 days after menses is completed. An attempt should be made not to collect pelvic specimens within 2 days prior to menses. If despite the above, visible blood is noted in the vagina, the specimen may be collected. The presence of visible blood in the vagina should be noted on the Specimen Collection workbook form.

[a] Although complete review of the subject's gynecologic/medical history will not be scheduled for the Month 2, and Month 6 visits, their history will be updated as needed at these visits and at unscheduled visits.

[b] The pregnancy test (either serum or urine test) must be sensitive to 25 IU β-hCG.

[c] Serum for antibody measurements may be collected after the pelvic exam, but must be collected before vaccination.

[d] Specimens will be tested by type-specific HPV PCR at a central laboratory selected by Sponsor.

[e] Tests may be performed if clinically indicated (at the investigator's discretion).

[f] Pap test to be performed by central laboratory selected by Sponsor. A gonorrhea and chlamydia test will be performed by the **Sponsor's selected central laboratory on the ThinPrep**™ sample at Day 1, and Months 12, 24, 36, and 48 only.

[g] Temperature will be measured prior to each injection.

[h] Serious and non-serious adverse experiences will be collected for all subjects. All reports of pregnancy will be collected and forwarded to the Sponsor. Each participant will record on a Vaccination Report Card (VRC) her oral temperature 4 hours after each injection and daily for the next 4 days. Any injection-site or systemic complaint, which may occur on Day 1 or during the 14 calendar days after each injection, will also be recorded on the VRC. At Months 2, 6, and 7, the study personnel together with the participant will review the VRC. At months 2, 6, and 7, subjects will be solicited for any gynecologic health concerns and any serious AEs that they may have encountered.

Source: Original sBLA 125126/773; Clinical Study Report V503-019, p.138

8.1.7 Statistical Considerations

This study employed a fixed event design such that the tests of hypotheses were scheduled to be conducted, possibly in 2 stages, at the time(s) when a specific target number of cases of the coprimary and secondary efficacy endpoints had been observed in the per-protocol efficacy (PPE) population.

The test of hypothesis relating to the HPV 6/11/16/18-related persistent infection, CIN, or EGL endpoint was conducted as planned, using a 1-sided 〈 = 0.025) level of significance. Having achieved success on that hypothesis, and having observed 27 cases of HPV 16/18-related persistent infection, CIN, or EGL, the final (i.e., not interim analysis) testing of the hypothesis relating to the HPV 16/18-related persistent infection or disease endpoint was conducted, using the planned 1- sided 〈 = 0.025) level of significance without adjusting for multiplicity due to interim analysis, because no interim analysis was conducted.

8.1.8 Results

8.1.8.1 Analysis Populations

For purposes of analysis, several subsets of the recruited subjects were defined in the protocol. The subsets were grouped under three different categories of analysis – efficacy, immunogenicity, and safety. The populations were defined as follows:

Efficacy Analysis Populations

- Per-protocol efficacy (**PPE**): subjects who: received all 3 doses of vaccine or placebo within 1 year; had Month 7 PCR results on swab samples collected within 14 to 72 days post dose 3; were HPV-naïve (i.e., seronegative at Day 1 and PCR negative from Day 1 through Month 7) to the vaccine HPV type being analyzed (HPV-naïve to both types 6 and 11 in analysis of HPV 6-related and HPV 11-related endpoints); and did not violate protocol. Cases for the PPE evaluation were counted starting after Month 7.

- Naïve to the Relevant-HPV-type (**HNRT**): subjects who: received at least 1 dose of vaccine or placebo and were HPV-naïve (i.e., seronegative and PCR negative) at Day 1 to the vaccine HPV type being analyzed (HPV-naïve to both types 6 and 11 in analysis of HPV 6-related and HPV 11-related endpoints)

- Full analysis set (**FAS**), consisting of subjects who received at least 1 dose of vaccine or placebo

- Generally HPV Naïve (**GHN**): subjects who: were seronegative and PCR negative at enrollment to HPV 6, 11, 16 and 18, who were PCR-negative at enrollment to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59, who were Pap negative for SIL at enrollment, and who received at least one dose of study material, who had follow-up after Day 1.

Immunogenicity Analysis Populations

- Per-protocol immunogenicity (**PPI**): subjects who: received all 3 doses of vaccine or placebo within 1 year; had Month 7 serum sample collected within 14 to 49 days post dose 3; were HPV-naïve (i.e., seronegative at Day 1 and PCR negative from Day 1 through Month 7) to the vaccine HPV type being analyzed (HPV-naïve to both types 6 and 11 in analysis of HPV 6-related and HPV 11-related endpoints); and did not violate protocol.

Safety Analysis Population

All-Subjects-As-Treated (**ASaT**): all randomized subjects who received at least 1 injection and had follow-up data.

8.1.8.2 Populations Enrolled/Analyzed

A total of 4082 subjects were screened for the study, of whom 3817 (94%) were enrolled, randomized and received at least one vaccination. Of the 3817 subjects who received one vaccination, 3710 (97%) received all three vaccinations and 3692 (97%) completed follow-up to study completion. The vast majority of discontinuations were "lost to follow-up"; discontinuation due to clinical AE was <1%.

> **Clinical Reviewer Note:** Among the women who were screened, the sponsor reports that 171 (~5%) were excluded from enrollment because of a history of cervical biopsy within the past 5 years or any history of cervical definitive therapy (see eligibility criteria above). Along with the exclusion for history of genital warts, this tended to enrich the population for women with less past exposure to HPV. Although the effect is likely to be modest, this might result in estimates of efficacy that tend overestimate the impact of the vaccine in a broader population.

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8.1.8.3 Subject Demographics/Characteristics

Table 3 displays the selected demographics of study participants. There were not any notable imbalances between groups.

Table 3: Demographics of Subjects Enrolled Total N=3819

Demographic	Total: n(%)
Region: Asia-Pacific	1182 (31)
Region: Europe	482 (12.6)
Region: Latin America	1610 (42.2)
Region: North America	545 (14.3)
Race/Ethnicity: Asian	1192 (31.2)
Race/Ethnicity: Black	182 (4.8)
Race/Ethnicity: Hispanic American	1649 (43.2)
Race/Ethnicity: White	785 (20.6)
Race/Ethnicity: Other	8 (0.2)

Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.236

Table 4 displays select baseline characteristics of study participants, including sero- and PCR status on Day 1.

Table 4: **Baseline Characteristics of Subjects Enrolled**

Characteristic	**Gardasil** (Total N = 1911) n(%)	**AAHS control** (Total N=1908) n(%)
Age (mean in years)	34.3	34.3
Age at first sexual intercourse (mean in years)	19	19
0 New Male or Female Sexual Partners in the 6 Months Prior to Study Start	1737 (90.9)	1728 (90.6)
1 New Male or Female Sexual Partners in the 6 Months Prior to Study Start	143 (7.5)	151 (7.9)
2 New Male or Female Sexual Partners in the 6 Months Prior to Study Start	15 (0.8)	16 (0.8)
3 New Male or Female Sexual Partners in the 6 Months Prior to Study Start	6 (0.3)	6 (0.3)
4 New Male or Female Sexual Partners in the 6 Months Prior to Study Start	3 (0.2)	1 (0.1)
> 4 New Male or Female Sexual Partners in the 6 Months Prior to Study Start	1 (0.1)	0 (0.0)
Pap at Day 1: Negative for SIL	1749 (93.2)	1718 (92.8)
Pap at Day 1: ASC-US (HR pos), LSIL, or worse	88 (4.7)	92 (5.0)
Pap at Day 1: HSIL	5 (0.3)	10 (0.5)
PCR status at Day 1 Pos(+) for 6, 11, 16, or 18	159/1889 (8.4)	139/1876 (7.9)
Serostatus on Day 1 Pos (+) for 6, 11, 16, or 18	575/1910 (30.1)	560/1905 (29.4)
Pos (+) by serology or PCR to 6, 11, 16, or 18	635/1893 (33.5)	617/1880 (32.8)

Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.236 - 250

8.1.8.4 Efficacy Endpoints/Outcomes

8.1.8.4.1 Primary Endpoint

Efficacy Against HPV 6/11/16/18-Related Persistent Infection, CIN, and EGL

Per Protocol Efficacy (PPE) Population

The results of the primary efficacy objective analyses in the PPE population are displayed in Table 5. The primary composite endpoint (PI, CIN and EGL) is in bold.

Table 5: Efficacy Against HPV 6/11/16/18-Related Persistent Infection, CIN, and EGL - PPE Population

Endpoint	Gardasil (N=1910) n	Gardasil (N=1910) # of cases	AAHS control (N=1907) n	AAHS control (N=1907) # of cases	Efficacy % (95%CI)
Persistent Infection, CIN, or EGL	1,601	**10**	1,599	**86**	**88.7%** (78, 95)
Persistent Infection	1,581	9	1,586	85	89.6% (79, 95)
CIN (any grade)	1,581	1	1,584	17	94.1% (63, 100)
CIN 2/3 or worse	1,581	1	1,584	6	83.3% (-38, 100)
EGL	1,600	0	1,599	7	100% (31, 100)
Condyloma	1,600	0	1,599	7	100% (31, 100)
VIN 2/3 or VaIN 2/3	1,600	0	1,599	0	NA

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the PPE population eligible for the respective analysis
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.291

Clinical Reviewer Note: CBER acknowledges the 2004 agreement to "consider virologic and less advanced histopathologic lesions as data supportive of efficacy in the older population of women". However, in the intervening period, more data have emerged that undermine the scientific rationale for basing efficacy against cervical cancer on such an early surrogate marker in an older population.

Primarily, the inverse correlation between HPV vaccine efficacy and pre-existing HPV exposure (which increases with age) has become clearer. That correlation is readily apparent in most, if not all, analyses of HPV vaccine studies. For example, for the primary endpoint in the study currently being considered (019) of HPV 6, 11, 16, 18-related PI, CIN, and EGL, the estimate of efficacy rises from 47.2% (34, 58) in FAS to 79.9% (69, 87) in HNRT simply by removing from the analysis women who have any serologic or PCR evidence of exposure at baseline to the vaccine types being analyzed.

In addition, HPV infection may have a different outcome in older compared with younger women. For example, in one studied cohort, HPV 16 infections that persisted to 30 months lead to CIN2+ in 53% of women <30 years of age compared with 12% of women ≥30 years of age (Rodriguez et al 2008). In another publication (Rodriguez et al 2010), new (as opposed to prevalent) hrHPV infections were followed in this cohort and the cumulative rate of CIN3+ per infection followed was: 18-25yo: 4/151 (2.7%); 26-33yo: 7/161 (4.4%); 34-41yo: 0/85 (0.0%); ≥42: 1/97 (1.0%). Though the numbers are small and there are acknowledged caveats and potential sources of bias, this evidence suggests that newly diagnosed hrHPV infections progress to advanced disease slightly less often in older women.

Finally, more evidence has emerged suggesting that some portion of "new" hrHPV infections in older women actually represent reactivation of latent, occult (i.e., undetectable with PCR), established infections instead of acquisition *de novo* via

transmission. The data from the qHPV vaccine trials is suggestive of such a phenomenon. For example, in the PPE analysis of vaccine type persistent infection, the vaccine failure rate was higher in MAW (9 vs 85 (89.6%, CI 79, 95) (from Table 5 above)) compared with YAW (2 vs 45 (95.6%, CI 83, 100) (from Study 007 clinical study report, p.47)). This doubling of the rate of vaccine failures suggests that some portion of the vaccine type infections in MAW were not a failure to prevent infection but rather a failure to prevent reactivation of latent infection. The phenomenon is markedly more pronounced for the advanced disease endpoint. Vaccine type-related CIN2+ in PPE was 2 vs 112 (98.2%, CI 94, 100) in YAW (from Table 11 in the Gardasil label) compared with 1 vs 6 (83.3%, CI -38, 100) in MAW (Table 5 above), respectively. This is a nearly 10 fold increase in the rate of vaccine failure for vaccine type-related advanced disease in subjects who were all sero- and PCR-negative for the relevant type through Month 7. Obviously, the numbers are very small in the MAW data. However, the one MAW case of CIN2+ (Subject AN 83362), was an HPV 16- and 51-related CIN2 in a 40yo female in which neither type was detected by PCR until the biopsy diagnosis at Day 541; hence, this is quite plausibly a case of HPV 16 reactivation. In a similar analysis in the HNRT population (YAW: MITT-2 from Study 015, clinical study report, p. 235) (MAW: HNRT from Study 019, clinical study report, p. 361), vaccine failure in prevention of HPV 16/18-related CIN2+ was 13.5 fold higher in MAW compared with YAW (MAW: 3 to 8, 62.9%, CI -55, 94; YAW: 1 to 36, 97.2%, CI 83, 100). These analyses tend to support the hypothesis, based on epidemiological evidence, that latency/reactivation is not uncommon in older women. The analyses also support the prediction (based on the hypothesis that the mechanism of protection is antibody-mediated prevention of initial infection) that reactivation would not be vaccine-preventable and would thus lead to lower apparent vaccine efficacy in older women. Overall, these data suggest that persistent infection may tend to over-predict efficacy in the prevention of advanced disease in older women compared with younger women.

In light of these considerations, CBER concluded that the advanced disease endpoint of CIN2+ is an important efficacy benchmark to consider in older women, perhaps even more so than in younger women. Although CBER recognized that the study was not powered for an advanced disease endpoint, the insubstantial efficacy and/or lack of statistical significance for CIN2+ apparent in every possible analysis of the 019 data was an important consideration in the ultimate clinical reviewer recommendation not to extend the current indications for Gardasil to females 27 to 45 years of age.

In addition, compared with the original BLA application for use in younger women, CBER placed less weight on the PPE analyses in the evaluation of this supplement. In the original application, efficacy in the PPE population was critical as proof-of-concept data for predicting how effective the vaccine would be in HPV naïve young adolescents (9-15 years of age), to whom the sponsor requested to bridge the indication based on data from young women (16-26 years of age). That concept is not relevant to this application. In the context of this submission, the sponsor asserts that the PPE population is expected to have the least amount of confounding due to prevalent infection or disease, and therefore is the best test for a prophylactic vaccine. However, the sponsor has not proposed, nor have they studied, a scenario wherein mid-adult women would be selected for receipt of the vaccine using commercially available assays or screening tests. The potential for confounding bias works in the opposite direction to that asserted

by the sponsor. Removing subjects with prevalent infection or disease (such as in the PPE analyses) would tend to exaggerate the potential overall prophylactic efficacy of the vaccine in the general population.

Because it is not feasible in clinical practice to select a population that is both sero- and PCR-negative before vaccination and ensure that the vaccinated individuals remain sero- and PCR-negative throughout the 7 month vaccination course, the clinical importance of the efficacy in such a population (PPE) in this study is not paramount. Instead, the analyses in the FAS population are the most clinically relevant. Much of the following data will therefore be taken from the FAS analyses.

Given the low point estimates of efficacy against disease (CIN2+, EGL, genital warts) in the FAS population, even against vaccine type-related lesions (and perhaps more importantly, even lower estimates of efficacy against disease due to any HPV type – see below), CBER concluded that the overall benefit in the general population is likely to be insubstantial.

8.1.8.4.2 Estimates of Efficacy in the General Population – Full Analysis Set (FAS) Analyses

The results of the primary efficacy objective analyses in the FAS population are displayed in Table 6. The primary composite endpoint (PI, CIN and EGL) is in bold.

Table 6: Efficacy Against HPV 6/11/16/18-Related Persistent Infection, CIN, and EGL - FAS Population

Endpoint	**Gardasil** (N=1910) n	**Gardasil** (N=1910) # of cases	**AAHS control** (N=1907) n	**AAHS control** (N=1907) # of cases	**Efficacy** % (95%CI)
Persistent Infection, CIN, or EGL	1,886	**116**	1,883	**214**	**47.2%** (34, 58)
Persistent Infection	1,856	110	1,857	211	49.0% (36, 60)
Day 1 HPV Naïve to all 6/11/16/18	1228	16	1232	90	82.6% (70, 91)
CIN (any grade)	1,862	29	1,861	55	47.5% (16, 68)
CIN 2/3 or worse	1,862	21	1,861	27	22.4% (-43, 58)
EGL	1,884	11	1,882	12	8.5% (-127, 63)
Condyloma	1,884	7	1,882	12	41.8% (-60, 81)
VIN 2/3 or VaIN 2/3	1,884	2	1,882	0	NA

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the FAS population eligible for the respective analysis
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.292, 325, 342

Efficacy against any HPV type-related disease in the FAS population is displayed in Table 7.

Table 7: Efficacy Against Disease Endpoints Due to Any HPV Type - FAS Population

Endpoint	Gardasil (N=1910) n	Gardasil (N=1910) # of cases	AAHS control (N=1907) n	AAHS control (N=1907) # of cases	Efficacy % (95%CI)
CIN (any grade)	1862	147	1861	155	5.5% (-19, 25)
CIN 2/3 or worse	1862	62	1861	51	-21.5% (-80, 18)
EGL	1884	23	1882	17	-35.5% (-170, 31)
Condyloma	1884	12	1882	14	14.5% (-99, 64)
VIN 2/3 or VaIN 2/3	1884	3	1882	1	-199.8% (-15639, 76)

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the FAS population eligible for the respective analysis
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.378, 456

Clinical Reviewer Note: Table 7 is perhaps the most rigorous analysis of the likely impact of the vaccine in the general population. These data are fairly unambiguous in suggesting that the benefit of vaccination for older women in the prevention of vulvovaginal and cervical dysplastic disease due to HPV is likely to be virtually nonexistent. Efficacy in the prevention of genital warts also appears to be insubstantial. The lack of demonstrable efficacy in this particular analysis was an important factor in CBER's evaluation of this BLA supplement.

Clinical Reviewer Note: The negative case splits on the disease endpoints (in Table 7, above) were noted by CBER. Because this finding was driven by disease due to the non-vaccine types (compare vaccine type-related CIN2+ in FAS: 21 vs 27 cases, 22.4% (-43, 58) to non-vaccine type related CIN2+ in FAS: 40 vs 25 cases, -59.9% (-80, 18) (CSR019, p. 411)), it initially raised the possibility that the vaccine may potentiate disease due to non-vaccine types.

CBER carefully reviewed multiple analyses to evaluate this possibility. This review led to the following observations:

1. Randomization in Study 019 resulted in a pronounced imbalance in non-vaccine type prevalent infection at study entry: 25 cases were PCR positive for a non-vaccine HPV type on Day 1 in the Gardasil group compared with 17 cases in the control group (STN #125126/773, Amendment #9, Response to CR Letter #1, Fig 3-1, p. 24). During the additional study follow-up starting at the 2007 endpoint-driven interim analysis, after which the effects of prevalent infection at randomization would be expected to be diminished, the case split on CIN2+ due to any type in FAS was reversed in favor of the vaccine (Gardasil = 10, control = 15). Similarly, a number of other time-to-event analyses did not support the possibility of a detrimental effect of the vaccine vis a vis the non-vaccine types.

2. In the analyses of CIN2+ due to non-vaccine HPV types in younger women (16-26 years of age), a reverse case split *was not observed*. In the MITT-3 (comparable to FAS in the MAW study (019)) population pooled from Studies 013 and 015, a larger, more robust analysis of CIN2+ events could be performed. The results are as follows:
   - CIN 2+ due to any HPV type: Gardasil = 421, control = 516; 18.4% (7, 28)
   - CIN2+ due to non-vaccine HPV types: Gardasil = 340, control = 374; 9.0% (-6, 22)

3. Extensive epidemiological and pathophysiological studies of HPV demonstrate that there is little or no competition among HPV types as evidenced by the commonality of subjects with multiple HPV type infections in prevalence studies and by the fact that dysplastic progression due to one HPV type appears to occur independently of other types. These data do not support the biological plausibility of a type replacement phenomenon.

4. The study protocol included an algorithm for evaluating subjects after cervical biopsy. Subjects who met certain criteria (e.g., CIN2+, repetitive HSIL on Pap, or repetitive CIN1 on biopsy) were referred for definitive cervical therapy (usually, a loop electrosurgical excision procedure (LEEP)). Because LEEP removes an ample portion of the cervix that includes the entire transformation zone, subjects harboring multiple HPV types could have most or all of the infected tissue removed as a result of the procedure, not just the tissue harboring the causative type. For example, consider a hypothetical subject in the placebo group who presents for a routine clinical study visit 2 years into the trial. She tests positive for HPV types 16 and 58 and her Pap comes back HSIL. She is referred for colposcopy, and the biopsy is CIN2. After LEEP, CIN2 is confirmed and the dysplastic tissue is PCR+ for HPV16. Her subsequent PCR results are negative (including for HPV16 and 58). A similar subject in the vaccine group, hypothetically exposed to the same HPV types, would not acquire HPV16 but might eventually develop dysplasia due to HPV58. On average, this would tend to cull non-vaccine type infections from the placebo group (but not from the vaccine group) before they progressed to disease, thus leading to the appearance of more non-vaccine type disease in the vaccine group. The fact that HPV types 16 and 18 tend to drive dysplastic progression faster and more aggressively than the non-vaccine types would tend to exaggerate this phenomenon.

Given the above considerations, the reviewer concluded that it is unlikely that the vaccine has a potentiating effect on disease due to non-vaccine types. Furthermore, even if such a phenomenon were real, the effect would be so diminutive compared with the effect of preventing HPV 16/18-related disease that it would likely be of negligible clinical significance.

Another important and related issue is one that was raised by the analyses in YAW, in which there were reverse case splits on advanced dysplasia associated with HPV 6/11/16/18 in subjects who were PCR+ and seropositive to the relevant type at baseline. CBER concluded at the time (and VRBPAC concurred) that it is unlikely that the vaccine is somehow potentiating dysplastic progression of pre-existing disease due to vaccine types. That assessment is substantiated by this dataset, in which the comparable

analysis of the CIN2+ endpoint yielded the following results:
Gardasil = 7, control = 9; 40.4% (-80, 81)

Detailed review of these data did not discover substantial evidence that vaccination results in an unfavorable effect on acquisition of HPV or on progression of HPV-associated disease. Nevertheless, the analyses provide further support for the observation that increasing age and increasing exposure to HPV, which tend to track together, are both negatively correlated with potential benefit from vaccination.

8.1.8.4.3 Estimates of Efficacy in Naive Population – Generally HPV Naïve (GHN) Analyses

Efficacy against any HPV type-related disease in the GHN population is displayed in Table 8.

Table 8: Efficacy Against Disease Endpoints Due to Any HPV Type - GHN Population

Endpoint	**Gardasil** (N=1910) n	**Gardasil** (N=1910) # of cases	**AAHS control** (N=1907) n	**AAHS control** (N=1907) # of cases	**Efficacy** % (95%CI)
CIN (any grade)	968	24	976	37	34.5% (-13, 63)
CIN (any grade) related to 10 non-vaccine HPV types	968	15	976	14	-8.4% (-142, 51)
CIN2/3 or worse	968	5	976	7	27.7% (-165, 82)

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the GHN population eligible for the respective analysis
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.376

Clinical Reviewer Note: The essentially neutral case split on CIN (any grade) due to the 10 non-vaccine HPV types in this population naïve for all HPV types at Day 1 substantiates the assertion that higher rates of non-vaccine type-related disease in the FAS vaccinated groups was due to higher burden of pre-existing non-vaccine type HPV infection and disease at the time of randomization of those groups (see Section 8.1.8.4.2, above, for discussion of negative case splits).

8.1.8.4.4 Estimates of Efficacy in Prevention of Other Clinically Important Endpoints (e.g., Pap diagnoses)

Efficacy against any HPV type-related Pap abnormalities and cervical procedures is displayed in Table 9.

Table 9: Efficacy in the Prevention of Pap Abnormalities and Genital/Cervical Procedures Due to Any HPV Type

Endpoint	Gardasil (N=1910) n	Gardasil (N=1910) # of cases	AAHS control (N=1907) n	AAHS control (N=1907) # of cases	Efficacy % (95%CI)
GHN Population: Pap – ASCUS hrHPV+, LSIL, or worse	968	89	976	102	12% (-18, 35)
GHN Population: Any genital or cervical biopsy	976	102	988	123	16.3% (-10, 36)
GHN Population: Any genital or cervical definitive therapy	976	30	988	44	30.9% (-12, 58)
GHN Population: Cervical definitive therapy	968	21	976	33	35.5% (-15, 65)
FAS Population: Pap – ASCUS hrHPV+, LSIL, or worse	1,775	258	1,772	271	5.0% (-13, 20)
FAS Population: Any genital or cervical biopsy	1,886	387	1,883	402	3.7% (-11, 16)
FAS Population: Any genital or cervical definitive therapy	1,885	150	1,883	164	8.8% (-15, 27)
FAS Population: Cervical definitive therapy	1,862	128	1,863	140	8.8% (-17, 29)

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the GHN or FAS population eligible for the respective analysis
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.483-487

> **Clinical Reviewer Note:** In addition to having normal Pap at baseline, the GHN population is also PCR negative for HPV 6 and 11, PCR negative for 12 oncogenic HPV types and seronegative for the vaccine HPV types at baseline. In standard clinical practice, it would not be feasible to identify or select individuals for vaccination that are comparably HPV naïve. Nonetheless, although it would tend to overestimate benefit in the general population, the GHN analyses are perhaps the best predictors of impact in a relatively HPV naïve population. The efficacy estimates are modest, and none reaches statistical significance, but the GHN analyses for prevention of CIN, abnormal Pap, and cervical procedures indicate that there may be a weak beneficial effect among minimally HPV-exposed mid-adult women, especially if they are vaccinated prior to becoming sexually active with new partners. This was the basis of the decision to display select efficacy analyses in the package insert.

8.1.8.5 Immunogenicity

The immunogenicity of Gardasil was measured using a competitive Luminex-based immunoassay (cLIA), which measures antibody titer against known neutralizing epitopes on the capsid surface. The assay has been validated as an indirect measure of total HPV neutralizing antibody titer; the applicant has used it throughout the clinical development program. Assay validation data was reviewed and accepted by CBER as part of the original Gardasil licensure.

The primary immunogenicity endpoints assessed were as follows: (1) anti-HPV geometric mean titers (GMTs); and (2) seroconversion rate (SCR) at 4 weeks post-dose 3. In addition, long term follow-up immunogenicity data includes GMTs and SCRs at months 12, 24, 36, and 48. Tables 10 and 11 display the immunogenicity data in mid-adult women stratified by age group and compared with the data from younger women and adolescents.

> **Clinical Reviewer Note:** The seroconversion rate was uniformly high across all age groups, with ≥96% of all subjects seroconverting against all 4 VLP types in all age strata. As expected, the immune response is less robust with increasing age. This may contribute to the slightly lower efficacy demonstrated in mid-adult women compared with younger women (discussed at length in Section 8.1.8.4.1). This possibility can be neither confirmed nor ruled out with these data, but it seems unlikely given the near-uniform long term protection (5+ years) against infection noted in younger women, some of whom failed to maintain detectable titer, particularly against HPV 18. Overall, the clinical significance of the lower GMTs in older subjects remains unclear but likely is negligible.

Table 10: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI Population of Girls and Women

Population	N*	n**	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 6: 9 to 15-year-old girls	1122	917	99.9 (99.4, 100.0)	929.2 (874.6, 987.3)
Anti-HPV 6: 16 to 26-year-old girls and women	9859	3329	99.8 (99.6, 99.9)	545.0 (530.1, 560.4)
Anti-HPV 6: 27 to 34-year-old women	667	439	98.4 (96.7, 99.4)	435.6 (393.4, 482.4)
Anti-HPV 6: 35 to 45-year-old women	957	644	98.1 (96.8, 99.0)	397.3 (365.2, 432.2)
Anti-HPV 11: 9 to 15-year-old girls	1122	917	99.9 (99.4, 100.0)	1304.6 (1224.7, 1389.7)
Anti-HPV 11:16 to 26-year-old girls and women	9859	3353	99.8 (99.5, 99.9)	748.9 (726.0, 772.6)
Anti-HPV 11: 27 to 34-year-old women	667	439	98.2 (96.4, 99.2)	577.9 (523.8, 637.5)
Anti-HPV 11: 35 to 45-year-old women	957	644	97.7 (96.2, 98.7)	512.8 (472.9, 556.1)
Anti-HPV 16: 9 to 15-year-old girls	1122	915	99.9 (99.4, 100.0)	4918.5 (4556.6, 5309.1)
Anti-HPV 16: 16 to 26-year-old girls and women	9859	3249	99.8 (99.6, 100.0)	2409.2 (2309.0, 2513.8)
Anti-HPV 16: 27 to 34-year-old women	667	435	99.3 (98.0, 99.9)	2342.5 (2119.1, 2589.6)
Anti-HPV 16: 35 to 45-year-old women	957	657	98.2 (96.8, 99.1)	2129.5 (1962.7, 2310.5)

Population	N*	n**	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 18: 9 to 15-year-old girls	1122	922	99.8 (99.2, 100.0)	1042.6 (967.6, 1123.3)
Anti-HPV 18: 16 to 26-year-old girls and women	9859	3566	99.4 (99.1, 99.7)	475.2 (458.8, 492.1)
Anti-HPV 18: 27 to 34-year-old women	667	501	98.0 (96.4, 99.0)	385.8 (347.6, 428.1)
Anti-HPV 18: 35 to 45-year-old women	957	722	96.4 (94.8, 97.6)	324.6 (297.6, 354.0)

*Number of individuals randomized to the respective vaccination group who received at least 1 injection.
**Number of individuals contributing to the analysis.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers
†mMU = milli-Merck Units per mL
Source: Immunogenicity analysis proposed for the Gardasil package insert, Table 17.

Table 11: Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 45-Year-Old Girls and Women

Assay (cLIA)/ Time Point	9- to 15-year-old Girls (N* = 1122) n** / GMT (95% CI) mMU/mL***	16- to 26-year-old Girls (N* = 9859) n** / GMT (95% CI) mMU/mL***	27- to 34-year-old Women (N* = 667) n** / GMT (95% CI) mMU/mL***	35- to 45-year-old Women (N* = 957) n** / GMT (95% CI) mMU/mL***
Anti-HPV 6 Month 07	917 / 929.2 (874.6, 987.3)	3329 / 545.0 (530.1, 560.4)	439 / 435.6 (393.4, 482.4)	644 / 397.3 (365.2, 432.2)
Anti-HPV 6 Month 24	214 / 156.1 (135.6, 179.6)	2788 / 109.1 (105.2, 113.1)	421 / 70.7 (63.8, 78.5)	628 / 69.3 (63.7, 75.4)
Anti-HPV 6 Month 36†	356 / 129.4 (115.6, 144.8)	-	399 / 79.5 (72.0, 87.7)	618 / 81.1 (75.0, 87.8)
Anti-HPV 6 Month 48‡	-	2514 / 73.8 (70.9, 76.8)	391 / 58.8 (52.9, 65.3)	616 / 62.0 (57.0, 67.5)
Anti-HPV 11 Month 07	917 / 1304.6 (1224.7, 1389.7)	3353 / 748.9 (726.0, 772.6)	439 / 577.9 (523.8, 637.5)	644 / 512.8 (472.9, 556.1)
Anti-HPV 11 Month 24	214 / 218.0 (188.3, 252.4)	2817 / 137.1 (132.1, 142.3)	421 / 79.3 (71.5, 87.8)	628 / 73.4 (67.4, 79.8)
Anti-HPV 11 Month 36†	356 / 148.0 (131.1, 167.1)	-	399 / 81.8 (74.3, 90.1)	618 / 77.4 (71.6, 83.6)
Anti-HPV 11 Month 48‡	-	2538 / 89.4 (85.9, 93.1)	391 / 67.4 (60.9, 74.7)	616 / 62.7 (57.8, 68.0)
Anti-HPV 16 Month 07	915 / 4918.5 (4556.6, 5309.1)	3249 / 2409.2 (2309.0, 2513.8)	435 / 2342.5 (2119.1, 2589.6)	657 / 2129.5 (1962.7, 2310.5)
Anti-HPV 16 Month 24	211 / 944.2 (804.4, 1108.3)	2721 / 442.6 (425.0, 460.9)	416 / 285.9 (254.4, 321.2)	642 / 271.4 (247.1, 298.1)
Anti-HPV 16 Month 36†	353 / 642.2 (562.8, 732.8)	-	399 / 291.5 (262.5, 323.8)	631 / 276.7 (254.5, 300.8)
Anti-HPV 16 Month 48‡	-	2474 / 326.2 (311.8, 341.3)	394 / 211.8 (189.5, 236.8)	628 / 192.8 (176.5, 210.6)

Assay (cLIA)/ Time Point	9- to 15-year-old Girls (N* = 1122) n** / GMT (95% CI) mMU/mL***	16- to 26-year-old Girls (N* = 9859) n** / GMT (95% CI) mMU/mL***	27- to 34-year-old Women (N* = 667) n** / GMT (95% CI) mMU/mL***	35- to 45-year-old Women (N* = 957) n** / GMT (95% CI) mMU/mL***
Anti-HPV 18 Month 07	922 / 1042.6 (967.6, 1123.3)	3566 / 475.2 (458.8, 492.1)	501 / 385.8 (347.6, 428.1)	722 / 324.6 (297.6, 354.0)
Anti-HPV 18 Month 24	214 / 137.7 (114.8, 165.1)	3002 / 50.8 (48.2, 53.5)	478 / 31.8 (28.1, 36.0)	705 / 26.0 (23.5, 28.8)
Anti-HPV 18 Month 36†	357 / 87.0 (74.8, 101.2)	-	453 / 32.1 (28.5, 36.3)	689 / 27.0 (24.5, 29.8)
Anti-HPV 18 Month 48‡	-	2710 / 33.2 (31.5, 35.0)	444 / 25.2 (22.3, 28.5)	688 / 21.2 (19.2, 23.4)

*N = Number of individuals randomized in the respective group who received at least 1 injection.
**n = Number of individuals in the indicated immunogenicity population.
***mMU = milli-Merck Units per mL
†Month 37 for 9- to 15-year-old girls. No serology samples were collected at this time point for 16- to 26-year-old girls and women.
‡Month 48/End-of-study visits for 16- to 26-year-old girls and women were generally scheduled earlier than Month 48. Mean visit timing was Month 44. The studies in 9- to 15-year-old girls were planned to end prior to 48 months and therefore no serology samples were collected.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers
Source: Immunogenicity analysis proposed for the Gardasil package insert, Table 19.

8.1.8.6 Safety

The summary analysis of AEs revealed a slightly higher overall rate of AEs among Gardasil recipients compared with placebo recipients (see Table 12). This was largely due to the higher rate of injection site AEs among Gardasil recipients compared with placebo recipients, as similar percentages in each group experienced a systemic AE or an SAE.

There was an imbalance in the number of deaths in the Gardasil versus placebo group. All deaths in the trial were assessed as unrelated to treatment (see clinical reviewer evaluation below).

Table 12: Clinical Adverse Event Summary – Entire Study Period, All Vaccinated Subjects

Adverse Event	Gardasil (N=1890)n	Gardasil (N=1890) (%)	AAHS control (N=1888)n	AAHS control (N=1888) (%)
With one or more AEs	1645	(87)	1535	(81.3)
Injection-site AEs	1450	(76.7)	1213	(64.2)
Systemic AEs	1121	(59.3)	1135	(60.1)
With vaccine-related AEs*	1565	(82.8)	1391	(73.7)

Adverse Event	Gardasil (N=1890)n	Gardasil (N=1890) (%)	AAHS control (N=1888)n	AAHS control (N=1888) (%)
Vaccine-related injection-site AEs*	1449	(76.7)	1213	(64.2)
Vaccine-related systemic AEs*	746	(39.5)	697	(36.9)
With SAEs	14	(0.7)	16	(0.8)
Vaccine-related SAEs*	0	(0)	0	(0)
Who died	7	(0.4)	1	(0.1)
Discontinued due to an AE	7	(0.4)	2	(0.1)
Discontinued due to an SAE	2	(0.1)	0	(0)

N = number of subjects in the ASaT analysis set in the respective vaccination group who had follow-up data
n = number of cases
*Causality as assessed by the investigator
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.566

8.1.8.6.1 Systemic Adverse Events

Analysis of the most common systemic AEs was unremarkable. The event rates of systemic AEs in the Gardasil group compared to the placebo group by system organ class (SOC) were similar. Table 13 displays the most common systemic AEs reported.

Table 13: Number (%) of Subjects Who Reported Systemic AEs With ≥ 1% Incidence (Days 1 to 15 Following Any Vaccination Visit)

Adverse Event Term	Gardasil (N=1908) n (%)	AAHS control (N=1902) n (%)
With one or more systemic AEs	1118 (59.2)	1131 (60.0)
Abdominal pain	60 (3.2)	58 (3.1)
Diarrhea	54 (2.9)	56 (3.0)
Nausea	71 (3.8)	65 (3.4)
Toothache	30 (1.6)	26 (1.4)
Vomiting	19 (1.0)	25 (1.3)
Asthenia	31 (1.6)	44 (2.3)
Chills	21 (1.1)	18 (1.0)
Fatigue	13 (0.7)	19 (1.0)
Hypothermia	23 (1.2)	29 (1.5)
Malaise	21 (1.1)	28 (1.5)
Pyrexia	219 (11.6)	232 (12.3)
Influenza	98 (5.2)	101 (5.4)
Nasopharyngitis	80 (4.2)	88 (4.7)
Tonsillitis	18 (1.0)	22 (1.2)
Upper respiratory tract infection	37 (2.0)	25 (1.3)
Back pain	45 (2.4)	55 (2.9)
Myalgia	27 (1.4)	14 (0.7)
Neck pain	19 (1.0)	13 (0.7)
Pain in extremity	88 (4.7)	42 (2.2)
Dizziness	79 (4.2)	82 (4.3)
Headache	526 (27.8)	518 (27.5)
Migraine	37 (2.0)	40 (2.1)
Dysmenorrhea	48 (2.5)	66 (3.5)
Pelvic pain	22 (1.2)	33 (1.7)
Cough	17 (0.9)	28 (1.5)
Pharyngolaryngeal pain	41 (2.2)	43 (2.3)
Pruritis	9 (0.5)	19 (1.0)

N = number of subjects in the ASaT analysis set in the respective vaccination group who had follow-up data
n = number of cases
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019v1 (interim report), p.441

8.1.8.6.2 Injection Site Adverse Events

Gardasil recipients experienced somewhat higher rates of injection site AEs compared to subjects in the AAHS control group. The most pronounced imbalances in the event rates occurred in the analysis of injection site pain and swelling. These data are taken from vaccine diary cards, in which the specific adverse events are solicited (see Table 14).

Table 14: Subjects Reporting Specific Injection-Site Adverse Experiences With ≥ 1% Incidence (Days 1 to 5 Days Following Any Vaccination Visit)

Injection-Site AE	Gardasil (N=1908) n (%)	AAHS control (N=1902) n (%)
One or more injection-site AEs	1443 (76.4)	1210 (64.2)
Injection-site erythema	273 (14.5)	200 (10.6)
Injection-site pain	1423 (75.3)	1170 (62)
Injection-site pruritis	31 (1.6)	25 (1.3)
Injection-site swelling	353 (18.7)	214 (11.3)

N = number of subjects in the ASaT analysis set in the respective vaccination group who had follow-up data
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019V1 (interim report), p.425

> **Clinical Reviewer Note:** In the injection site AE data from a pooled safety population of 14,034 subjects from Protocols 007, 013, 015, 016, 018, *and 019*, the rates of injection site AEs were uniformly higher in the pooled population (mainly adolescents and young adults) compared with rates in the mid-adult women in the analysis of Study 019 alone. For example, in the pooled data, the rates of injection site pain were 79.9% (Gardasil) and 70.7% (AAHS control). (sBLA 125126/773; 2.7.4 Summary of Clinical Safety, p. 45) These trends suggest that the vaccine is slightly better tolerated by mid-adult women compared with younger women with regard to local reactogenicity.

8.1.8.6.3 Pregnancy Outcomes

A total of 499 subjects reported at least one pregnancy during the entire study period. Table 15 displays selected pregnancy outcomes from all the pregnancies that occurred during the study. In addition to the data displayed in Table 15, the SAEs that occurred among the infants potentially exposed to Gardasil or AAHS control were reviewed. There were 29 SAEs in each group. In general, the events were those commonly diagnosed in the neonatal period (e.g., hyperbilirubinemia, gastroenteritis, pneumonia, gastro-esophageal reflux). There was no pattern of outcomes to suggest a safety signal.

Table 15: Pregnancy Outcome Summary, Entire Study Period, All Vaccinated Subjects

Pregnancy Outcome	Gardasil (N=1908) n (%)	AAHS control (N=1902) n (%)
Subjects with pregnancies	236 (12.4)	263 (13.8)
Subjects without pregnancies	1672 (87.6)	1639 (86.2)
Number of pregnancies †	277 (-)	297 (-)
Number of fetuses/infants with known outcome	266 (-)	290 (-)
Live Births‡	210 (78.9)	223 (76.9)
Infant Outcome - Normal	196 (93.3)	212 (95.1)
Infant Outcome - Abnormal	14 (6.7)	11 (4.9)
Infant Outcome - Congenital Anomaly	5 (2.4)	4 (1.8)
Infant Outcome - Other Abnormality	11 (5.2)	7 (3.1)
Infant Outcome - Unknown	0 (0)	0 (0)
Fetal Loss‡	50 (18.8)	62 (21.4)
Type of Loss - Spontaneous Abortion	42 (84.0)	51 (82.3)
Type of Loss - Late Fetal Death	1 (2.0)	1 (1.6)
Type of Loss - Elective Abortion	7 (14.0)	9 (14.5)
Fetal Outcome - Normal	6 (12.0)	5 (8.1)
Fetal Outcome - Abnormal	2 (4.0)	5 (8.1)
Fetal Outcome - Congenital Anomaly	2 (4.0)	1 (1.6)
Fetal Outcome - Other Abnormality	1 (2.0)	4 (6.5)
Fetal Outcome - Unknown	42 (84.0)	52 (83.9)
Ectopic Pregnancy‡	6 (2.3)	5 (1.7)

N = number of subjects in the ASaT analysis set in the respective vaccination group who had follow-up data
n = number of cases
† A subject may have more than one pregnancy during the study. Each pregnancy is counted once. A pregnancy with multiple fetuses is counted as a single pregnancy, but outcome for each fetus/infant is counted individually.
‡ Percentages of 'Live Births', 'Fetal Loss', and 'Ectopic Pregnancy' are calculated based on the number of fetuses/infants with known outcome. Percentages under 'Infant Outcome' are calculated based on 'Live Births'. Percentages under 'Type of Loss' and 'Fetal Outcome' are calculated based on 'Fetal Loss'.
Source: Adapted from - original sBLA 125126/773; Clinical Study Report V503-019, p.589

Clinical Reviewer Note: Overall, the pregnancy outcomes do not suggest that there is a safety signal in Gardasil-exposed pregnancies. The slight imbalance in congenital anomalies in the Gardasil group compared with the control group was noted. These data were included in a pooled dataset of pregnancies that occurred during the clinical development program. The pregnancy outcomes from this pooled dataset were meticulously reviewed at the time of the original BLA submission and they were the subject of extensive discussion at the May 2006 VRBPAC. The review and discussions focused particularly on the event rates for congenital anomalies. CBER reviewers, VRBPAC panelists, and a group of independent teratologists blinded to the intervention (vaccine or placebo) received by study participants came to the same conclusions: that the widely divergent pathology among the cases, the consistency with commonly observed anomalies, the fact that no signal for teratogenicity was apparent in the preclinical reproductive toxicology studies, the fact that vaccine exposure was temporally remote from the gestational critical period in each case, and the fact that the rates were consistent with expected background rates did not suggest a safety signal with regard to congenital anomalies. There are no new data in this submission to suggest a different conclusion. In addition, these cases are already reported in the current Gardasil package insert.

The most recent evaluation of congenital anomalies comes from the Gardasil Pregnancy Registry Annual Report, received by CBER in May of 2010. In the Pregnancy Registry, the rate of major congenital anomalies reported in Gardasil-exposed pregnancies was 2.4%, which is within the range of the expected background rate of 2.67%. In their review, CBER's Office of Biostatistics and Epidemiology (OBE) concluded that no further action is indicated based on these data.

8.1.8.6.4 Serious Adverse Events

A total of 30 subjects experienced a nonfatal serious adverse event (SAE) during the entire study period – 14 in the Gardasil group and 16 in the placebo group. In the Gardasil group, there was a wide variety of medical events that did not constitute a clinical pattern. None of the SAEs was assessed by the Investigator as being related to treatment.

Clinical Reviewer Note: The subject narratives from each of the SAEs were reviewed. Given the available information, the reviewer agreed that it was reasonable to conclude that in each case, the event was not likely related to treatment.

8.1.8.6.5 Deaths

A total of 8 deaths occurred during the study - 7 in the Gardasil group and 1 in the placebo group. What follows is a narrative summary of each case:

<u>Gardasil</u>
AN 81322: 34yo Asian female diagnosed with pulmonary tuberculosis on Day 139 postdose 2. The subject was noncompliant with medical therapy, including being discharged from the hospital against medical advice during an episode of respiratory distress. She died 4 months later of acute respiratory failure due to pulmonary tuberculosis.

AN 81654: 32yo Asian female with history of hepatitis B (diagnosed Feb 2006) and hyperthyroidism (diagnosed in May 2005 – approximately one month postdose 2), was vaccinated with her first, second, and third doses of qHPV vaccine on 18-Feb-2005, 26-Apr-2005, and 13-Aug-2005, respectively. On approximately Day 203 postdose 3, the subject hospitalized for treatment of thyrotoxicosis. The subject was discharged against medical advice, and died on 05-Mar-2005, one hour after discharge, with cardiorespiratory arrest due to cardiac failure secondary to thyrotoxicosis.

AN 84097: 39yo Hispanic female was diagnosed with systemic lupus erythematosus on Day 671 postdose 3. Approximately 3 months later, the subject was hospitalized to rule out a coronary event and a possible pulmonary thromboembolism. After 4 days of treatment, the subject died of cardiac arrest.

AN 84366: 43yo Asian female was hospitalized on Day 571 postdose 3 for abdominal hysterectomy for uterine fibroids. The subject died of a massive pulmonary embolus 12 days post-operatively.

AN 81011: 26yo Asian female was diagnosed on Day 250 postdose 3 with breast cancer. Two years later, the subject died; immediate cause of death was cardiomyopathy and lung and liver metastases secondary to breast cancer.

AN 83962: 36yo Asian female was admitted to the hospital on Day 859 postdose 3 with a hemorrhagic stroke. She died the following day after uncal herniation.

AN 84150: 40yo Asian female diagnosed on Day 1059 postdose 3 with nasopharyngeal carcinoma. The subject died ~3 months later of cardiorespiratory arrest secondary to brain metastases.

Placebo

AN 81009: 34yo Asian female was diagnosed on Day 595 postdose 3 with acute lymphoblastic leukemia. The subject died one month later of a pulmonary thromboembolism.

> **Clinical Reviewer Note:** The case history from each of the deaths in the Gardasil group was reviewed. Given the available information, the reviewer agreed that it was reasonable to conclude that in each case the event was not likely related to treatment.
>
> The reviewer noted that in one case (AN 81654), the subject's diagnosis of hyperthyroidism was made approximately one month postdose 2. To further investigate the possibility of a safety signal related to thyroid disease, the reviewer tallied all the thyroid-related new medical diagnoses made during the follow-up period in all the subjects from Protocols 007, 013, 015, 016, 018, and 019. (Source: sBLA 125126/773, 2.7.4 Summary of Clinical Safety, Appendix 2.7.4: 88, p. 478.) The diagnoses included Autoimmune Thyroiditis, Goiter, Hyperthyroidism, Hypothyroidism, Thyroid Cyst, Thyroid Disorder, Thyroiditis, and Toxic Nodular Goiter. The total number of cases among the 12,308 Gardasil recipients was 60 (0.49%). The total number of cases among the 11254 placebo recipients was 62 (0.55%). The reviewer concluded that the evidence does not support a safety signal for thyroid disease associated with the vaccine.

9 Additional Clinical Issues

9.1 Special Populations

9.1.1 Pregnancy

Gardasil is Pregnancy Category B. It is not recommended for use during pregnancy. See Section 8.1.8.6.3 for review of pregnancy data in mid-adult women.

9.1.2 Geriatric Use

The safety and effectiveness of Gardasil have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

9.1.3 Immunocompromised Patients

The safety and effectiveness of Gardasil have not been evaluated in an immunocompromised patient population.

9.1.4 Pediatrics

This application simply requested an extension of the current indications to an older population. Therefore, the application does not invoke any of the requirements enumerated in the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

10 Conclusions - Overall

Data submitted to the BLA supplement do not establish the efficacy of Gardasil in the prevention of advanced cervical dysplasia in women 27 to 45 years of age.

Data submitted to the BLA supplement do not establish a substantial likelihood of benefit in a general population of women aged 27 to 45 years on a number of other clinically important outcomes, such as prevention of genital warts, prevention of abnormal Paps, or prevention of definitive cervical or genital therapy.

It is theoretically possible that women 27 to 45 years of age who are relatively HPV naïve, as determined by medical/sexual history and by commercially available assays, could experience a modicum of benefit from Gardasil, but benefit in that scenario was not definitively established by the data submitted to the BLA supplement.

The antibody response to Gardasil among women 27 to 45 years of age is less robust than among younger individuals, a phenomenon that is of uncertain, but likely negligible, clinical significance.

The safety profile of Gardasil in women 27 to 45 years of age is comparable to that in younger females. No safety signals were identified in the population studied for this BLA supplement.

11 Recommendations

11.1 Approval Recommendations

The clinical reviewer does not recommend approval for the request to extend the current indications for Gardasil to the population of women 27-45 years of age.

The clinical reviewer recommends including in the package insert specific safety, immunogenicity and key efficacy data (including Naïve to the Relevant HPV Type (HNRT) population analyses of prevention of persistent infection, prevention of CIN (any grade), and prevention of genital warts) in women 27-45 years of age in order to inform health care providers and the public of important findings from the clinical evaluation of Gardasil in mid-adult women.

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11.2 Recommendations on Postmarketing Actions

No new postmarketing actions are recommended or required in association with approval of the BLA supplement.

11.3 Labeling

CBER communicated with the sponsor on multiple occasions to achieve consistency with CBER's current guidance on the intent and format of package inserts. The final label was reviewed by the clinical team and by the Advertising and Promotional Labeling Branch (APLB) and found to be acceptable.