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# 125126/1297.0 – male indication for GARDASIL

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

Date of submitted application:	17 Dec 2008
Date of completed review:	29 Sep 2009

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To: BLA #125126/1297

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Michael Nguyen, M.D.	Epidemiologist	Assigned June 30, 2009
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1.0 General Information

1.1 Medical Officer's Review Identifiers and Dates

1.1.1 sBLA #:

125126/1297.0

1.1.2 Related IND #(s):

Gardasil IND#: -b(4)-
Original Gardasil BLA#: 125126

1.1.3 Reviewer Name, Division and Mail Code:

Jeff Roberts, M.D.
Division of Vaccines and Related Products Applications
HFM-475

1.1.4 Submission Received by FDA: (date)

17 Dec 2008

1.2 Product

1.2.1 Proper 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
EGL	external genital lesions
GW	genital warts
HM	heterosexual males
MSM	men having sex with men
PIN	penile/perianal/perineal intraepithelial neoplasia
qHPV	Quadrivalent HPV vaccine, or Gardasil
VLP	Virus-like particles

1.2.4 Product Formulation:

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

1.4.2 Indication for Gardasil Proposed Under This sBLA:

Original proposed indication:

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of external genital lesions caused by HPV types 6, 11, 16, and 18.

Revised indication submitted by the applicant during the review process:

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.

1.5 Dosage Forms and Routes of Administration:

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

2.0 Table of Contents

3.0 Executive Summary

Gardasil is currently licensed for prevention of cervical, vulvar and vaginal cancer, the associated precancerous lesions, and genital warts in females 9 to 26 years of age. With this Biologic License Application supplement (sBLA), the applicant is seeking approval for the following new indication in males: "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."

The pivotal phase 3 trial submitted to the sBLA was a randomized, placebo controlled study of 4065 males aged 16-26 years. The point estimate for efficacy against genital warts in the per protocol population was 89.4% with 95% CI (65.5%-97.9%). Analysis of safety outcomes after Gardasil compared to AAHS control was unremarkable, with similar rates of overall adverse events (AEs) - 69% vs. 64%, respectively, and serious adverse events (SAEs) – 0.4% vs. 0.6%, respectively.

Because the incidence of HPV-related genital lesions is very low before the onset of sexual activity, a placebo-controlled efficacy trial in subjects <16 years of age would be impractical. Therefore, the applicant conducted bridging studies to compare antibody responses in male subjects from the pivotal trial to males 9-15 years of age. CBER considered this to be an acceptable approach for inferring protection against genital warts in this population. Antibody responses to each of the 4 virus like particle (VLP) types in adolescent subjects were non-inferior to those of older subjects.

CBER convened a Vaccines and Related Biological Products Advisory Committee (VRBPAC) on September 9, 2009, to seek input on the efficacy and safety data presented to the sBLA. The committee voted that the efficacy data support the use Gardasil in males for the indication cited above. In addition the committee voted that the safety data support the use of Gardasil in males 9-26 years of age.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application for a new indication is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric age groups. The applicant requested a partial waiver from the requirements of PREA for children 0-8 years of age. The review team agreed to grant the waiver request because necessary studies are impossible or highly impractical and the product is not likely to be used in a substantial number of children 8 years of age and younger. The Pediatric Review Committee (PeRC) concurred with this decision. Effective upon approval of the supplement, the product will be labeled for use in children 9 years of age and older.

No safety signals were identified in males in the pre-licensure data. Therefore, consistent with the regulations associated with Title IX of the FDA Amendments Act of 2007, the applicant will conduct postmarketing safety surveillance as a commitment enumerated in the approval letter. This study will be conducted to expand the safety database in male recipients of Gardasil and to enable detection of rare adverse events that may be associated with use of the vaccine in

males. The primary component of the postmarketing program is a descriptive, observational safety study in males 9-26 years of age that is similar to the postmarketing study being conducted in females.

In addition to the postmarketing safety surveillance study, the applicant has committed to a clinical program to assess long term efficacy in males. Studies 020 (the pivotal efficacy study in males) and 018 (adolescent immunogenicity bridging study that includes males) were amended to provide for up to 10 years of follow-up with penile/perineal/perianal intraepithelial neoplasia (PIN), penile cancer, and genital warts as efficacy endpoints.

Based on the review of the safety and efficacy data submitted to the BLA supplement, the clinical reviewer supports the approval of Gardasil for use in males 9-26 years of age for the prevention of genital warts caused by HPV types 6 and 11.

4.0 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)

The CBER CMC reviewer noted that all lots of vaccine used in this study were reviewed and released for distribution by CBER.

The CMC review also included evaluation of the assays used to measure pre-immunization HPV status and immune response and infection status post-immunization, which include an HPV PCR assay to detect HPV infection and an anti-HPV Competitive Luminex Immunoassay (cLIA). The reviewer concluded that the assays have been qualified appropriately and validation data support the use of these assays in the clinical studies as outlined in the submission.

4.2 Animal Pharmacology/Toxicology

A CBER toxicologist reviewed the data submitted from a reproductive toxicology study performed in male rats. The reviewer concluded that no impairment of male fertility was observed. The results of the study are reflected in changes to the Gardasil label.

4.3 Statistics

A CBER statistician reviewed the clinical efficacy and safety data submitted to the sBLA. The reviewer noted that in the per-protocol efficacy cohort, 28 out of 31 endpoint cases in the placebo group were diagnoses of condyloma. Given that only 3 cases of PIN 1 or worse occurred in the study, the confidence intervals for vaccine efficacy in the prevention of PIN 1or worse were very wide, and the reviewer indicated that more data should be collected for assessing this endpoint.

The reviewer made the following conclusions:

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is efficacious in preventing development of HPV 6/11-related genital warts.

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men generates robust anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses.

- Prophylactic administration of a 3-dose regimen of qHPV vaccine is generally well tolerated in men 16-26 years of age.

5.0 Clinical and Regulatory Background

5.1 Disease Studied and Available Interventions

Human papillomavirus (HPV) infects the epithelium at multiple anatomic sites, resulting in a variety of distinct clinical entities. The disease burden in males includes common skin warts and genital warts, penile intraepithelial neoplasia (PIN) and penile cancer, anal intraepithelial neoplasia (AIN) and anal cancer, oropharyngeal cancer, and recurrent respiratory papillomatosis (RRP). A comprehensive discussion of prevention and treatment of HPV in males would also include estimates of the impact on transmission to females. However, the indication sought by the applicant centers on a specific subset of HPV-related disease in males. This review will focus entirely on that subset as discussed below.

With this Supplement, the applicant is seeking approval for the indication of prevention of HPV 6 and 11 associated genital warts in males. However, the endpoint for the pivotal study and the subject of the indication initially submitted was “external genital lesions” (EGL). In the pivotal study, and therefore in the sBLA and in this review, EGL are defined as external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), and penile, perianal, or perineal cancer.

Condyloma acuminata, or genital warts (GW), are the most common presenting complaint in both males and females with HPV infection (Dempsey et al). Prevalence is estimated to be ~1% of all sexually active adults in the U.S. (Koutsky et al). Among males, approximately 200 per 100,000 are newly diagnosed with GW’s per year (Koshiol et al). The impact of GW’s is significant, both in terms of individual psychosocial distress and in terms of the burden on the U.S. health care system. Treatment options, which range from topical immune modifiers to ablative or excisional procedures, can themselves be the source of significant distress and discomfort, and recurrences requiring multiple procedures are common.

The vast majority of genital warts arise in the setting of genital infection with HPV, particularly types 6 and 11, which are found in 70% to 100% of lesions (Partridge and Koutsky). To date, attempts to develop effective preventive strategies largely have failed. As the World Health Organization recently noted, “Abstinence and condom use can reduce the risk of acquiring warts, but limited use of these methods reduces their impact at a population level. Condoms cannot prevent skin-to-skin HPV transmission in genital areas not covered by the condom or during non-penetrative intercourse” (WHO, 2008).

Penile cancer is a relatively rare cause of cancer the U.S., affecting ~0.5 per 100K men per year. In contrast to cervical cancer, in which oncogenic HPV DNA is detected in virtually all cases, HPV is detected in between 42% to 80% of penile cancers (Partridge and Koutsky). However, the strong correlation between oncogenic HPV infection and penile cancer precursor lesions, PIN, indicates that persistent infection of the penile epithelium may lead to cancer through dysplastic progression similar to that seen in cervical cancer. As in cervical dysplasia, HPV 16 and 18 are the most common types associated with PIN and penile cancer.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

At the time of submission of the sBLA, Gardasil was the only HPV vaccine currently licensed in the U.S.

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

2000 Submission of the original IND for the quadrivalent VLP vaccine containing the L1 protein from HPV types 6, 11, 16, and 18. Additional phase 1, phase 2, and phase 3 studies were conducted under this IND.

2001 November: VRBPAC discussion of the endpoints to be used in the phase III development program 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)

2004 August: Merck submitted Protocol 020 for studying Gardasil in males 16-26 years of age.

2005 August: Merck agreed to CBER's recommendation to increase the sample size of the study by 1,000 subjects in order increase the lower bound of the 95% CI for vaccine efficacy from >0 to >20%. CBER recommended that Merck bridge immunogenicity data for boys to men (for whom efficacy would be assessed). CBER also commented that "if Protocol 020 is successful in its objectives, it may be feasible to make a claim that the vaccine reduces genital warts, persistent infection, and AIN."

2006 June: Approval of original BLA for prevention of cervical cancer, cervical, vulvar and vaginal precancerous lesions, and genital warts.

2007 January: Consistent with CBER's request (comments sent November 14, 2005), Merck agreed to use sera from boys enrolled in Protocols 016 and 018 in order to test a formal hypothesis to demonstrate non-inferiority of immune responses in boys relative to men.

2008 June: Approval of sBLA for prevention of vulvar and vaginal cancer.

2008 December: In a pre-sBLA meeting for the males indication, CBER noted that the number of penile precancerous lesions, Penile Intraepithelial Neoplasia (PIN), in the efficacy analysis population is very small, resulting in a 95% confidence interval that includes 0.

2009 May: CBER informed Merck that the original requested indication for prevention of "external genital lesions" (EGL) was too broad. Due to the marked difference in the number of PIN or penile cancer cases versus genital warts cases and because of the fundamental pathophysiological differences between the two disease processes, CBER considered the approach of combining the two under one definition to be unsuitable. CBER indicated a preference for separating the two categories of pathology for the purposes of labeling indications. CBER therefore requested that Merck revise the proposed label indication to include only genital warts.

2009 June: Merck submitted a label revision with the proposed indication limited to prevention of genital warts. The term "external genital lesions", which would have encompassed PIN/cancer, was removed from the indication.

6.0 Clinical Data Sources and Review Strategy

6.1 Material Reviewed

6.1.1 BLA Supplement #125126/1297 – Files Reviewed

The following files formed the basis for the clinical review:
V501-020 – Clinical Study Report
V501-016 – Clinical Study Report
V501-018 – Clinical Study Report
V501-017 – MRL Statistical Report: Study to evaluate sampling methods for detection of human papillomavirus (HPV) in the anogenital region of men who have sex with men (MSM)
Reference 2272 – MRL Internal Memo: Integrated Immunogenicity Analyses in Support of Gardasil Men's Filing
Summary of Clinical Efficacy in Men
Summary of Clinical Safety
Clinical Overview

6.1.2 Literature

Cook IF. Sexual dimorphism of humoral immunity with human vaccines. Vaccine. 2008 Jul 4;26 (29-30):3551-5.

Dempsey AF, Koutsky LA, Golden M. Potential impact of human papillomavirus vaccines on public STD clinic workloads and on opportunities to diagnose and treat other sexually transmitted diseases. Sex Transm Dis. 2007 Jul;34(7):503-7.

Koshiol JE, Laurent SA, Pimenta JM. Rate and predictors of new genital warts claims and genital warts-related healthcare utilization among privately insured patients in the United States. Sex Transm Dis. 2004 Dec;31(12):748-52.

Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. Epidemiol Rev. 1988;10:122-63.

Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. Lancet Infect Dis. 2006 Jan;6(1):21-31.

Weaver BA, Feng Q, Holmes KK, Kiviat N, Lee SK, Meyer C, Stern M, Koutsky LA. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J Infect Dis. 2004 Feb 15;189(4):677-85.

World Health Organization. Human Papillomavirus (HPV) Vaccine Background Paper. September 2008.
http://www.who.int/immunization/documents/HPVBGpaper_final_03_04_2009.pdf

6.1.3 Post-Marketing Experience

In accordance with the terms of original licensure, the applicant is conducting post-marketing studies of safety and efficacy in females. The status of the postmarketing studies to which the applicant committed at the time of licensure can found at
http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

6.2 Table of Clinical Studies

Table 2 below summarizes the clinical studies submitted to the sBLA in support of a male indication for Gardasil.

Table 2: Studies Submitted in Support of Licensure of Gardasil for Males

Study Identifier	Type of Study	Primary Efficacy Objective	Number of Subjects	Treatment Groups
V501-020	Randomized (1:1), double blind, placebo-controlled, multicenter international study - phase III pivotal efficacy and safety in males	Demonstrate reduced incidence of vaccine type-related "external genital lesions" (PIN; penile, perianal, and perineal cancer; and genital warts) in males	Total: **4065** males 16-26 years of age Gardasil: 2032 Placebo: 2033	**Gardasil**: 0.5mL IM dose of quadrivalent HPV (Types 6, 11,16,18) L1 VLP vaccine on Day 1, month 2, and month 6 **Placebo**: 0.5mL IM dose of placebo (225 mcg of aluminum as AAHS in normal saline) on Day 1, month 2, and month 6
V501-016	Double-blind, multicenter international study - phase III immunogenicity and tolerability	Demonstrate similar anti-HPV titers in males and females 10-15 years of age compared with females 16-23 years of age	**510** males (10-15 years of age) **506** females (10-15 years of age) **513** females (16-23 years of age)	All 3 groups received identical treatment - **Gardasil**: 0.5mL IM dose of quadrivalent HPV (Types 6, 11,16,18) L1 VLP vaccine on Day 1, month 2, and month 6
V501-018	Randomized (2:1), double-blind, placebo-controlled, multicenter international study – phase III safety and immunogenicity	Demonstrate similar anti-HPV titers in males 9-15 years of age compared with females 9-15 years of age	Total: **939** females 9-15 years of age; **842** males 9-15 years of age Gardasil: 617 females; 567 males Placebo: 322 females; 275 males	**Gardasil**: 0.5mL IM dose of quadrivalent HPV (Types 6, 11,16,18) L1 VLP vaccine on Day 1, month 2, and month 6 ***Placebo**: 0.5mL IM dose of placebo (normal saline without adjuvant) on Day 1, month 2, and month 6

*This is the only study in the applicant's clinical development program in which vaccine was compared to unadjuvanted placebo.

6.3 Review Strategy

All the clinical data from the three primary studies involving males were examined. Study V501-020 was reviewed in detail. Study reports describing safety and immunogenicity analyses in populations pooled from the studies in the sBLA were reviewed. Studies 016 and -018 are not presented separately in this review; the subsets of data from those studies which are relevant to this application are covered under Section 9 (Overview of Efficacy Across Trials) and Section 10 (Overview of Safety Across Trials).

In some cases, post-hoc analyses submitted by the applicant (for example, a comparison of immunogenicity data between age-matched cohorts of males and females from different studies) and related clinical study reports (for example, the evaluation of sampling techniques for detecting HPV infection in males) were reviewed.

In assessing the overall risk/benefit ratio for administering Gardasil to males for the proposed indication, data from the pivotal safety and efficacy study in males, V501-020, were considered to be of primary importance.

6.4 Good Clinical Practices (GCP) and Data Integrity

Results of data audits and bioresearch monitoring inspections of two clinical investigators did not reveal any problems that impact the quality or integrity of the data submitted in the BLA.

6.5 Financial Disclosures

On Form 3454, the applicant certified that the following statement is correct:

> *"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."*

7.0 Human Pharmacology

See Section 8.

8.0 Clinical Studies

8.1 Study V501-020

Title: A Study to Evaluate the Efficacy of GARDASIL in Reducing the Incidence of HPV 6- 11-, 16-, and 18-Related External Genital Warts, PIN, Penile, Perianal and Perineal Cancer, and the Incidence of HPV 6-, 11-, 16-, and 18-Related Genital Infection in Young Men

8.1.1 Design Overview

This was a randomized, double-blind, placebo-controlled, multicenter study. Subjects were screened on Day 1 and randomized 1:1 to receive qHPV (VLP's plus aluminum adjuvant) or placebo (aluminum adjuvant) on Day 1, Month 2 and Month 6. Subjects were recruited at 71 study sites in 18 different countries - Australia, Brazil, Canada, Costa Rica, Croatia, Finland, Germany, Mexico, Netherlands, Norway, Peru, Philippines, Portugal, South Africa, Spain, Sweden, Taiwan, and the United States.

Each subject underwent genitourinary exam, had specimens collected for HPV PCR, and underwent lesion biopsy, if indicated, at Month 7, 12, 18, 24, 30 and 36. Sera were collected for immunogenicity at screening and at months 7, 24 and 36. Safety assessments were obtained

at each visit and every 3 months after Month 6 by phone or email until study completion (3 years).

A substudy was designed to recruit a cohort of men having sex with men (MSM) to investigate the prevention of anal intraepithelial neoplasia (AIN) and anal cancer. This cohort was to participate in the primary study as well.

8.1.2 Objectives

Primary Efficacy Objective: To demonstrate that qHPV when given in a 3-dose regimen reduces the incidence of HPV 6-, 11-, 16- or 18-related external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal or perineal cancer in young men who are naïve to the relevant HPV type, compared with placebo.

Men having Sex with Men (MSM) Substudy Efficacy Objective: To investigate the impact of administration of a 3-dose regimen of qHPV on the combined incidence of HPV 6-, 11-, 16-, or 18- related anal intraepithelial neoplasia (AIN) or Anal Cancer in MSM subjects who are naïve to the relevant HPV type.

Clinical Reviewer Note: Because the close-out data on the MSM substudy were not submitted to the sBLA and because the efficacy objective of the MSM substudy has no bearing on the indication sought by the applicant at this time, the MSM substudy data are not addressed in this review.

Secondary Efficacy Objectives:

- To demonstrate that qHPV, when given in a 3-dose regimen, reduces the incidence of persistent HPV 6, 11, 16, or 18 infection in young men who are naïve to the relevant HPV type, compared with placebo

- To demonstrate that qHPV, when given in a 3-dose regimen, reduces the incidence of HPV 6, 11, 16, or 18 detection at one or more visits, in young men who are naïve to the relevant HPV type, compared with placebo.

Immunogenicity Objective: To evaluate the vaccine-induced serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in young men.

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 young men.

8.1.3 Population

8.1.3.1.1 Eligibility Criteria

8.1.3.1.2 Inclusion Criteria:

- For HM: healthy, males between the ages 16 years and 0 days and 23 years and 364 days.
- For MSM: healthy, males between the ages 16 years and 0 days and 26 years and 364 days.

- No clinical evidence of gross genital lesion suggesting sexually-transmitted disease and no clinically present anogenital warts.
- No temperature ≥100°F or ≥37.8°C (oral) within 24 hours prior to vaccinations (vaccinations were to be scheduled at a later date when the temperature fell into normal range).
- Must have agreed to refrain from sexual activity (including vaginal and anal penetration and any genital contact) for 2 calendar days prior to any scheduled visit that included sample collection, to avoid detection of viral DNA which had been deposited in the male genital area during sexual intercourse and is not the result of ongoing infection.
- HM who have experienced sexual debut but have had no more than 5 lifetime sexual partners.

For protocol purposes, a female sexual partner is defined as a woman with whom the subject has engaged in vaginal intercourse. For protocol purposes, a male sexual partner is defined as a man with whom the subject engaged in insertive or receptive anal intercourse.

- MSM subjects may have had fewer than one lifetime sexual partner but no greater than 5 lifetime sexual partners. For MSM subjects with fewer than one lifetime sexual partner, they must have identified themselves as a man who has had sex with men and must have engaged in oral sex with another man within the past year.

- Must have agreed to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes.

Additional inclusion criteria for heterosexual male subjects:

- Subjects must be a heterosexual male, who has had exclusively female sexual partners.

Additional inclusion criteria for MSM subjects:

- Subjects must have identified themselves as a man who has had sex with men and must have engaged in either insertive or receptive anal intercourse or oral sex with another male sexual partner within the past year.

8.1.3.1.3 Exclusion Criteria:

Candidate subjects who manifest ANY of the following exclusion criteria at the time of randomization were NOT be eligible for the study:

- Individuals concurrently enrolled in clinical studies of investigational agents or studies involving collection of genital specimens.
- History of known prior vaccination with an HPV vaccine.
- Receipt of inactivated vaccines within 14 days prior to enrollment or receipt of live virus vaccines within 21 days prior to enrollment.
- Individuals who have had a history of anogenital warts, or who have had clinically present anogenital warts at Day 1.
- 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 have received any immune globulin or blood derived products within the 6 months prior to the first injection, or plan 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 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, were excluded. Subjects using topical steroids (i.e., inhaled or nasal) were eligible for vaccination.
- Individuals who were immunocompromised or have been diagnosed as having Human Immunodeficiency Virus (HIV) infection.
- Individuals with known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
- History of recent (within the last 12 months) or ongoing alcohol or drug abuse. Alcohol and drug abusers are defined as those who drank or used drugs despite recurrent social, interpersonal, and legal problems as a result of alcohol or drug use.
- Any condition which 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.
- HM with fewer than one or greater than 5 lifetime sexual partners.
- MSM subjects with greater than 5 lifetime sexual partners**.**
- Inability to give informed consent/assent

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.

Gardasil is a sterile suspension, with each 0.5mL dose containing approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein, 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate (AAHS) adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, < 7 mcg yeast protein/dose, and water for injection. The product does not contain a preservative or antibiotics.

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.

The formulation numbers for the lots of Gardasil used in the trial include:
V501 VAI047T001
V501 VAS048T001
V501 VAS048T001
WL00013783

WL00023429

The formulation numbers for the lots of placebo used in the trial include:
V501 VAI045P001
PV501 VAS046P001
PV501 VAS046P001
WL00013712
WL00022172

8.1.5 Endpoints

8.1.5.1.1 Efficacy/Immunogenicity Endpoints

8.1.5.1.2 Primary Endpoint

The primary endpoint was HPV 6-, 11-, 16-, 18-related EGL, which includes external genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), and penile, perianal or perineal cancer.

An EGL endpoint occurred if on a single biopsy or excised tissue block, the following conditions were met:

- the Pathology Panel consensus diagnosis was condylomata acuminate (genital warts), PIN 1, PIN 2/3, penile, perianal, or perineal cancer; and

- at least one of HPV types 6, 11, 16, or 18 was detected by Thinsection PCR in an adjacent section from the same tissue block.

This endpoint was evaluated in both HM and MSM subjects. In the primary analysis of this endpoint, cases were counted beginning at 4 weeks post-dose 3 (i.e., after Month 7).

Clinical Reviewer Note: The primary endpoint, external genital lesions, encompasses penile/perianal/perineal intraepithelial neoplasia (PIN) as well as genital warts (GW). PIN is analogous to cervical intraepithelial neoplasia (CIN) in that it is a precursor lesion in the progression to invasive cancer at the relevant anatomic site. However, the pathophysiology of PIN, including the rates of progression for PIN1, 2, and 3, is not as well characterized as it is for CIN. In addition, unlike cervical cancer, a substantial percentage of penile cancers are known to arise in the absence of detectable HPV. The reviewer was cognizant of these issues in the assessment of the primary endpoint.

Clinical Reviewer Note: An independent Pathology Panel, consisting of 4 pathologists, reviewed all biopsy specimens. The Panel was blinded to the results of the PCR analysis of the biopsy and of HPV PCR swabs obtained at routine visits. The consensus diagnosis of the Pathology Panel was used in the definition of study endpoints

Clinical Reviewer Note: For an EGL endpoint to occur, the Pathology Panel had to issue a consensus diagnosis of one of the disease endpoints *AND* a vaccine type HPV had to be detected in the tissue. Since many studies identify a small subset of genital warts in which no

HPV is detected (0-30% (Partridge and Koutsky)), it is possible that the population impact in terms of prevention of genital warts regardless of HPV type may slightly overestimate the effect.

8.1.5.1.3 Secondary Endpoints

Persistent Infection:

This endpoint occurred if at least one of the following conditions occurred:

- HPV 6, 11, 16, and/or 18 DNA was detected by a PCR for the same HPV type in 2 consecutive anogenital swab or biopsy samples collected at least 4 months apart; or

- the Pathology Panel consensus diagnosis for a biopsy sample was of external or anal disease and HPV 6, 11, 16, or 18 DNA was detected by Thinsection PCR in an adjacent section of the same biopsy block and HPV 6, 11, 16, or 18 DNA was detected by PCR for the same HPV type on a sample obtained at a separate adjacent visit, prior to or following the visit where the biopsy showing HPV disease was obtained.

Incident Infection:

This endpoint occurred if HPV 6, 11, 16, and/or 18 was detected by PCR on an anogenital swab or biopsy sample at one or more visits.

Clinical Reviewer Note: The secondary endpoints rely on detection of HPV DNA in anogenital swab specimens. Sampling techniques for detecting HPV infection and disease in men are not as well established as those used for women. Based on review of Merck's sampling method study (V501-017) and the available literature (Weaver et al), the reviewer concluded that the sampling techniques employed in the study were appropriate. To the extent that systematic error may be introduced by sampling technique imperfections, randomization and blinding should be adequate to assure balance across the treatment groups and minimize the bias.

8.1.5.1.4 Exploratory Endpoints

Exploratory endpoints were as follows:

- Incidence of clinically diagnosed external genital warts, PIN, penile, perianal or perineal cancer, as defined in the primary endpoint, but regardless of HPV relatedness;

- incidence of procedures for the treatment of external genital warts, PIN, penile, perianal or perineal cancer, regardless of the HPV-relatedness of the lesion;

- the duration of persistent infection;

- the incidence of clearance of infection, in the sets of subjects who were (i) PCR positive and seronegative at Day 1, or (ii) PCR positive and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine;

- the recurrence of persistent infection and DNA detection, in the set of subjects who were PCR negative and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine;

- the incidence of clinically diagnosed external genital warts, PIN, penile, perianal or perineal cancer, as defined in the primary endpoint, in the sets of subjects who were (i) PCR positive and seronegative at Day 1, (ii) PCR positive and seropositive at Day 1, or (iii) PCR negative and seropositive at Day 1, to assess the potential therapeutic effects of the vaccine;

8.1.5.2 Safety Endpoints

Pre-specified safety endpoints were as follows:

- the number and percent of subjects with serious adverse experiences Days 1 to 15 following any vaccination visit;

- the number and percent of subjects with serious vaccine-related adverse experiences at any time during the study;

- the number and percent of subjects with one or more injection-site adverse experiences, with ≥ 1% incidence Days 1 to 5 following any vaccination visit;

- the number and percent of subjects with severe injection-site adverse experiences Days 1 to 5 following any vaccination visit;

- the number and percent of subjects with specific systemic clinical adverse experiences with ≥ 1% incidence Days 1 to 15 following any vaccination visit;

- the number and percent of subjects with maximum oral temperature ≥37.8°C (≥100°F) Days 1 to 5 following any vaccination visit.

8.1.5.2.1 Adverse Events

Severity:
Mild: awareness of signs or symptoms, but easily tolerated.
Moderate: discomfort, enough to interfere with usual activity.
Severe: incapable of work or usual activity.

8.1.5.2.2 Injection Site Adverse Events

The tolerability of the study vaccine at the injection site was evaluated by the subject and noted on the VRC. Any swelling or redness at the injection site was evaluated by size. Subjects were instructed to estimate the size of the reaction at its largest from edge to edge.

8.1.5.2.3 Systemic Adverse Events

Any systemic clinical adverse experience that developed on Day 1 or during the 14 days after vaccination was recorded on the VRC along with the date it started and the last date it was present.

8.1.5.2.4 Serious Adverse Events

An SAE was defined as any untoward medical occurrence at any dose that:

- resulted in death
- was life-threatening
- required in-subject hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- was another medically important condition (e.g., an event that may require medical or surgical intervention to prevent one of the outcomes listed above
- cancer
- overdose (whether accidental or intentional)

Investigators were instructed to report any serious clinical adverse experience, including death due to any cause, occurring in any subject from the time the consent was signed through 14 days following the first vaccination and from the time of any subsequent vaccinations through 14 days thereafter, whether or not related to the investigational product.

8.1.5.2.5 Laboratory Parameters

No clinical laboratory evaluations to assess the safety of the vaccine were performed in the conduct of the clinical trials in support of this Application.

8.1.6 Surveillance/Monitoring

The surveillance and monitoring for the heterosexual male (HM) subjects in the trial is listed in Table 3.

In addition to what is listed in Table 3, 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.

Clinical Reviewer's Note: Men having sex with men (MSM) subjects underwent some additional procedures (such as anal cytology) in addition to all the surveillance for HM's. Those additional procedures are not listed and the data they produced are not reviewed, because they are not relevant to the indication sought under this BLA supplement.

Table 3: Study Procedures for V503-020

Visit	1	2	3	4	5	6	7	8	9
		Months							
Event/Test	D 1	2	6	7	12	18	24	30	36
Obtain informed consent	+								
Allocation number assigned†	+								
Genitourinary/medical history‡	+			+	+	+	+	+	+
Sexual history	+	+	+	+	+	+	+	+	+
Physical examination	+								+
Procedures/specimen collection (in serial order)									
Genitourinary examination of for external genital lesions	+			+	+	+	+	+	+
Photograph of external genital lesion (if indicated) ‡‡	+			+	+	+	+	+	+
Penile/glans penis file and wetted swab for HPV PCR	+			+	+	+	+	+	+
Scrotal file and wetted swab for HPV PCR	+			+	+	+	+	+	+
Perianal examination for external genital lesions	+			+	+	+	+	+	+
Perineal/perianal file and wetted swab for HPV PCR	+			+	+	+	+	+	+
External genital lesion biopsy (if indicated)§				+	+	+	+	+	+
Treatment for external genital lesions (if indicated)				+	+	+	+	+	+
Serum for HPV (6, 11, 16, 18) antibody measurements	+			+			+		+
Serum for hepatitis B (if indicated)††	+			+	+	+	+	+	+
Serum for hepatitis C (if indicated)††	+			+	+	+	+	+	+
Serum for syphilis (if indicated)††	+			+	+	+	+	+	+
Serum for HIV (if indicated)‖,††	+			+	+	+	+	+	+
Urine for gonorrhea PCR or LCR or SDA (if indicated)††	+			+	+	+	+	+	+
Urine for chlamydia PCR or LCR or SDA (if indicated)††	+			+	+	+	+	+	+
Swab for HSV culture (if indicated)††	+			+	+	+	+	+	+
Vaccination¶	+	+	+						
Clinical follow-up for safety	+	+	+	+					
Clinical contact visit documentation#	+	+	+	+	+	+	+	+	+

Note: Any test was repeated if medically indicated.
The Month 2 visit could have been performed within ±3 weeks. The Month 6 visit and all scheduled visits from Month 12 through Month 36 could have been performed ±4 weeks. The interval between the Month 6 and Month 7 visits should have been a minimum of 3 weeks and a maximum of 7 weeks from the Month 6 vaccination.

† Allocation number assignment should have only occurred AFTER the subject has been examined for the presence of HPV-related genital lesions. If a lesion was found, the subjects should not have been allocated, and should have been excluded from the study.

‡ Although complete review of the subject's genitourinary/medical history was not scheduled for the Month 2 and Month 6 visits, their history was updated as needed at these visits and at unscheduled visits.

§ Processed and analyzed at Central Laboratory.

‖ In South Africa only, HIV testing was mandatory and occurred at Day 1, Months 12, 24, and 36 visits. In addition, any subject from any other country that was found to be HIV infected was not discontinued from the trial and was referred for appropriate counseling and treatment and could participate in all study procedures.

¶ Temperature was to be measured prior to each injection.

Contact visit documentation was required every 3 months between study visits after Month 6 (Month 9, 12, 15, 18, 21, 24, 27, 30, 33). This information could have been obtained via telephone or electronic mail contact. For the Month 12, 18, 24, and Month 30 contacts, the information could have been obtained during the visit.

†† Testing to be performed by the local laboratory affiliated with the Investigative Site.

‡‡ Chronic, non HPV-related lesions (e.g. hemorrhoids, nevus, skin tag) present at Day 1 did not require photographs. At Day 1, only acute, non HPV-related lesions (e.g., molluscum contagiosum, folliculitis) were to be photographed.

Source: Original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.62

8.1.7 Statistical considerations

The analyses of the study are case driven. At the time when 32 cases of HPV 6, 11, 16 or 18-related genital warts/PIN/penile/perineal/perianal cancer have been observed in the Per Protocol Efficacy (PPE) population, the primary efficacy analysis were conducted, along with secondary and exploratory analyses.

The primary hypothesis to be tested is

$$H_0: \lambda \leq 0.2 \text{ vs. } H_1: \lambda \geq 0.2$$

where λ is vaccine efficacy (defined as [1 – Relative Risk]*100%). The corresponding 95% confidence intervals were estimated using an exact procedure which accounted for the amount of follow-up (i.e., person-time at risk) in the vaccine and placebo groups.

8.1.8 Results

8.1.8.1 Populations enrolled/analyzed

A total of 4065 subjects were enrolled in the study and randomized of whom 4055 received at least one vaccination and 3706 received all three vaccinations. Approximately 20% (815) of subjects discontinued the study before completing the three years of follow-up after initial vaccination. At the time the study report was written, 1225 subjects were still being followed (follow-up period – month 7 to month 36).

8.1.8.2 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:

8.1.8.2.1 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 received at least one dose of study material, who had follow-up after Day 1. Serostatus for the non-vaccine HPV types were not considered because no baseline serology testing was conducted for the non-vaccine HPV types.

- Day 1 Seronegative and PCR Positive (**S0P1**): subjects who: were seronegative and PCR positive at Day 1 to the relevant HPV type.

- Day 1 Seropositive and PCR Negative (**S1P0**): subjects who: were seropositive and PCR negative at Day 1 to the relevant HPV type.

- Day 1 Seropositive and PCR Positive (**S1P1**): subjects who: were seropositive and PCR positive at Day 1 to the relevant HPV type.

8.1.8.2.2 Immunogenicity Analysis Populations:

- Per-protocol immunogenicity (**PPI**): subjects who: received all 3 doses of vaccine or placebo within acceptable day ranges; had serum samples collected within acceptable day* ranges 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.
  *"Acceptable day ranges" is defined as follows: *The Month 2 visit could have been performed within ±3 weeks. The Month 6 visit and all scheduled visits from Month 12 through Month 36 could have been performed ±4 weeks. The interval between the Month 6 and Month 7 visits should have been a minimum of 3 weeks and a maximum of 7 weeks from the Month 6 vaccination.*

- All naïve subjects with serology (**ANSS**): subjects who: received at least one dose of the study vaccine, provided serology data, and were seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type(s).

Immunogenicity analyses were also performed on the **SP** populations (#'s 5, 6, and 7 above).

8.1.8.2.3 Safety Analysis Populations:

All-Subjects-As-Treated (**ASaT**): all randomized subjects who received at least 1 injection and had follow-up data*.
*"Follow-up data" was not defined, either quantitatively or qualitatively, in the clinical study report. The clinical reviewer assumed that the following was intended: any subject who had any data recorded in a visit that occurred after Day1 was eligible for analysis in the ASaT population.

8.1.9 Subject Disposition/Characteristics/Demographics

Table 4 displays the number of subjects eligible for the PPE analysis. Table 5 summarizes the disposition of all the subjects enrolled.

Table 4: PPE Populations Eligible for Efficacy Analyses

	Gardasil (N=2025)	Alum control (N=2030)	Total (N=4065)
Eligible for HPV 6/11/16/18-Related **EGL** Analysis	1397	1408	2805
Eligible for HPV 6/11/16/18-Related **Persistent Infection** Analysis	1390	1400	2790
Eligible for HPV 6/11/16/18-Related **DNA Detection** Analysis	1390	1400	2790

N = Number of subjects randomized to the respective vaccination group.

Table 5: Subject Disposition – All Subjects

	qHPV		Placebo		Total	
	n	(%)	n	(%)	n	(%)
SCREENING FAILURES					99	
RANDOMIZED	2032		2033		4065	
VACCINATED AT:						
Dose 1	2025	(99.7)	2030	(99.9)	4055	(99.8)
Dose 2	1936	(95.3)	1929	(94.9)	3865	(95.1)
Dose 3	1860	(91.5)	1846	(90.8)	3706	(91.2)
Vaccination Period (Day 1 Through Month 7)						
ENTERED	2025		2030		4055	
COMPLETED†	1819	(89.8)	1814	(89.4)	3633	(89.6)
DISCONTINUED	206	(10.2)	216	(10.6)	422	(10.4)
WITH LONG-TERM FOLLOW-UP‡	4	(0.2)	7	(0.3)	11	(0.3)
Clinical AE	2	(0.1)	4	(0.2)	6	(0.1)
Other reasons	2	(0.1)	2	(0.1)	4	(0.1)
Uncooperative	0	(0.0)	1	(0.0)	1	(0.0)
WITHOUT LONG-TERM FOLLOW-UP §	202	(10.0)	209	(10.3)	411	(10.1)
Lost to follow-up	110	(5.4)	112	(5.5)	222	(5.5)
Moved	20	(1.0)	21	(1.0)	41	(1.0)
Other reasons	5	(0.2)	5	(0.2)	10	(0.2)
Protocol deviations	2	(0.1)	2	(0.1)	4	(0.1)
Withdrew consent	64	(3.2)	69	(3.4)	133	(3.3)
Site terminated	1	(0.0)	0	(0.0)	1	(0.0)
Follow-up Period (After Month 7)						
ENTERED	1821		1820		3641	
COMPLETED	1018	(55.9)	1005	(55.2)	2023	(55.6)
CONTINUING	608	(33.4)	617	(33.9)	1225	(33.6)
DISCONTINUED	195	(10.7)	198	(10.9)	393	(10.8)
Clinical AE	3	(0.2)	10	(0.5)	13	(0.4)
Lost to follow-up	129	(7.1)	119	(6.5)	248	(6.8)
Moved	22	(1.2)	25	(1.4)	47	(1.3)
Other reasons	7	(0.4)	4	(0.2)	11	(0.3)
Withdrew consent	34	(1.9)	40	(2.2)	74	(2.0)

† Subjects completed 3 doses of vaccinations and entered the long-term follow-up period.
‡ Subjects received fewer than 3 doses of vaccinations and entered the long-term follow-up period.
§ Subjects discontinued on or before Month 7 and did not enter the long-term follow-up period.
Status percentages are calculated based on the number of subjects who entered the respective time period.

Source: Original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.138

Subjects were recruited at 71 study sites in 18 different countries - Australia, Brazil, Canada, Costa Rica, Croatia, Finland, Germany, Mexico, Netherlands, Norway, Peru, Philippines, Portugal, South Africa, Spain, Sweden, Taiwan, and the United States.

Table 6 summarizes the subject demographics. The two vaccination groups were well-balanced with regard to each demographic characteristic.

Table 6: Demographic characteristics by vaccination group

	qHPV (N = 2,029)	Placebo (N = 2,036)	Total (N = 4,065)
	n (%)	n (%)	n (%)
Gender			
Male	2,029 (100)	2,036 (100)	4,065 (100)
Age (years)			
Mean	20.5	20.5	20.5
Standard Deviation	2.0	2.0	2.0
Median	20	20	20
Range	15 to 26	16 to 27	15 to 27
Race/Ethnicity			
Asian	201 (9.9)	205 (10.1)	406 (10.0)
Black	412 (20.3)	393 (19.3)	805 (19.8)
Hispanic American	388 (19.1)	447 (22.0)	835 (20.5)
Native American	2 (0.1)	1 (0.0)	3 (0.1)
White	734 (36.2)	697 (34.2)	1,431 (35.2)
Other	292 (14.4)	293 (14.4)	585 (14.4)
Region			
Africa	277 (13.7)	261 (12.8)	538 (13.2)
Asia-Pacific	164 (8.1)	197 (9.7)	361 (8.9)
Europe	250 (12.3)	246 (12.1)	496 (12.2)
Latin America	766 (37.8)	809 (39.7)	1,575 (38.7)
North America	572 (28.2)	523 (25.7)	1,095 (26.9)
Smoking Status			
Current smoker	747 (36.8)	730 (35.9)	1,477 (36.3)
Ex-smoker	139 (6.9)	154 (7.6)	293 (7.2)
Never smoked	1,120 (55.2)	1,143 (56.1)	2,263 (55.7)
Missing or Unknown	23 (1.1)	9 (0.4)	32 (0.8)
Circumcision			
Yes	794 (39.1)	749 (36.8)	1,543 (38.0)
No	1,232 (60.7)	1,286 (63.2)	2,518 (61.9)
Missing or Unknown	3 (0.1)	1 (0.0)	4 (0.1)

Percent calculated as 100*(n/N)

N = Number of subjects randomized.

Source: Original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.150

By design the vast majority of subjects – 4035 (99.4%) - were non-virgins. Table 7 summarizes the sexual history of subjects at enrollment.

Overall, approximately 4% of subjects had a sexually transmitted infection (STI) at enrollment. The most frequent infection was anal chlamydia trachomatis, which was only seen in the MSM population. Other infections noted were chlamydia, gonorrhea, and genital herpes. In general, the proportions were comparable between the two vaccination groups.

Table 7: Sexual demographics of all subjects at enrollment

	qHPV N=2032	Placebo N=2033	Total N=4065
	n (%)	n (%)	n (%)
Subjects With Sexual History Data at Enrollment	2029	2030	4059
All Virgins †	14 (0.7)	10 (0.5)	24 (0.6)
HM Virgins	3 (0.1)	1 (0.0)	4 (0.1)
MSM Virgins	11 (0.5)	9 (0.4)	20 (0.5)
All Non-Virgins	2015 (99.3)	2020 (99.5)	4035 (99.4)
HM Non-Virgins	1725 (85.0)	1729 (85.2)	3454 (85.1)
MSM Non-Virgins	290 (14.3)	291 (14.3)	581 (14.3)
Age at First Sexual Intercourse Among Non-Virgins (years)			
Mean	16.8	16.8	16.8
Standard Deviation	2.1	2.2	2.2
Median	17	17	17
Range	5 to 24	5 to 26	5 to 26
Lifetime Number of Male or Female Sexual Partners at Enrollment Among Non-Virgins			
Unknown ‡	0 (0.0)	0 (0.0)	0 (0.0)
1	409 (20.2)	448 (22.1)	857 (21.1)
2	384 (18.9)	408 (20.1)	792 (19.5)
3	436 (21.5)	447 (22.0)	883 (21.8)
4	425 (20.9)	364 (17.9)	789 (19.4)
5	359 (17.7)	347 (17.1)	706 (17.4)
>5	2 (0.1)	6 (0.3)	8 (0.2)
Lifetime Condom Usage With Male or Female Sexual Partners at Enrollment Among Non-Virgins §			
Unknown	3 (0.1)	0 (0.0)	3 (0.1)
Never	172 (8.5)	203 (10.0)	375 (9.2)
Less than 1/2 the time	419 (20.7)	356 (17.5)	775 (19.1)
More than 1/2 the time	653 (32.2)	701 (34.5)	1354 (33.4)
Always	770 (37.9)	754 (37.1)	1524 (37.5)
Number of New Male or Female Sexual Partners in the 6 Months Prior to Study Start Among Non-Virgins			
Unknown	2 (0.1)	0 (0.0)	2 (0.0)
0	1149 (56.6)	1126 (55.5)	2275 (56.0)
1	669 (33.0)	685 (33.7)	1354 (33.4)
2	159 (7.8)	158 (7.8)	317 (7.8)
3	30 (1.5)	38 (1.9)	68 (1.7)
4	6 (0.3)	8 (0.4)	14 (0.3)
5	2 (0.1)	3 (0.1)	5 (0.1)
>5	0 (0.0)	0 (0.0)	0 (0.0)
Condom Usage With Male or Female Sexual Partners in the 6 Months Prior to Study Start Among Non-Virgins §			
Unknown	37 (1.8)	44 (2.2)	81 (2.0)
Never	565 (27.8)	552 (27.2)	1117 (27.5)
Less than 1/2 the time	298 (14.7)	266 (13.1)	564 (13.9)
More than 1/2 the time	372 (18.3)	427 (21.0)	799 (19.7)
Always	742 (36.6)	728 (35.9)	1470 (36.2)

† Virgins are defined as subjects who have had no vaginal intercourse with a female partner and no insertive or receptive anal intercourse with a male partner.
‡ Unknown means that the subject has had at least one sexual partner prior to study entry but did not remember or did not document their lifetime number of sexual partners.
§ Condom usage is as reported with females for HM subjects and is as reported with males for MSM subjects.
Percentages calculated as 100*(n/number of subjects with sexual history data at enrollment).
N = Number of subjects randomized.
n = Number of subjects with the indicated characteristic.
HM = Heterosexual men; MSM = Men having sex with men.

Source: Original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.150

8.1.10 Efficacy Endpoints/Outcomes

8.1.10.1 Primary Endpoint: Efficacy Against HPV 6/11/16/18-Related EGL

PPE Population

The results of the primary efficacy endpoint in the PPE population are displayed in Table 8.

Table 8: Efficacy Against HPV 6/11/16/18-Related EGL in the PPE Population

Endpoint	Gardasil (N=2025)		Alum control (N=2030)		Efficacy % (95%CI)
	n	Number of cases	n	Number of cases	
HPV 6/11/16/18-Related EGL	1397	3	1408	31	90.4% (69.2, 98.1)*
HPV 6-Related EGL	1245	3	1244	19	84.3% (46.5, 97.0)
HPV 11-Related EGL	1245	1	1244	11	90.9% (37.7, 99.8)
HPV 16-Related EGL	1295	0	1271	2	100% (-420.8, 100)
HPV 18-Related EGL	1335	0	1354	1	100% (-3804.6, 100)
Condyloma	1397	3	1408	28	89.4% (65.5, 97.9)
PIN1	1397	0	1408	2	100% (-431.1, 100)
PIN1 or worse	1397	0	1408	3	100% (-141.2, 100)
PIN2/3	1397	0	1408	1	100% (-3788.2, 100)
PIN2/3 or worse	1397	0	1408	1	100% (-3788.2, 100)
Penile/Perianal/Perineal Cancer	1397	0	1408	0	N/A

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the PPE population eligible for the respective analysis
* p-value <0.001
Source: Adapted from - original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.195

Clinical Reviewer Note: Although efficacy was statistically significant for the combined efficacy endpoint (HPV 6/11/16/18-Related EGL), the vast majority of the cases contributing to the combined endpoint were either condylomata or PIN1. The reviewer considered the category of PIN2/3 or worse (analogous to CIN2+) to be the most important measure of efficacy against dysplastic precursors to cancer. With a lower bound on the 95%CI of -3788.2%, efficacy against PIN2+ has not been demonstrated. Therefore, the reviewer recommended that efficacy against condylomata and PIN should be considered separately, and labeling claims regarding these indications should likewise be considered separately. The applicant agreed and revised the proposed indication to address genital warts only. Genital warts are therefore highlighted in each of the primary efficacy tables – tables 8, 9, and 10.

Naïve to the Relevant HPV Type (HNRT) Population
The results of the primary efficacy endpoint in the HNRT population are displayed in Table 9.

Table 9: Efficacy Against HPV 6/11/16/18-Related EGL in the HNRT Population

Endpoint	Gardasil (N=2025)		Alum control (N=2030)		Efficacy % (95%CI)
	n	Number of cases	n	Number of cases	
HPV 6/11/16/18-Related EGL	1775	13	1770	52	75.5% (54.3, 87.7)*
HPV 6-Related EGL	1603	10	1607	36	72.5% (43.4, 87.8)
HPV 11-Related EGL	1603	1	1607	16	93.8% (60.2, 99.9)
HPV 16-Related EGL	1674	1	1649	3	67.5% (-305.1, 99.4)
HPV 18-Related EGL	1713	2	1715	1	-98.1% (-11587.0, 89.7)
Condyloma	1775	10	1770	48	79.6% (59.1, 90.8)
PIN1	1775	2	1770	3	34.2% (-474.7, 94.5)
PIN1 or worse	1775	4	1770	4	1.2% (-430.5, 81.6)
PIN2/3	1775	2	1770	1	-97.6% (-11555.6, 89.7)
PIN2/3 or worse	1775	2	1770	1	-97.6% (-11555.6, 89.7)
Penile/Perianal/Perineal Cancer	1775	0	1770	0	N/A

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the HNRT population eligible for the respective analysis
Source: Adapted from - original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.202

Clinical Reviewer Note: The reverse case splits in the HPV 18-related EGL and the PIN2+ categories were noted. The small number of relevant cases makes interpretation difficult. However, given the fact that acquisition of HPV infection after Day 1 was possible in this population and given that this phenomenon did not occur in the PPE population, nor has it occurred in any analysis with substantial numbers, and given the lack of biological plausibility, the reviewer did not give significant weight to this observation in weighing risks/benefits or in making final recommendations. This issue should be evaluated again when the close-out data from the MSM substudy are submitted.

Full Analysis Set (FAS) Population
The results of the primary efficacy endpoint in the FAS population are displayed in Table 10.

Table 10: Efficacy Against HPV 6/11/16/18-Related EGL in the FAS Population

Endpoint	Gardasil (N=2025)		Alum control (N=2030)		Efficacy % (95%CI)
	n	Number of cases	n	Number of cases	
HPV 6/11/16/18-Related EGL	1943	27	1937	77	65.5% (45.8, 78.6)
HPV 6-Related EGL	1943	21	1937	51	59.4% (31.2, 76.8)
HPV 11-Related EGL	1943	6	1937	25	76.3% (40.8, 92.0)
HPV 16-Related EGL	1943	3	1937	10	70.3% (-15.5, 94.7)
HPV 18-Related EGL	1943	2	1937	3	33.9% (-467.7, 94.5)
Condyloma	1943	24	1937	72	67.2% (47.3, 80.3)
PIN1	1943	3	1937	4	25.6% (-339.9, 89.1)
PIN1 or worse	1943	6	1937	5	-19.2% (-393.8, 69.7)
PIN2/3	1943	3	1937	2	-48.9% (-1682.6, 82.9)
PIN2/3 or worse	1943	3	1937	2	-48.9% (-1682.6, 82.9)
Penile/Perianal/Perineal Cancer	1943	0	1937	0	N/A

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 BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.205

8.1.10.1.1 Analysis of Efficacy Stratified by Baseline Characteristics

Efficacy was analyzed in subpopulations according to subject characteristics (Table 11). In some instances there were too few cases to yield definitive results. For example, although the point estimate for efficacy among MSM subjects is lower than for HM subjects, the smaller number of MSM subjects results in a wide confidence interval. See Table 11.

Table 11: Efficacy Against Any HPV Type* Related Condyloma Stratified by Subject Baseline Characteristics (FAS Population)

Subject Characteristic	Gardasil (N=2025)		AAHS control (N=2030)		Efficacy % (95%CI)
	n	# of cases	n	# of cases	
Any HPV Type Related Condyloma overall	1943	32	1937	83	62.1% (42.4, 75.6)
15-20 years old	966	17	1004	49	63.9% (36.2, 80.5)
21-27 years old	977	15	933	34	59.2% (23.1, 79.4)
Sexual Orientation – HM	1653	22	1648	61	64.6% (41.6, 79.3)
Sexual Orientation - MSM	290	10	289	22	54.7% (0.2, 80.8)
Lifetime # of Sexual Partners: 0	12	0	10	1	100% (-3349, 100)
Lifetime # of Sexual Partners: 1	395	2	424	12	82.3% (20.5, 98.1)
Lifetime # of Sexual Partners: 2	365	6	399	12	46.1% (-55.1, 83.4)
Lifetime # of Sexual Partners: 3	405	9	421	10	10.8% (-144, 67.9)
Lifetime # of Sexual Partners: 4	407	3	341	27	90.8% (70.1, 98.2)
Lifetime # of Sexual Partners: 5	356	12	335	20	44% (-20.2, 75.1)
Lifetime # of Sexual Partners: >5	2	0	5	1	100% (-7470, 100)
Circumcised	743	11	699	24	56.2% (7.2, 80.6)
Not Circumcised	1200	21	1238	59	64.5% (40.8, 79.5)
PCR(+) and/or sero(+) for 6 and/or 11 at Day 1	186	19	178	22	20.9% (-53.2, 59.5)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the FAS population eligible for the respective analysis
*Any HPV Type Tested = PCR (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59); serology (6, 11, 16, and 18)
Source: Analysis provided by the applicant as a result of CBER information request.

Clinical Reviewer Note: Generally, subject characteristics, including sexual demographics, seemed to have limited effect on efficacy. The exceptions were PCR and serostatus; evidence of prior exposure to, or current infection with, HPV 6 and/or 11 resulted in markedly lower efficacy. The reviewer focused on the FAS population for the subgroup analysis displayed in Table 11 because many of these baseline characteristics are largely irrelevant in an HPV-naive pre-adolescent population. The FAS analysis above is perhaps the best estimate of efficacy against genital warts in the broader population of males >15 years of age. The analysis displayed in Table 11 was also performed in the Generally HPV-Naive (GHN) population. In that analysis the point estimates for efficacy were substantially higher, although the 95% Confidence Intervals were wider because of the smaller number of subjects in that population. The efficacy against genital warts in that analysis, 85.3% (62.1, 95.5) is perhaps the best estimate of overall efficacy in a naïve, pre-adolescent population.

8.1.10.2 Secondary Endpoints

8.1.10.2.1 Persistent Infection

Persistent infection, defined by the applicant as PCR detection of the same HPV type on two occasions at least 4 months apart, was one of the secondary endpoints. Table 12 displays efficacy against persistent infection in the PPE population.

Table 12: Efficacy Against HPV 6/11/16/18-Related Persistent Infection (PI) in the PPE Population

Endpoint	Gardasil (N=2025)		AAHS control (N=2030)		Efficacy % (95%CI)
	n	Number of cases	n	Number of cases	
HPV 6/11/16/18-Related PI	1350	15	1400	101	85.6% (73.4, 92.9)
HPV 6-Related PI	1239	4	1238	33	88.0% (66.3, 96.9)
HPV 11-Related PI	1239	1	1238	15	93.4% (56.8, 99.8)
HPV 16-Related PI	1290	9	1264	41	78.7% (55.5, 90.9)
HPV 18-Related PI	1327	1	1347	25	96.0% (75.6, 99.9)

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 BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.219

Clinical Reviewer's Note: Efficacy in the prevention of persistent infection was noted. The logic employed to justify use of persistent infection as a surrogate endpoint for penile cancer is indisputable: HPV infection cannot lead to penile cancer if HPV infection does not occur. And it is important to note that epidemiological studies demonstrate a consistent association between persistent infection and subsequent histopathologically proven dysplastic disease. However, in contrast to cervical cancer, in which virtually 100% of cases are associated with oncogenic HPV infection, penile cancer is associated with oncogenic HPV infection in only 40%-50% of cases. In addition, because penile cancer is so rare compared with cervical cancer, oncogenic HPV infection evidently clears without sequelae much more commonly in males than in females. Finally, the epidemiology of persistent infection in males is much less well described than it is for females. Therefore, compared with females, the benefit of preventing persistent infection in males is less certain and probably much less. Prevention of persistent infection in males may result in decreased transmission to females and among MSM, but the applicant has not submitted data to support this claim, and the degree to which this phenomenon will occur remains a matter of conjecture. Compared with the data on disease endpoints, this reviewer placed much less emphasis on persistent infection in assessing the sought after indication in males. The same is true of the incident infection data displayed below.

8.1.10.2.2 Incident Infection

Incident infection, defined as PCR detection of HPV 6, 11, 16, or 18 at one or more visits, was one of the secondary endpoints. Table 13 displays efficacy against incident infection in the PPE population.

Table 13: Efficacy Against HPV 6/11/16/18-Related Incident Infection (II) in the PPE Population

Endpoint	Gardasil (N=2025)		AAHS control (N=2030)		Efficacy % (95%CI)
	n	Number of cases	n	Number of cases	
HPV 6/11/16/18-Related II	1,390	136	1,400	241	44.7% (31.5, 55.6)
HPV 6-Related II	1,239	51	1,238	99	49% (27.9, 64.4)
HPV 11-Related II	1,239	16	1,238	37	57% (20.7, 77.6)
HPV 16-Related II	1,290	62	1,264	103	41.1% (18.5, 57.7)
HPV 18-Related II	1,327	25	1,347	66	62.1% (39.2, 77.1)

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 BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.235

8.1.11 Immunogenicity

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

The immunogenicity endpoints assessed in males were also similar to those assessed in females: (1) anti-HPV geometric mean titers (GMTs); and (2) seroconversion rate (SCR) at 4 weeks post-dose 3. See Tables 14 and 15 for anti-HPV GMTs and SCRs in males from Protocol 020.

Clinical Reviewer Note: Serum antibody titer associated with protection against HPV infection remains unknown. Seroconversion was defined as follows:

> *Subjects who at Day 1 have HPV 6, 11, 16, and 18 titers less than the serostatus cutoffs of 20, 16, 20, and 24 mMU/mL, respectively, and have HPV titers greater than or equal to aforementioned HPV type-specific serostatus cutoffs during followup, are defined to have seroconverted to HPV type 6, 11, 16, and 18 respectively.*

Table 14: Anti-HPV Geometric Mean Titers by Vaccination Group (PPI Population)

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=2,025)			Placebo (N=2,030)		
	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	1,093	< 7	(<7, <7)	1,110	< 7	(<7, <7)
Month 7	1,093	447	(422.1, 473.5)	1,110	< 7	(<7, <7)
Month 24	906	80.3	(76.2, 84.6)	904	< 7	(<7, <7)
Anti-HPV 11						
Day 1	1,093	< 8	(<8, <8)	1,109	< 8	(<8, <8)
Month 7	1,093	624.2	(594.4, 655.6)	1,109	< 8	(<8, <8)
Month 24	906	94.5	(89.8, 99.5)	902	< 8	(<8, <8)
Anti-HPV 16						
Day 1	1,136	< 11	(<11, <11)	1,128	< 11	(<11, <11)
Month 7	1,136	2,402.50	(2,270.6, 2,542.0)	1,128	< 11	(<11, <11)
Month 24	937	347.8	(329.3, 367.4)	904	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1,175	< 10	(<10, <10)	1,205	< 10	(<10, <10)
Month 7	1,175	402.2	(380.2, 425.6)	1,205	< 10	(<10, <10)
Month 24	966	38.7	(36.2, 41.3)	952	< 10	(<10, <10)

The estimated GMTs and associated CIs are calculated using an ANOVA model with a term for vaccination group.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Source: Adapted from - original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.271

Table 15: Anti-HPV Percent Seroconversion by Vaccination Group (PPI Population)

Anti-HPV Response	qHPV Vaccine (N=2,025) Seroconversion				Placebo (N=2,030) Seroconversion			
Study Time	n	m	Percent	95% CI	n	m	Percent	95% CI
HPV 6 cLIA ≥20 mMU/mL								
Day 1	1,093	0	0	(0.0%, 0.3%)	1,110	0	0	(0.0%, 0.3%)
Month 7	1,093	1,081	98.9	(98.1%, 99.4%)	1,110	18	1.6	(1.0%, 2.6%)
Month 24	906	823	90.8	(88.8%, 92.6%)	904	19	2.1	(1.3%, 3.3%)
HPV 11 cLIA ≥16 mMU/mL								
Day 1	1,093	0	0	(0.0%, 0.3%)	1,109	0	0	(0.0%, 0.3%)
Month 7	1,093	1,084	99.2	(98.4%, 99.6%)	1,109	23	2.1	(1.3%, 3.1%)
Month 24	906	866	95.6	(94.0%, 96.8%)	902	11	1.2	(0.6%, 2.2%)
HPV 16 cLIA ≥20 mMU/mL								
Day 1	1,136	0	0	(0.0%, 0.3%)	1,128	0	0	(0.0%, 0.3%)
Month 7	1,136	1,122	98.8	(97.9%, 99.3%)	1,128	20	1.8	(1.1%, 2.7%)
Month 24	937	930	99.3	(98.5%, 99.7%)	904	7	0.8	(0.3%, 1.6%)
HPV 18 cLIA ≥24 mMU/mL								
Day 1	1,175	0	0	(0.0%, 0.3%)	1,205	0	0	(0.0%, 0.3%)
Month 7	1,175	1,144	97.4	(96.3%, 98.2%)	1,205	21	1.7	(1.1%, 2.7%)
Month 24	966	602	62.3	(59.2%, 65.4%)	952	10	1.1	(0.5%, 1.9%)

Percent is calculated as 100*(m/n).
The CIs are computed based on exact methods.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
m = Number of subjects with the indicated response.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Source: Adapted from - original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.272

8.1.12 Duration of Immune Response

The median follow-up at the time of primary efficacy analysis for Study 020 was 2.9 years. The applicant asserted that analysis of the immunogenicity data was complete on too few subjects to include month 36 data in Tables 14 and 15. See Section 9.3 below regarding duration of efficacy and immunity.

8.1.13 Safety outcomes

8.1.13.1 Adverse Events

The summary analysis of AEs revealed a slightly higher overall rate of AEs among Gardasil recipients compared with placebo recipients. See Table 16. 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.

The summary analysis of AEs was otherwise unremarkable, with similar percentages of subjects in each group discontinuing due to an AE or experiencing an SAE or fatality.

Table 16: Clinical Adverse Event Summary – Entire Study Period, All Vaccinated Subjects

	Gardasil (N=1945)		**AAHS control** (N=1950)	
	n	(%)	n	(%)
With one or more AEs	1346	(69.2)	1252	(64.2)
Injection-site AEs	1169	(60.1)	1047	(53.7)
Systemic AEs	616	(31.7)	622	(31.9)
With vaccine-related AEs*	1242	(63.9)	1134	(58.2)
Vaccine-related injection-site AEs*	1169	(60.1)	1046	(53.6)
Vaccine-related systemic AEs*	274	(14.1)	284	(14.6)
With SAEs	8	(0.4)	11	(0.6)
Vaccine-related SAEs*	0	(0.0)	0	(0.0)
Who died	3	(0.2)	10	(0.5)
Discontinued due to an AE	5	(0.3)	14	(0.7)
Discontinued due to an SAE	3	(0.2)	10	(0.5)

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 BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.289

8.1.13.2 Systemic Adverse Events

Analysis of the most common systemic AEs was unremarkable. The case splits of systemic AEs in the Gardasil group compared to the placebo group by system organ class (SOC) were similar. Table 17 displays the most common systemic AEs reported.

Table 17: Number (%) of Subjects Who Reported Systemic AEs With ≥ 1% Incidence (Days 1 to 15 Following Any Vaccination Visit)

Adverse Event Term	Gardasil (N=1945)	AAHS control (N=1950)
	n (%)	n (%)
With one or more systemic AEs	615 (31.6)	613 (31.4)
Abdominal pain, upper	19 (1)	23 (1.2)
Diarrhea	40 (2.1)	36 (1.8)
Nausea	27 (1.4)	16 (0.8)
Fatigue	13 (0.7)	19 (1.0)
Pyrexia	118 (6.1)	125 (6.4)
Influenza	42 (2.2)	44 (2.3)
Nasopharyngitis	44 (2.3)	50 (2.6)
Pharyngitis	22 (1.1)	20 (1.0)
Upper respiratory tract infection	27 (1.4)	20 (1.0)
Dizziness	19 (1.0)	18 (0.9)
Headache	179 (9.2)	207 (10.6)
Pharyngolaryngeal pain	38 (2.0)	37 (1.9)

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 BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.299

8.1.13.3 Injection Site Adverse Events

Gardasil recipients experienced a somewhat higher rate of injection site AEs compared to subjects in the placebo group. The most pronounced imbalance in the case splits occurred in the analysis of injection site pain. See Table 18.

Table 18: Subjects Reporting Specific Injection-Site Adverse Experiences With ≥ 1% Incidence (Days 1 to 5 Days Following Any Vaccination Visit)

	Gardasil (N=1945)		**AAHS control** (N=1950)		**Risk Difference** qHPV – control (95%CI)	**p-Value***
	n	(%)	n	(%)		
One or more injection-site AEs	1166	(59.9)	1046	(53.6)	6.30 (3.2, 9.4)	ND
Injection-site erythema	304	(15.6)	275	(14.1)	1.50 (-.07, 3.8)	0.180
Injection-site pain	1113	(57.2)	991	(50.8)	6.40 (3.3, 9.5)	<0.001
Injection-site pruritis	22	(1.1)	24	(1.2)	-0.10 (-0.8, 0.6)	ND
Injection-site swelling	219	(11.3)	187	(9.6)	1.70 (-0.3, 3.6)	0.088

* p-Values, unadjusted for multiple comparisons, were calculated only for adverse experiences prompted on the vaccination report card.
N = number of subjects in the ASaT analysis set in the respective vaccination group who had follow-up data
ND = not done
Source: Adapted from - original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.295

Clinical Reviewer Note: Concerning injection-site AEs, the fact that Gardasil was less well tolerated than placebo is especially noteworthy considering that the placebo formulation contained the same amount of amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant as Gardasil. The difference in local tolerability is even more pronounced in Study HPV-018, the only protocol in which saline alone is used in the placebo arm. CBER noted similar trends in local tolerability in females. See Section 10 – Safety Across Trials.

8.1.13.4 Serious Adverse Events

A total of 6 nonfatal serious adverse events (SAE) occurred during the study - 5 in the Gardasil group and 1 in the placebo group. In the Gardasil group, there was an appendicitis, a lower extremity cellulitis, non-cardiac chest pain related to an upper respiratory infection, an allergic reaction to peanuts, and a seizure secondary to varicella infection. 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.

8.1.13.5 Deaths

A total of 13 deaths occurred during the study - 3 in the Gardasil group and 10 in the placebo group. In the Gardasil group, the fatalities resulted from a car accident, a motorcycle accident, and a gunshot wound. None of the deaths were assessed by the Investigator as being related to treatment.

Clinical Reviewer Note: The subject narratives from each of the deaths 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.

8.1.14 Comments and Conclusions

Because the pathophysiology, epidemiology, natural history, prognosis, etc, of PIN/penile cancer and genital warts are so different, the approach of combining these two disease entities into one endpoint, "external genital lesions" was not optimal. The trial was adequately powered to demonstrate reduced incidence of *external genital lesions* in the Gardasil compared to placebo group, but so few cases of PIN/penile cancer occurred that a meaningful analysis could not be done on this subset of the data.

However, since the vast majority of "external genital lesions" were genital warts, there were a sufficient number of cases to allow for a robust analysis. This analysis supports the conclusion that Gardasil is efficacious in the prevention of genital warts caused by HPV 6 and 11 in males 16-26 years of age.

The trial was adequate in design and execution to address the primary safety objective of demonstrating that Gardasil is generally well-tolerated in young men. Injection site AEs were higher in Gardasil compared to placebo recipients, even though placebo contained the same adjuvant as the vaccine. This difference was mainly due to higher reported rates of injection site pain among Gardasil recipients. No other imbalances in AEs or potential safety signals were noted in the safety analysis.

9.0 Overview of Efficacy Across Trials

9.1 Immunobridging to Males Aged 9-15 Years

Anti-HPV responses (Month 7 GMTs and SCRs) among 9 to15 year old male subjects from previously conducted Protocols 016 and 018 were compared with responses from 16- to 26-year-old men in Protocol 020. Compared with the older male subjects, GMTs and SCRs were non-inferior in the younger male subjects. SCRs were uniformly high and comparable across age groups. See Table 19.

Clinical Reviewer Note: The criteria for non-inferiority were as follows:
For GMT: *For the null hypothesis that GMTBoys/GMTMen <=0.5 (2-fold decrease), a p-value <0.025 supports a conclusion that the specific type anti-HPV response in Boys is non-inferior to the response in Men.*
For SCR: *For the null hypothesis that %Boys/%Men <= -0.05, a p-value <0.025 supports a conclusion that the specific type anti-HPV seroconversion rate in Boys is non-inferior to the seroconversion rate in Men.*
Non-inferiority criteria were met because the p value in the case of each VLP type for both GMT and SCR was <0.001. For the sake of space and clarity, therefore, the p values are not displayed in Tables 19 and 20.

Clinical Reviewer Note: The sera from Protocols 016 and 018 were collected and the immunogenicity assays were performed ~4 years prior to those from Protocol 020. To address the possibility that such an approach could produce inaccurate results, a parallel testing

procedure was undertaken to support the overall analysis. Randomly chosen samples from 490 vaccinated subjects (240 adult men and 250 boys) were tested in parallel, and the results confirmed non-inferior responses in the younger subjects compared to the older subjects.

Table 19: Month 7 Anti-HPV cLIA GMTs and SCRs in the PPI Population of Boys and Men

Population	N*	n**	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 6				
9- through 15-year old boys	1073	885	99.9 (99.4, 100.0)	1036.9 (962.9, 1116.6)
16- through 26-year old boys and men	2025	1093	98.9 (98.1, 99.4)	447.0 (418.2, 477.8)
Anti-HPV 11				
9- through 15-year old boys	1073	886	99.9 (99.4, 100.0)	1386.3 (1298.1, 1480.4)
16- through 26-year old boys and men	2025	1093	99.2 (98.4, 99.6)	624.2 (588.4, 662.3)
Anti-HPV 16				
9- through 15-year old boys	1073	883	99.8 (99.2, 100.0)	6047.1 (5592.8, 6538.3)
16- through 26-year old boys and men	2025	1136	98.8 (97.9, 99.3)	2402.5 (2242.6, 2573.7)
Anti-HPV 18				
9- through 15-year old boys	1073	888	99.8 (99.2, 100)	1356.9 (1249.0, 1474.2)
16- through 26-year old boys and men	2025	1175	97.4 (96.3, 98.2)	402.2 (374.3, 432.3)

*Number of individuals randomized to the respective vaccination group who received at least 1 injection.
**Number of individuals contributing to the analysis.
†mMU = milli-Merck units
CI = Confidence interval

Source: Adapted from - original BLA 125126.1297.0, 1.14.1.3 – Draft Labeling Text, p.25

9.2 Immunogenicity in Males Compared to Females

In response to a CBER request, the applicant submitted an analysis of the immune responses of males 16-26 years of age (from Protocol 020) compared to the immune responses of females 16-26 years of age (from multiple studies). Because this objective was not specified prospectively, no formal hypothesis tests were performed, and the comparisons are descriptive rather than statistical. Those caveats notwithstanding, it was noted that anti-HPV GMTs were lower in males compared to females, particularly for types 6, 11, and 18. The differences persisted at month 24. See Table 20.

Table 20: Anti-HPV Geometric Mean Titers Among 16-26 Year Old Subjects Vaccinated with Gardasil by Gender (Per-Protocol Immunogenicity Population)

	Females† (N=9,885)			Males‡(N=2,025)		
Assay Study time	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Month 07	3,333	545.2	(528.1, 562.9)	1,093	447	(422.8, 472.7)
Month 24	2,792	109.1	(105.1, 113.1)	906	80.3	(75.3, 85.6)
Anti-HPV 11						
Month 07	3,357	749	(725.6, 773.2)	1,093	624.2	(590.4, 659.9)
Month 24	2,821	137	(132.0, 142.2)	906	94.5	(88.5, 101.0)
Anti-HPV 16						
Month 07	3,253	2,411.30	(2,312.1, 2,514.9)	1,136	2,402.50	(2,237.5, 2,579.6)
Month 24	2,725	442.6	(424.8, 461.2)	937	347.8	(324.2, 373.1)
Anti-HPV 18						
Month 07	3,571	475.60	(458.3, 493.6)	1,175	402.20	(377.1, 429.1)
Month 24	3,007	50.8	(48.2, 53.5)	966	38.7	(35.3, 42.3)

†16-26 year-old female subjects from Protocols 007, 013, 015 (consistency lot substudy), 016 and 019. Month 24 testing was not included in Protocol 016

‡16-26 year-old male subjects from Protocol 020

The estimated GMTs and associated CIs are calculated using the ANOVA model with a term for gender.

N = Number of subjects randomized in the respective group who received at least 1 injection.

n = Number of subjects in the indicated immunogenicity population.

ANOVA = Analysis of variance; CI = Confidence interval; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units.

Source: Adapted from - sBLA 125126.1297.0, 5.4, Reference 2272 – Integrated immunogenicity analyses in support of Gardasil™ men's filing, p.14

In contrast to the comparison between 16-23 year old males and females, in which females had higher titers, 9-15 year old males and females had titers that were similar. One exception is the anti-HPV 18 titers, which were slightly higher in *males*. Table 21 displays month 7 GMTs from Protocol 018, in which 9-15 year old males and females were compared directly. The results from Protocol 016, in which 10-15 year old males and females were compared directly, were similar to those from 018.

Table 21: Anti-HPV Geometric Mean Titers Among 9-15 Year Old Subjects Vaccinated with Gardasil by Gender (Per-Protocol Immunogenicity Population) From Protocol 018

		Boys (N=564)			Girls (N=615)		
Assay (cLIA)	Time Point	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Day 1	471	<8	(<8, <8)	501	<8	(<8, <8)
	Month 7	471	967.6	(884.8, 1,058.1)	501	884.3	(813.3, 961.6)
Anti-HPV 11	Day 1	471	<8	(<8, <8)	501	<8	(<8, <8)
	Month 7	471	1,383.50	(1,263.8, 1,514.4)	501	1,336.30	(1,225.4, 1,457.2)
Anti-HPV 16	Day 1	471	<12	(<12, <12)	502	<12	(<12, <12)
	Month 7	471	6,193.00	(5,540.0, 6,923.0)	502	5,006.90	(4,500.9, 5,569.8)
Anti-HPV 18	Day 1	474	<8	(<8, <8)	503	<8	(<8, <8)
	Month 7	474	1,474.50	(1,317.9, 1,649.8)	503	1,127.80	(1,017.0, 1,250.6)

N = Number of subjects in the respective demographic cohort who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.
Source: Adapted from - original BLA 125126, 5.3.5.1.1 - Clinical Study Report(v1) V503-018, p.121

Clinical Reviewer Note: With regard to the differences in titers between males and females 16-26 years of age, the fact that the analysis was performed *post hoc* in different study populations was noted. In addition, the difference in titers did not seem to correlate with any difference in clinical efficacy for condyloma. For example, in the generally HPV naïve (GHN) population analysis, the point estimate for efficacy in prevention of genital warts related to any HPV type in males 16-26 years of age from Study 020 was 85.3 (62.1, 95.5) compared to 82.8 (74.3, 88.8) in a comparable pooled population of females. (Data taken from Tables 14 and 16 of the Gardasil label.)

9.3 Duration of Immunity/Efficacy

In females, no correlate of protection has yet been established for prevention of HPV infection and disease, primarily because the low number of breakthrough cases among vaccinees prevents meaningful analysis of a possible correlation between vaccine failure and vaccine-induced anti-HPV titers. Generally, the same phenomenon was observed with regard to prevention of genital warts in males. Therefore, the duration of protection beyond the 3 years demonstrated in the pivotal efficacy study is yet to be determined.

Near the end of the review process, the applicant responded to CBER requests by proposing an extension of the pivotal efficacy study. The extension (020-20) will allow an open label monitoring of vaccine effectiveness in subjects vaccinated as part of the trial. At the end of the current study, subjects in the placebo group will be offered vaccination; hence all subjects eligible for the long-term extension will have received Gardasil. All study subjects who consent to enroll in the study extension will be actively followed for up to 10 years for the occurrence of external genital lesions. Efficacy endpoints include penile/perineal/perianal intraepithelial neoplasia (PIN), penile cancer, and genital warts. CBER concurs with the applicant's commitment to this study extension as one of the postmarketing commitments for the indication in males.

Protocol 018, one of the safety and immunogenicity studies in 9-15 subjects (males and females), continues in an extension (018-10) with visits at 6-month intervals. Submission of the

interim data (5.5 years post-dose 3) is expected Q4 2010. The purpose of the extension is to evaluate the persistence of antibody titers and to assess the long term safety and effectiveness (by genital swabs and biopsy if indicated in subjects starting at 16 years of age) of the vaccine for up to 10 years in subjects participating in the extension. Efficacy endpoints include penile/perineal/perianal intraepithelial neoplasia (PIN), penile cancer, and genital warts.

In addition to the study extensions for 018 and 020, CBER asked the applicant to explore the possibility of amending the Nordic long-term efficacy studies (to which the applicant committed at the time of initial licensure in June 2006) to include prevention of genital warts in males. The applicant determined that for a number of reasons, this approach would not be likely to produce meaningful efficacy data in males, primarily because, unlike screening for cervical precancerous lesions, no screening program and no registry exists for genital warts in males. CBER concurred with the applicant's assessment.

9.4 Overall Efficacy Conclusions

Gardasil is efficacious in the prevention of genital warts caused by HPV 6 and 11 in males 16-26 years of age.

In the pivotal efficacy trial (020), too few cases of genital precancerous lesions occurred to determine efficacy in the prevention of genital cancer or precancerous lesions.

Immunogenicity bridging is an acceptable approach to inferring protection of 9-15 year old males against genital warts. Studies V501-016 and -018 demonstrate that anti-HPV GMTs against each of the 4 VLP types in 9-15 year old males are non-inferior to those in 16-26 year old males.

Antibody titers in 16-23 year old male vaccinees were nominally lower than those in 16-23 year old female vaccinees, although the comparison was a *post hoc* analysis from several different studies. The difference in titers does not appear to translate into a discernible difference in clinical efficacy. In the younger cohort of 9-15 year olds, titers are similar across genders.

No correlate of protection has been established for HPV vaccines in males.

The duration of efficacy of Gardasil in males has not yet been established beyond the 3 years subjects were followed in the pivotal efficacy trial (020). The applicant has committed to a extensions of studies 018 and 020 that will generate clinical efficacy data in the prevention of genital warts up to 10 years.

10.0 Overview of Safety

10.1 Safety Across Trials

The total safety database of male subjects vaccinated in the clinical development program is displayed in Table 22.

Table 22: Overall Extent of Exposure – Male Subjects (Protocols 016, 018, and 020)

Protocol	Age	Gardasil (N)	Placebo* (N)	Total
016	10-15 years	508	0	508
018	9-15 years	564	275	839
020	16-26 years	2025	2030	4055
Total	9-26 years	3097	2305	5402

*Placebo was saline alone in Protocol 018, the only study in the clinical development program in which placebo did not contain adjuvant.

Source: Adapted from - original BLA 125126.1297.0, 2.7.4 – Summary of Clinical Safety, p.15

The results of the AE analyses in the combined males dataset led to overall safety conclusions that were similar to those for 16-26 year old males alone, so they are not repeated here in detail. One notable exception was that the imbalance in the number of SAEs in the Gardasil group compared with the control group was more pronounced in the pooled population; this is addressed in Section 10.1.2 below.

Another exception is that the overall rate of AEs was slightly higher in the younger population. To a large degree, this was driven by a higher rate of injection site AEs in younger males. For example, in the 016 dataset, injection site pain was reported by 357 (71.4%) of the 10-15 year old boys, whereas 1113 (57.2%) reported injection site pain in the 16-26 year old 020 dataset. However, compared directly with 10-15 year old girls enrolled in 016, the 10-16 year old boys had proportionally lower injection site reactions, e.g. injection site pain was reported by 398 (79.4%) of girls.

10.1.1 Analysis of Events Associated with Autoimmune Disorders

Given the theoretical risk of inducing autoimmunity due to the immune activation inherent to vaccination, the applicant performed an analysis on the combined males dataset to evaluate potential autoimmune disorder signaling. No difference was noted between Gardasil and control groups in the overall rate of new onset autoimmune disorders (see Table 23). The applicant will carry out a postmarketing study in males in which will include evaluation of autoimmune events, which will be pre-specified based on age- and gender-stratified epidemiological data.

Table 23: Males 9-26 Years of Age Who Reported an Incident Condition Potentially Indicative of Autoimmune Disorder Regardless of Causality

Conditions	GARDASIL (N = 3092)	AAHS Control* or Saline Placebo (N = 2303)
	n (%)	**n (%)**
Alopecia Areata	1 (0.0)	0 (0.0)
Ankylosing Spondylitis	1 (0.0)	2 (0.1)
Arthralgia/Arthritis/Reactive Arthritis	30 (1.0)	17 (0.7)
Autoimmune Thrombocytopenia	1 (0.0)	0 (0.0)
Diabetes Mellitus Type 1	3 (0.1)	2 (0.1)
Hyperthyroidism	0 (0.0)	1 (0.0)
Hypothyroidism**	3 (0.1)	0 (0.0)
Inflammatory Bowel Disease***	0 (0.0)	2 (0.1)
Myocarditis	1 (0.0)	1 (0.0)
Proteinuria	1 (0.0)	0 (0.0)
Psoriasis	0 (0.0)	2 (0.1)
Vitiligo	2 (0.1)	5 (0.2)
All Conditions	43 (1.4)	32 (1.4)

*AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate
**Hypothyroidism includes the following terms: Hypothyroidism and Autoimmune thyroiditis
***Inflammatory bowel disease includes the following terms: Colitis ulcerative and Crohn's disease
N = Number of individuals who received at least one dose of either vaccine or placebo
n = Number of individuals with specific new Medical Conditions
NOTE: Although an individual may have had two or more new Medical Conditions, the individual is counted only once within a category. The same individual may appear in different categories.

Source: Adapted from - original BLA 125126.1297.0, 1.14.1.3 – Draft Labeling Text, p.12

10.1.2 Serious Adverse Events

In the analysis of SAEs occurring Days 1-15 following vaccination in the safety population pooled from 016, 018, and 020, there was a substantial imbalance in events occurring in the Gardasil group compared with control. See Table 24.

Table 24. Serious Adverse Events, Days 1 to 15 Following Vaccination, Pooled Safety Population

Serious Adverse Event	**Gardasil*** (N=3092)	**Control (AAHS or saline)*** (N=2303)
	n (%)	n (%)
With Serious AEs	**9** (0.3)	**1** (0.0)
abdominal pain	1 (0.0)	0
acute renal failure	1 (0.0)	0
New onset type 1 diabetes mellitus	1 (0.0)	0
localized infection and pain (lower extremity)	1 (0.0)	0
appendicitis	1 (0.0)	0
cellulitis (lower extremity)	1 (0.0)	0
chest pain	1 (0.0)	0
peanut allergy	1 (0.0)	0
varicella infection with seizure	1 (0.0)	0
contusion	0	1 (0.0)

*There were a total of 7 subjects who received a mixed vaccine/placebo regimen that are not counted in the safety tables.

Clinical Reviewer Note: The case history from each of SAEs in the analysis was reviewed and is briefly summarized below. In each case, the reviewer concurred with the investigator assessment of causality as being unlikely related or unrelated to the vaccine.

Case Histories from SAEs in Gardasil recipients listed in Table 24.

Study 016, Clinical Study Report, p.211

Abdominal pain w/ vomiting and diarrhea – 15yo white male presented with symptoms 9 days post-dose 1. Subject was hospitalized, but symptoms resolved and subject was discharged without a definitive diagnosis.

Study 018, Clinical Study Report, p.172

Acute renal failure – 15yo hispanic male presented with finger fracture 5 days post-dose 1. Had external fixation same day; treated with sufentanil, lidocaine, bupivicaine, tetanus toxoid, dipyrone (an NSAID), and ketorolac (toradol). POD#1 (post-dose day 6) - evaluated for nausea, vomiting and dizziness. POD#3 (p dose day 8) - lab results were consistent with acute renal failure. The acute renal failure was thought to be secondary to medications. Symptoms had resolved and labs were normal by 21 days post-dose. Reporting investigator assessment: not related to study vaccine.

New onset type 1 diabetes mellitus – 13yo white male diagnosed with IDDM 2 days post-dose 1. Although the diagnosis was made 2 days post-dose 1, disease onset likely occurred prior to vaccination, as evidenced by a hemoglobin A1C of 6.5% at the time of initial work-up.

Localized infection and pain (lower extremity) – 13yo white male presented 2 days post-dose 2 with infected toe and pain. Symptoms resolved without sequelae (apparently only with soaking toe in soap and water).

Study 020, Clinical Study Report, p.315

Appendicitis – 20yo white male diagnosed with appendicitis on day10 post-dose 3. Uneventful recovery post-appendectomy.

Cellulitis (lower extremity) – 20yo multiracial male diagnosed day3 post-dose 3. Resolved without sequelae.

Chest pain – 20yo white male admitted for non-cardiac chest pain day 12 p dose 3. Discharged same day with diagnosis of non-cardiac chest pain.

Peanut allergy – 18yo black male with history of asthma and peanut allergy ate food with peanut oil and was hospitalized and intubated 12 days post-dose 1. Recovered and discharged from hospital the following day.

Varicella infection with seizure – 22yo black male presented with "chickenpox" day8 post-dose 3 and experienced a febrile seizure. Resolved without sequelae.

10.1.3 Deaths

The deaths that occurred in Protocol 020 are discussed above. (See Section 8.1.13.5). In the remainder of the males dataset, one other death occurred. The subject was a 15 year old white male who had a ventricular arrhythmia 27 days after receiving the second dose of Gardasil. An aneurysm was the suspected cause of death, but the autopsy was inconclusive. The death was assessed as not related to study vaccine by the reporting physician.

10.2 Other Safety Findings

10.2.1 Product-Demographic Interactions

Age

No safety signals were identified in males across the age range (9-26 years) of subjects included in the studies submitted to the BLA. CBER noted that a higher percentage of younger subjects (9-15 years) experienced injection site adverse reactions compared with older subjects (16-26 years), and this was the result primarily of differences in the reporting of injection site pain. See Section 10 – Overview of Safety Across Studies – for details.

Gender

No safety signals were identified in the pre-licensure data for either males or females. However, the safety profile with regard to injection site adverse reactions appears to be slightly different in males compared with females. As displayed in Table 25, rates of injection site reactions are higher in females compared with males. No other differences were noted in the safety data from males compared with the data from females, but it is important to emphasize that a systematic comparison of gender differences was not a primary focus of this review.

Table 25. Injection Site Adverse Reactions* in Males and Females 9-26 Years of Age, Pooled Safety Populations*, Days 1-5 Following Vaccination

Adverse Reaction	Females, 9-26 Years of Age			Males, 9-26 Years of Age		
	Gardasil (N = 5088) %	AAHS Control (N = 3470) %	Saline Placebo (N = 320) %	Gardasil (N = 3092) %	AAHS Control (N = 2029) %	Saline Placebo (N = 274) %
Pain	83.9	75.4	48.6	61.5	50.8	41.6
Swelling	25.4	15.8	7.3	13.9	9.6	8.2
Erythema	24.7	18.4	12.1	16.7	14.1	14.5

*The three most common reactions for both males and females are displayed.
**Safety data was pooled from 6 clinical studies in the Gardasil clinical development program, three of which included males (01, 018, and 010)
Source: Adapted from Tables 1 and 2, Gardasil package insert.

10.2.2 Product-Product Interactions

Safety and immunogenicity of Gardasil when administered concomitantly with Recombivax HB were evaluated in females, and information in approved labeling supports this concomitant use. However, CBER has not reviewed data supporting concomitant use of Gardasil with any other vaccine in males.

10.2.3 Human Reproduction and Pregnancy Data

Section 4.2 summarizes the reproductive toxicology study in male rats that was submitted to the BLA supplement. Human studies were not designed or powered to evaluate the effect on male fertility/reproduction.

10.2.4 Person-to-Person Transmission, Shedding

Gardasil is a recombinant, non-infectious vaccine, which is produced in yeast in the absence of the HPV genome. The issue of transmission/shedding is therefore not applicable.

10.2.5 Post-Marketing

The ongoing postmarketing evaluation of the safety of Gardasil in females is summarized at FDA's website:
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm179549.htm

The postmarketing experience in males is limited to the use of Gardasil outside the U.S. CBER requested a report on all the adverse events in males reported to the New Worldwide Adverse Experience System (NWAES) database maintained by the applicant. At the time of the report (Dec 2008), the database contained 171 reports involving males, of which 7 were serious. The most common report overall was "off label use". No pattern suggesting a safety signal was apparent in the review of the events overall or in the review of the subset of events identified as serious.

No safety signals were identified in males in the pre-licensure data submitted to the BLA supplement. However, because evidence suggests that response to vaccination, including reactogenicity, differs by gender (Cook et al), CBER has requested that the applicant perform a Phase IV safety surveillance study in males, and the applicant has committed to conducting the study. The final details had not been established at the time of the completion of this review.

10.3 Safety Conclusions

In general, Gardasil appears to have an acceptable safety profile in healthy 9-26 year old males.

No safety signals were identified in the pre-licensure data in males. However, evaluation of the safety of Gardasil in a larger, broader population of males is appropriate. The applicant has committed to conducting a Phase IV study in males, the final details of which are pending at the time of this review.

11.0 Directions for Use

Directions for use are specified in detail in the Gardasil label.

12.0 Dose Regimens and Administration

Gardasil should be administered intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, 6 months.

13.0 Special Populations

13.1 Pregnancy

Not applicable to the review of this BLA supplement.

13.2 Geriatric Use

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

13.3 Immunocompromised Patients

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

13.4 Pediatrics

Effective upon approval of this BLA supplement, Gardasil has been adequately studied and labeled for use in children 9 years of age and older.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application for a new indication is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups. The applicant requested a partial waiver from

the requirements of PREA for children 0-8 years of age. The review team agreed to grant the waiver request because necessary studies are impossible or highly impractical and the product is not likely to be used in a substantial number of children 8 years of age and younger. The Pediatric Review Committee (PeRC) concurred with this decision.

14.0 Conclusions – Overall

Data submitted to the BLA supplement demonstrate that Gardasil is efficacious in the prevention of genital warts caused by HPV 6 and 11 in males 16-26 years of age.

Data from studies 016 and 018 demonstrate that anti-HPV GMTs against each of the 4 VLP types in 9-15 year old males are non-inferior to those in 16-26 year old males. Immunogenicity bridging provides a basis for inferring protection of 9-15 year old males against genital warts.

In the pre-licensure safety database, which includes approximately 5400 males, no safety signals have been identified. The applicant has committed to a Phase IV safety surveillance study in males.

The available safety and efficacy data support the approval of Gardasil for use in males 9-26 years of age for the prevention of genital warts caused by HPV types 6 and 11.

15.0 Recommendations

Gardasil is recommended for approval for use in males 9-26 years of age for the prevention of genital warts caused by HPV types 6 and 11.

16.0 Labeling

CBER communicated with the applicant 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.