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# 125126/1895.0 – anal cancer indication for GARDASIL

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

Date of submitted application: February 26, 2010
Date of completed review: December 6, 2010

From: Jeffrey N. Roberts, M.D.
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To: BLA #125126/1895

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1 General Information

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

1.1.1 sBLA #:

125126/1895.0

1.1.2 Related IND #(s):

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

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

Jeff Roberts, M.D.
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HFM-475

1.1.4 Submission Received by FDA:

February 26, 2010

1.1.5 Review Completed:

1.2 Product

1.2.1 Proper Name or Established Name:

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

1.2.2 Trade Name:

Gardasil

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

1.2.3 Abbreviations Used in This Review

Abbreviation	Definition
AC	anal cancer
AIN	anal intraepithelial neoplasia
cLIA	competitive luminex immunoassay
EGL	external genital lesions
FAS	full analysis set analysis population
GHN	generally HPV naïve analysis population
HM	heterosexual males

hrHPV	high risk Human Papillomavirus (oncogenic HPV types)
MSM	men having sex with men
PI	persistent infection
PPE	per protocol efficacy analysis population
qHPV	Quadrivalent HPV vaccine, or Gardasil
sBLA	Biologics License Application Supplement
VLP	Virus-like particles

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

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

The product does not contain a preservative or antibiotics.

Table 1: Contents of Each 0.5mL Dose of Gardasil

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

* Prepared in water for injection

1.3 Applicant:

Merck Research Laboratories

1.4 Indication(s):

1.4.1 Current Indications for Gardasil:

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

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

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

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

- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

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

1.4.2 Indication for Gardasil Proposed Under This sBLA:

For **girls and women 9 through 26 years**, anal cancer would be added to the list of cancers prevented; and anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 would be added to the list of dysplastic lesions prevented.

For **boys and men 9 through 26 years**, the indication would be revised as follows:

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:
- Anal 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:
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

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

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

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3 Executive Summary

Gardasil is currently licensed for prevention of cervical, vulvar and vaginal cancer and the associated precancerous lesions in females 9 to 26 years of age and for the prevention of genital warts in males and females 9 to 26 years of age. With this Biologic License Application supplement (sBLA), the applicant is seeking approval for the new indication of prevention of anal cancer and its associated precancerous lesions (anal intraepithelial neoplasia (AIN) grades 1, 2, and 3) in both males and females.

The pivotal Phase 3 trial submitted to the sBLA was a double-blind, placebo-controlled, study in which male subjects were randomized 1:1 to receive Gardasil or aluminum adjuvant-containing saline (herein referred to as AAHS control). Subjects were followed for a number of clinical endpoints associated with genital HPV infection. Of the 4065 males recruited and randomized, 602 were men who have sex with men (MSM) who underwent more extensive surveillance for anal pathology, including rectal exam, anal cytology, anal HPV PCR, and anoscopy with anal biopsy if indicated. The MSM subjects were then evaluated in a separate analysis referred to as the MSM Substudy, which comprises the pivotal data evaluated for this application.

On the primary composite endpoint of prevention of HPV 6/11/16/18-related AIN (any grade) and anal cancer, the point estimate of efficacy was **78%** with 95% CI (40, 93). On the advanced dysplasia endpoint of AIN2+, efficacy was **75%** with 95% CI (9, 95).

The safety profile of Gardasil in males was evaluated by CBER (and discussed at the September 2009 Vaccines and Related Biological Products Advisory Committee (VRBPAC)) in the context of the previous sBLA submission for the indication of prevention of genital warts in males. No new safety data in males were submitted to this application.

The applicant submitted data from clinical studies demonstrating that antibody responses in an adolescent male population (9 to 15 years of age) were non-inferior to those of older male subjects. In the previous application, these data were used to infer effectiveness in prevention of genital warts in 9 to 15 year olds based on the antibody response comparison to the efficacy study population (16 to 26 years of age). A similar request to bridge the AIN and anal cancer indication in both genders is being made in the context of this application.

A VRBPAC meeting was held on 17Nov2010 to discuss the efficacy data, particularly use of the AIN endpoint to assess efficacy in the prevention of anal cancer. In addition, because the applicant is requesting that the AIN and anal cancer indication be extended to females based on clinical data in males only, CBER sought input on this approach to the female indication. The VRBPAC consensus was that that the data support an indication for the prevention of AIN and anal cancer in males and that the rationale for extrapolating efficacy to females is appropriate and scientifically sound.

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 through 8 years of age. The review team agreed to grant the waiver request because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. The reason for the review team's conclusion was that evidence indicates that the rare cases of HPV-related disease that occur in this age group (0 to 8 years) are not vaccine-preventable. The Pediatric Review Committee (PeRC) concurred with this decision. Effective upon approval of the supplement, the product will be lableled for use in children 9 years of age and older for the prevention of AIN and anal cancer.

The applicant submitted a pharmacovigilance plan that included an update on their postmarketing safety surveillance efforts, including a descriptive, observational study in 44,000 males 9 through 26 years of age. No safety signals have been identified in the pre-licensure data. No revisions to the postmarketing safety surveillance program are recommended.

Based on the review of the data submitted to the BLA supplement, the clinical reviewer recommends approval of Gardasil for use in individuals 9 through 26 years of age for the prevention of anal intraepithelial neoplasia and anal cancer caused by HPV types 6, 11, 16, and 18.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)

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

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

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

4.2 Animal Pharmacology/Toxicology

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

4.3 Statistics

The CBER statistical reviewer concluded that the data presented in the application support that:

- Gardasil is indicated in males 9 through 26 years of age for the prevention of AIN grades 1, 2, and 3 caused by HPV types 6, 11, 16 and 18; and
- Gardasil is indicated in males 9 through 26 years of age for the prevention of anal cancer caused by HPV types 16 and 18.

The reviewer noted that the MSM substudy data support the proposed indications for the prevention of AIN 1+ and anal cancer in men, but no data were submitted to support extension of these indications to women. The reviewer deferred to the judgment of the clinical reviewer, acknowledging that the decision about whether to extend the indications to women will be made based on evaluation of a broader set of data, e.g., histology, pathophysiology, and epidemiology.

4.4 Pharmacovigilance

CBER review of the pharmacovigilance plan noted the status of three major postmarketing regulatory commitments: an active surveillance study in 189,000 female Gardasil recipients (complete), a pregnancy registry (ongoing), and an active surveillance study in 135,000 male Gardasil recipients (planning phase). The reviewer assessed the identified risks and the potential risks and commented on the responsive proposed and ongoing actions.

The reviewer noted that since the vaccine is currently indicated in both males and females 9 through 26 years of age, the new indication is not expected to fundamentally change the target population. The reviewer concluded that the pharmacovigilance plan is adequate. No further regulatory action for postmarketing safety surveillance was recommended.

5 Clinical and Regulatory Background

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

Anal cancer is relatively uncommon in the general population. It represents about 4% of all lower GI tract cancers in the U.S. (Partridge and Koutsky). The American Cancer Society estimates that the annual incidence of anal cancer in the U.S. is ~5300 cases, with a gender ratio of approximately 40% to 60%, male to female, respectively (Jemal et al). For context, the annual incidence of breast cancer is ~194,000 cases.

However, the incidence of anal cancer has increased considerably over the past few decades. The age adjusted rates from 1975 to 2007 doubled from 0.8 to 1.6 per 100,000 (www.seer.cancer.gov). Although females continue to have a higher incidence overall, certain male populations, such as those with HIV infection and those with history of receptive anal intercourse, are known to have extremely high relative risk for anal cancer (Palefsky and Rubin).

In contrast to cervical cancer, for which an established screening program has decreased the incidence substantially, there is currently no consensus regarding how best to implement screening for anal cancer. Some advocate anal cytology at regular intervals for high risk populations, such as HIV+ men who have sex with men (MSM), women with history of cervical cancer, and transplant recipients, but the efficacy and cost-effectiveness of anal cytology, especially in a broader population, are far from established.

Even if a universal screening program could be effectively implemented, patients with a positive anal cytology would continue to face a difficult clinical course. Excision and/or ablative therapy of dysplastic lesions in the anus can lead to post-procedural complications such as pain, bleeding, and anal stenosis. In addition, unlike treatment for cervical dysplastic lesions, the entire transformation zone of the anal canal cannot be safely removed; therefore, recurrences are more frequent and pervasive.

The Association Between Anal HPV Infection and Anal Cancer

Abundant evidence has established a link between anal infection with oncogenic, high risk HPV types (hrHPV) and anal cancer. The percentage of anal cancers associated with HPV is ~90% (Parkin and Bray). The rate of detection of hrHPV appears to increase with increasing severity of dysplasia of anal lesion biopsy specimens, i.e., AIN grades 1, 2, and 3 (Wong et al). Perhaps even more than cervical cancer, HPV 16 and 18 predominate in both precancerous lesions and anal cancer. For example, among HPV-positive cancerous lesions, up to 87% are HPV 16-positive and ~9% are 18-positive (Giuliano et al).

The epithelium of the anal canal undergoes a transition from a simple columnar epithelium to a zone of non-keratinized stratified squamous epithelium that is in some ways analogous to the cervical transformation zone. Similarities have also been noted between cervical and intra-anal cancers in pathophysiological characteristics, such as basaloid features, adjacent intraepithelial neoplasia, and lack of keratinization (Frisch et al). This led Frisch et al to make the following observation:

> *"Like cancer of the uterine cervix, the development of cancer of the anal canal may require infection with hrHPV, whereas a dual etiology of perianal skin cancers bears parallels to vulvar and penile cancers."*

Anal HPV Infection and Anal Cancer in Males and Females

Receptive anal intercourse is an established risk factor for acquisition of anal HPV infection in both genders. However, anal HPV infection is not uncommon among individuals with no history of anal intercourse. For example, in one cohort of HIV-negative men who have sex with women (MSW), ~88 % of subjects denied ever having had anal or oral sex with a man, yet among these

subjects, 11% were found to have anal HPV infection (Nyitray et al). In a study of HIV-negative women, 27% were positive for anal HPV and 29% were positive for cervical HPV (Hernandez et al), and the data suggested that many of the anal HPV infections occurred in the absence of anal intercourse. In some cases, acquisition of anal HPV in the absence of receptive anal intercourse may in both genders result from autoinoculation via viral particles shed from an active genital infection.

One caveat common to these studies is that they rely on self-reported sexual behaviors. Therefore, the proportion of anal HPV acquired in the absence of receptive anal intercourse has yet to be definitively determined. Regardless, the association between anal HPV infection and anal cancer appears to be robust regardless of the mode of acquisition. For example, in a case control study of anal cancer patients in which 86% to 89% of cancers were HPV-positive, 53% of men and 66% of women denied any history of anal intercourse (Daling et al).

An important issue in the evaluation of this sBLA is the extent to which there are differences between males and females in the natural history (e.g., progression of AIN) of anal HPV infection. CBER reviewers are not aware of data to suggest that there are fundamental differences between males and females, in terms of anal anatomy, histology, or physiology. There are not, therefore, reasons to presume, *a priori,* that there are fundamental differences in the pathophysiology of anal HPV infection. The data are clear that specific behavioral (e.g., receptive anal intercourse) and immune (e.g., HIV status) variables are strongly correlated with risk of HPV acquisition and progression of HPV-associated neoplasia. However gender, in and of itself, does not appear to be one of the factors that modulate these risks to any substantial degree. In addition, the percentages of anal cancers associated with HPV are quite similar in men compared with women – 89.6% and 90.0%, respectively (Parkin et al).

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

At the time of submission of the sBLA, Cervarix was the only other HPV vaccine licensed in the U.S. Although Cervarix would likely have an effect similar to Gardasil in the prevention of HPV 16- and 18-associated AIN and anal cancer, no studies have been conducted with Cervarix to evaluate prevention of anal pathology.

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, as well as the current safety data, 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 3 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: 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 in females.

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 December: In a pre-sBLA meeting for the males indication, Merck presented unblinded AIN endpoint data from the MSM substudy. CBER considered this an interim analysis and recommended adjustment for Type 1 error in the final analysis. Merck complied.

2009 October: Approval of sBLA for the indication of prevention of genital warts in males.

2010 February: Current sBLA submitted.

5.5 Vaccines and Related Biological Products Advisory Committee (VRBPAC)

During the review process CBER determined that a Vaccine and Related Biological Products Advisory Committee (VRBPAC) should be convened to discuss effectiveness of vaccinating males and females with Gardasil for prevention of anal dysplasia and anal cancer. The VRBPAC was held on Novermber 17, 2010. The review team asked the Committee to comment on the following:

1) the strength of the data to support an indication for the prevention of AIN and anal cancer in males, and
2) the scientific rationale for extrapolating efficacy in the prevention of AIN and anal cancer to females.

As a whole, the judgment of the Committee was that the data support an indication for the prevention of AIN and anal cancer in males and that the rationale for extrapolating efficacy to females is appropriate and scientifically sound. Several members expressed a desire to engage in more discussion regarding safety of the product, but it was recognized that the population for whom Gardasil is indicated would not change should the additional indication for prevention of AIN and anal cancer be approved.

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

6.1 Material Reviewed

6.1.1 BLA Supplement 125126/1895 - Files Reviewed

V501-020 – Clinical Study Report on Completed MSM Substudy
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

Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, Carter JJ, Porter PL, Galloway DA, McDougall JK. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer. 2004 Jul 15;101(2):270-80.

Frisch M, Fenger C, van den Brule AJ, Sørensen P, Meijer CJ, Walboomers JM, Adami HO, Melbye M, Glimelius B. Variants of squamous cell carcinoma of the anal canal and perianal skin and their relation to human papillomaviruses. Cancer Res. 1999 Feb 1;59(3):753-7.

Giuliano AR, Tortolero-Luna G, Ferrer E, Burchell AN, de Sanjose S, Kjaer SK, Muñoz N, Schiffman M, Bosch FX. Epidemiology of human papillomavirus infection in men, cancers other than cervical and benign conditions. Vaccine. 2008 Aug 19;26 Suppl 10:K17-28.

Hernandez BY, McDuffie K, Zhu X, Wilkens LR, Killeen J, Kessel B, Wakabayashi MT, Bertram CC, Easa D, Ning L, Boyd J, Sunoo C, Kamemoto L, Goodman MT. Anal human papillomavirus infection in women and its relationship with cervical infection. Cancer Epidemiol Biomarkers Prev. 2005 Nov;14(11 Pt 1):2550-6.

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009 Jul-Aug;59(4):225-49.

Nyitray AG, Smith D, Villa L, Lazcano-Ponce E, Abrahamsen M, Papenfuss M, Giuliano AR. Prevalence of and risk factors for anal human papillomavirus infection in men who have sex with women: a cross-national study. J Infect Dis. 2010 May 15;201(10):1498-508.

Palefsky JM, Rubin M. The epidemiology of anal human papillomavirus and related neoplasia. Obstet Gynecol Clin North Am. 2009 Mar;36(1):187-200.

Parkin DM, Bray F. The burden of HPV-related cancers. Vaccine. 2006 Aug 31;24 Suppl 3:S3/11-25.

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

Wong AK, Chan RC, Aggarwal N, Singh MK, Nichols WS, Bose S. Human papillomavirus genotypes in anal intraepithelial neoplasia and anal carcinoma as detected in tissue biopsies. Mod Pathol. 2010 Jan;23(1):144-50.

6.1.3 Post-Marketing Experience

In accordance with the terms of licensure in October 2009 of the indication of prevention of genital warts in males, the applicant is conducting a postmarketing safety study in males. The status of this and the other postmarketing studies to which the applicant has committed can found at http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

The applicant included in this sBLA submission a pharmacovigilance plan (PVP), which documented progress on each of their postmarketing commitments and updated the status of all their ongoing safety surveillance efforts in males and females. See Section 4.4 for a summary of CBER's review of the PVP.

6.2 Clinical Studies

The only study submitted to the sBLA was the end of study report for Protocol 020, which presents the primary analysis of the MSM Substudy efficacy endpoint. In addition to the MSM Substudy analysis, the final study report provides updated analyses of the primary and secondary efficacy endpoints, safety, and immunogenicity.

6.3 Good Clinical Practices (GCP) and Data Integrity

Results of data audits and bioresearch monitoring inspections during the review of the sBLA for the original males indication did not reveal any problems that impact the quality or integrity of the data submitted. CBER determined that further bioresearch monitoring inspections were not necessary for the review of the current sBLA.

6.4 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 Human Pharmacology

See Section 8.

8 Clinical Studies

8.1 Study V501-020 – MSM Substudy

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.

Each subject underwent genitourinary exam, had specimens collected for HPV PCR, and underwent external genital lesion biopsy, if indicated, at Month 7, 12, 18, 24, 30 and 36. Sera were collected for immunogenicity analyses 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 total of 4065 males were recruited and randomized, of whom 602 were men who have sex with men (MSM). The MSM subgroup underwent more extensive surveillance (for anal pathology, including rectal exam and anal cytology and HPV PCR at baseline and at Month 7, 12, 18, 24, 30 and 36, and anoscopy and anal biopsy if indicated). This subgroup was then analyzed separately in what is referred to as the MSM Substudy.

Unless otherwise indicated, this review will focus exclusively on the MSM Substudy data and outcomes.

8.1.2 Objectives

MSM SubstudyPrimary 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.

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 Eligibility Criteria

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.

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.

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

8.1.5 Endpoints

8.1.5.1 Efficacy Endpoints

Primary MSM Efficacy Endpoint
The primary efficacy endpoint within the MSM substudy is HPV 6-, 11-, 16-, 18-related AIN or anal cancer. This endpoint occurred if, on a single biopsy or excised tissue block, the following conditions were met:

- the Pathology Panel consensus diagnosis was condyloma acuminata, AIN 1, AIN 2, AIN 3, or anal 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.

To avoid ascertainment bias, any cases of AIN or anal cancer detected via HRA performed as a result of external genital lesions in the perianal region were not counted in the per protocol analysis of the MSM substudy.

In the analysis of this endpoint, cases were counted beginning at 4 weeks post-dose 3 (i.e., after Month 7).

> **Clinical Reviewer Note:** The diagnoses of condyloma acuminatum in an intra-anal specimen are grouped under AIN 1. Though they are low-grade lesions which have a histopathologic appearance similar to AIN 1, condyloma acuminatum are simply warts; they are unlikely to progress to advanced dysplasia; and their inclusion in an anal neoplasia // anal cancer endpoint is of questionable relevance. Therefore, CBER: (1) examined the proportion of condylomatous (warts) versus non-acuminate lesions that composed the AIN 1 endpoint in each analysis (see Tables 5 and 6 below), and (2) placed emphasis on the AIN 2+ endpoint analyses.

Secondary Efficacy 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.

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.

8.1.6 Surveillance/Monitoring

The surveillance and monitoring for the MSM subjects in the trial is listed in Table 2.

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

Table 2: Study Procedures for MSM Subjects in V501-020

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 ¶	+			+	+	+	+	+	+
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	+			+	+	+	+	+	+
Anal cytology using ThinPrep™ methodology§ ‖	+			+	+	+	+	+	+
Intra-anal wetted swab for HPV PCR	+			+	+	+	+	+	+
Rectal swab for gonorrhea culture	+				+		+		+
Rectal swab for chlamydia culture	+				+		+		+
Rectal Exam	+			+	+	+	+	+	+
Anoscopy (if indicated)§§	+			+	+	+	+	+	+
External genital lesion biopsy (if indicated)§				+	+	+	+	+	+
Treatment for external genital lesions (if indicated)				+	+	+	+	+	+
High resolution anoscopy and anal biopsy (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#‖‖	+				+		+		+
Serum for HIV#‖‖	+				+		+		+
Swab for HSV culture (if indicated)‖‖	+			+	+	+	+	+	+
Urine for gonorrhea PCR or LCR or SDA (if indicated)‖‖	+			+	+	+	+	+	+
Urine for chlamydia PCR or LCR or SDA (if indicated)‖‖	+			+	+	+	+	+	+
Vaccination††	+	+	+						
Clinical follow-up for safety	+	+	+	+					

Visit	1	2	3	4	5	6	7	8	9
		Months							
Event/Test	D 1	2	6	7	12	18	24	30	36
Clinical contact visit documentation‡‡	+	+	+	+	+	+	+	+	+

Note: Any test may have been 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.

‡ 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.

‖ High resolution anoscopy was performed, if the subjects received an anal cytology result of ASC-US, ASC-H, AGC, LSIL, HSIL or Cancer. A diagnosis of an HPV-related perianal lesion (e.g., perianal condyloma), as confirmed by the SPONSOR central laboratory ALSO constituted a reason for referral to HRA. If a histologically confirmed HPV-related perianal lesion was diagnosed as a consequence of a simple anoscopy, then the subject did not require another referral to anoscopy.

¶ High resolution anoscopy was performed on all subjects enrolled in the MSM substudy at the Month 36 visit.

Serum for HIV and Syphilis was to be performed at Day 1 and Month 12, 24, 36, and at any time point throughout the study if clinically indicated.

†† 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.

§§ If lesions were noted on the rectal exam, a simple anoscopy was performed to visualize the intra-anal region.

‖‖ Testing to be performed by the local laboratory affiliated with the Investigative Site. Urine testing for gonorrhea and chlamydia did not replace rectal swab testing for gonorrhea and chlamydia.

¶¶ 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 sBLA 125126/1895; Clinical Study Report V503-020, p.74

8.1.7 Statistical Considerations

This study employed a fixed event design. The primary efficacy analysis was scheduled to be conducted when at least 32 cases of the primary endpoint had been observed and the MSM substudy efficacy analyses was scheduled to be conducted when at least 17 cases of the MSM substudy endpoint had been observed. For the MSM substudy, a **multiplicity adjustment** was applied to the tests of the MSM substudy efficacy hypothesis because the primary efficacy analysis was performed prior to the MSM substudy efficacy analysis and an interim summary of the MSM endpoint was conducted at the time of the primary efficacy analysis.

The MSM Substudy null hypothesis states that vaccine efficacy against HPV 6, 11, 16 or 18-related AIN or anal cancer is 0% or less. The alternative hypothesis is that vaccine efficacy against this endpoint is greater than 0%.

$$H0: \lambda \leq 0 \text{ vs. } H1: \lambda > 0$$

where λ is vaccine efficacy (defined as [1 – Relative Risk]*100%).

A point estimate for vaccine efficacy was provided together with an exact two-sided **95.1**% confidence interval. The corresponding 95.1% 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. A one-sided test of the null hypothesis that vaccine efficacy (VE) was ≤ 0% at the $\alpha = 0.0245$ level of significance was used to address MSM endpoint hypotheses.

8.1.8 Results

8.1.8.1 Populations Enrolled/Analyzed

A total of 602 MSM subjects were enrolled in the study and randomized, of whom 598 (99%) received at least one vaccination and 555 (92%) received all three vaccinations. Of the randomized subjects, 53 (9%) of subjects discontinued the study before completing the vaccination period (Day 1 through Month 7). The vast majority of discontinuations were "lost to follow-up"; discontinuation due to clinical AE was <1%. Overall, 120 subjects discontinued before completion of the three year trial; again, the vast majority were "lost to follow-up".

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:

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.

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.*

Safety Analysis Population

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.

8.1.8.3 Subject Demographics/Characteristics

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

Table 3: Demographics of MSM Subjects Enrolled

	Total (N = 602)
	n(%)
Region	
Asia-Pacific	89 (14.8)
Europe	122 (20.3)
Latin America	132 (21.9)
North America	259 (43.0)
Race/Ethnicity	
Asian	33 (5.5)
Black	42 (7.0)
Hispanic American	149 (24.8)
White	363 (60.3)
Other	15 (2.5)

Source: Adapted from - original sBLA 125126/1895; Clinical Study Report V503-020, p.153

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

Table 4: Baseline Characteristics of MSM Subjects Enrolled

Characteristic	Gardasil (N = 301)	AAHS control (N=301)
	n(%)	n(%)
Age (mean in years)	22.2	22.1
Age at first sexual intercourse (mean in years)	17.9	17.9
Anal pap at Day 1		
Negative for SIL	241 (90.3)	233 (87.9)
ASC-US	12 (4.5)	11 (4.2)
LSIL	14 (5.2)	21 (7.9)
PCR status at Day 1		
Pos(+) for 6, 11, 16, or 18	86 (29.2)	94 (31.8)
Serostatus on Day 1		
Pos (+) for 6, 11, 16, or 18	61 (21.5)	71 (24.1)
Pos (+) by serology or PCR to 6, 11, 16, or 18	107 (36.5)	122 (41.6)

Source: Adapted from - original sBLA 125126/1895; Clinical Study Report V503-020, p.154, 173, 175

Clinical Reviewer Note: Because of the eligibility criteria that excluded MSMs with >5 lifetime sexual partners, HIV positive status, and those with any history of anogenital warts, the general population of MSMs 16 through 26 years of age likely has a relatively greater HPV-related infection and disease burden than the population recruited to this study.

This is an important clinical consideration for estimating the population impact of the vaccine in the MSM population. Even in this screened population, the rates of pre-existing vaccine type infection and anal pap abnormalities (~30% and ~10%, respectively), were high.

8.1.8.4 Efficacy Endpoints/Outcomes

8.1.8.5 Primary Endpoint: Efficacy Against HPV 6/11/16/18-Related AIN and Anal Cancer

Per Protocol Efficacy (PPE) Population

The results of the efficacy endpoint analyses in the PPE population are displayed in Table 5. The primary efficacy objective endpoint (AIN and AC) and the AIN2+ data are in bold.

Table 5: Efficacy Against HPV 6/11/16/18-Related AIN and Anal Cancer (AC) in the MSM PPE Population

Endpoint	Gardasil (N=299)		AAHS control (N=299)		Efficacy % (95%CI)
	n	# of cases	n	# of cases	
AIN and AC	194	**5**	208	**24**	**78%** (40, 93)
AIN1	194	4	208	16	73% (16, 93)
Condyloma acuminatum	194	0	208	6	100% (8, 100)
Non-acuminate	194	4	208	11	60% (-34, 91)
By HPV type					
HPV 6-Related AIN and AC	141	3	144	10	68% (-26, 94)
HPV 11-Related AIN and AC	141	0	144	6	100% (9, 100)
HPV 16-Related AIN and AC	167	2	170	6	65% (-92, 96)
HPV 18-Related AIN and AC	173	0	193	4	100% (-70, 100)
AIN2 or worse	194	**3**	208	**13**	**75%** (8, 95)
AIN3	194	2	208	6	64% (-103, 96)
Anal Cancer	194	0	208	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
Source: Adapted from - original sBLA 125126/1895; Clinical Study Report V503-020, p.199

Full Analysis Set (FAS) Population

The results of the efficacy endpoint analyses in the FAS population are displayed in Table 6. The primary efficacy objective endpoint (AIN and AC) and the AIN2+ data are in bold.

Table 6: Efficacy Against HPV 6/11/16/18-Related AIN and Anal Cancer (AC) in the MSM FAS Population

Endpoint	Gardasil (N=299)		AAHS control (N=299)		Efficacy % (95%CI)
	n	# of cases	n	# of cases	
AIN and Anal Cancer	275	**38**	276	**77**	**50%** (26, 67)
AIN1	275	31	276	62	50% (21, 68)
Condyloma acuminatum	275	13	276	31	57% (16, 80)
Non-acuminate	275	27	276	48	43% (7, 66)
AIN2 or worse	275	**18**	276	**39**	**54%** (18, 75)
AIN3	275	10	276	19	46.8% (-20, 80)
Anal Cancer	275	0	276	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 sBLA 125126/1895; Clinical Study Report V503-020, p.215

8.1.8.6 Analysis of Efficacy Stratified by Baseline Characteristics

The results of the primary efficacy endpoint analysis (prevention of HPV 6/11/16/18-Related AIN and AC) in the Per Protocol Efficacy (PPE) population stratified by subject baseline characteristics are displayed in Table 7.

Table 7: Efficacy Against HPV 6/11/16/18-Related AIN and Anal Cancer in the MSM PPE Population

Subject Characteristic	Gardasil (N=299)		AAHS control (N=299)		Efficacy % (95%CI)
	n	# of cases	n	# of cases	
HPV 6/11/16/18-related AIN and AC					
15-20 years old	45	2	63	8	64% (-76, 96)
21-27 years old	149	3	145	16	82% (36, 97)
Circumcised	75	0	87	12	100% (57, 100)
Not Circumcised	119	5	121	12	58% (29, 88)
PCR(-) to all vaccine types	148	3	160	18	82% (37, 97)
PCR(+) to at least one vaccine type	46	2	48	6	67% (-83, 97)
PCR(+) to the vaccine type being analyzed	56	21	63	21	-19.7 (-130, 38)

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the PPE population eligible for the respective analysis
Source: Adapted from - original sBLA 125126/1895; Clinical Study Report V503-020, p.219, 315

> **Clinical Reviewer Note:** The caveats are substantial when evaluating this kind of *post hoc* analysis, in which the numbers are relatively small. For example, the wide, overlapping confidence intervals were noted. However, the result in the last row was particularly noteworthy: among subjects who were infected with a vaccine type at the time of vaccination, there is no evidence of prevention of AIN caused by that vaccine type. This reinforces the concept that the vaccine has no therapeutic efficacy.

8.1.8.7 Analysis of Efficacy Regardless of HPV Detection

To evaluate the potential population impact, a series of analyses were conducted to examine prevention of AIN and anal cancer regardless of HPV detection. Table 8 displays those analyses in the generally HPV naïve (GHN) and full analysis set (FAS) populations.

Table 8: Efficacy Against AIN and Anal Cancer, Regardless of HPV Detection, in the MSM Population

Endpoint	Gardasil (N=299)		AAHS control (N=299)		Efficacy % (95%CI)
	n	# of cases	n	# of cases	
GHN Population					
AIN and Anal Cancer	129	12	126	28	55% (8, 79)
AIN2+	129	8	126	18	53% (-15, 82)
FAS Population					
AIN and Anal Cancer	275	74	276	103	26% (-1, 46)
AIN2+	275	44	276	59	24% (-14, 50)

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the respective population eligible for the respective analysis
GHN = generally HPV naïve; FAS = full analysis set.
Source: Adapted from - original sBLA 125126/1895; Clinical Study Report V503-020, p.280-289.

> **Clinical Reviewer Note:** The GHN analysis models the potential vaccine efficacy among sexually naïve (and therefore, HPV naïve) individuals. In other words, the GHN analysis estimates how effective the vaccine may be for individuals 9 to 15 years of age. In clinical practice, individuals are not likely to be screened for HPV infection prior to receipt of the vaccine. Therefore, the FAS analysis represents the best estimate of efficacy among individuals 16 to 26 years of age.

8.1.8.8 Analysis of Efficacy Against Persistent and Incident Infection

In the entire study population of 4055 from V501-020, persistent infection (PI) was a composite of cases of genital infection among all subjects and intra-anal infection among MSMs. The following is the analysis of prevention of intra-anal infection among MSMs. Table 9 displays point estimates for prevention of HPV 6/11/16/18-related PI, both as a composite and individually.

Table 9: Efficacy Against HPV 6/11/16/18-Related Intra-Anal Persistent Infection (PI) in the MSM PPE Population

HPV 6/11/16/18-Related Intra-Anal Persistent Infection	Gardasil (N=299)		AAHS control (N=299)		Efficacy % (95%CI)
	n	# of cases	n	# of cases	
HPV 6/11/16/18-Related PI	193	2	208	39	95% (80, 99)
By HPV Type					
HPV 6-Related PI	140	1	144	13	92% (47, 100)
HPV 11-Related PI	140	0	144	5	100% (-16, 100)
HPV 16-Related PI	166	1	170	16	94% (60, 99)
HPV 18-Related PI	172	0	193	10	100% (52, 100)

N = Number of subjects randomized to the respective vaccination group.
n = Number of subjects in the PPE population eligible for the respective analysis
Source: Adapted from - original sBLA 125126/1895; Clinical Study Report V503-020, p.266

8.1.8.9 Immunogenicity

See also Section 9 Overview Across Trials.

The primary immunogenicity endpoints assessed were as follows: (1) anti-HPV geometric mean titers (GMTs); and (2) seroconversion rate (SCR) at 4 weeks post-dose 3.

In the previous sBLA, immunogenicity data through Month 24 from Study 020 was submitted. Immunogenicity data is updated in this submission to include the Month 36 (end of study) data. See Tables 10 and 11 for anti-HPV GMTs and SCRs, respectively, in males through Month 36.

Table 10: 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	1,092	< 7	(<7, <7)	1,108	< 7	(<7, <7)
Month 7	1,092	447.6	(422.6, 474.1)	1,108	< 7	(<7, <7)
Month 24	941	79.8	(75.8, 84.1)	949	< 7	(<7, <7)
Month 36	847	71.5	(67.5, 75.8)	834	< 7	(<7, <7)
Anti-HPV 11						
Day 1	1,092	< 8	(<8, <8)	1,107	< 8	(<8, <8)
Month 7	1,092	624	(594.1, 655.4)	1,107	< 8	(<8, <8)
Month 24	941	94.6	(90.0, 99.5)	948	< 8	(<8, <8)
Month 36	847	82.6	(78.3, 87.1)	833	< 8	(<8, <8)
Anti-HPV 16						
Day 1	1,135	< 11	(<11, <11)	1,127	< 11	(<11, <11)
Month 7	1,135	2,404.30	(2,272.2, 2,544.0)	1,127	< 11	(<11, <11)

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=2,025) n	GMT (mMU/mL)	95% CI	Placebo (N=2,030) n	GMT (mMU/mL)	95% CI
Month 24	979	342.7	(324.7, 361.7)	951	< 11	(<11, <11)
Month 36	877	293.3	(276.5, 311.2)	839	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1,174	< 10	(<10, <10)	1,202	< 10	(<10, <10)
Month 7	1,174	402.3	(380.2, 425.7)	1,202	< 10	(<10, <10)
Month 24	1,011	38.4	(36.0, 41.0)	1,010	< 10	(<10, <10)
Month 36	905	33.1	(30.9, 35.4)	882	< 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: sBLA 125126/1895; Clinical Study Report V503-020, p.327

Table 11: 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	1,092	0	0	(0.0%, 0.3%)	1,108	0	0	(0.0%, 0.3%)
Month 7	1,092	1,080	98.9	(98.1%, 99.4%)	1,108	18	1.6	(1.0%, 2.6%)
Month 24	941	855	90.9	(88.8%, 92.6%)	949	20	2.1	(1.3%, 3.2%)
Month 36	847	753	88.9	(86.6%, 90.9%)	834	26	3.1	(2.0%, 4.5%)
HPV 11 cLIA ≥16 mMU/mL								
Day 1	1,092	0	0	(0.0%, 0.3%)	1,107	0	0	(0.0%, 0.3%)
Month 7	1,092	1,083	99.2	(98.4%, 99.6%)	1,107	23	2.1	(1.3%, 3.1%)
Month 24	941	900	95.6	(94.1%, 96.9%)	948	13	1.4	(0.7%, 2.3%)
Month 36	847	796	94	(92.2%, 95.5%)	833	19	2.3	(1.4%, 3.5%)
HPV 16 cLIA ≥20 mMU/mL								
Day 1	1,135	0	0	(0.0%, 0.3%)	1,127	0	0	(0.0%, 0.3%)
Month 7	1,135	1,121	98.8	(97.9%, 99.3%)	1,127	20	1.8	(1.1%, 2.7%)
Month 24	979	970	99.1	(98.3%, 99.6%)	951	7	0.7	(0.3%, 1.5%)
Month 36	877	859	97.9	(96.8%, 98.8%)	839	18	2.1	(1.3%, 3.4%)
HPV 18 cLIA ≥24 mMU/mL								
Day 1	1,174	0	0	(0.0%, 0.3%)	1,202	0	0	(0.0%, 0.3%)
Month 7	1,174	1,143	97.4	(96.3%, 98.2%)	1,202	21	1.7	(1.1%, 2.7%)
Month 24	1,011	630	62.3	(59.2%, 65.3%)	1,010	12	1.2	(0.6%, 2.1%)
Month 36	905	516	57	(53.7%, 60.3%)	882	9	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: sBLA 125126/1895; Clinical Study Report V503-020, p.333-334.

Clinical Reviewer Note: The Month 36 immunogenicity data does not change the overall conclusions regarding immunogenicity in males. The decline in GMTs followed an expected pattern, leveling off between Months 24 and 36.

Past CBER reviews of the immunogenicity data in both males and females have noted the lower responses to HPV 18 compared with the other VLP types. This phenomenon may simply reflect the fact that the assay measures only one of several neutralizing epitopes. Similar to the clinical data in females, prevention of HPV 18-related efficacy endpoints, such as persistent infection and disease, appears to be robust and durable. In the PPE population from Study 020, no cases of HPV 18-related AIN or EGL were observed throughout the study.

8.1.8.10 Safety

See Section 9 Overview Across Trials.

9 Overview Across Trials

9.1 Efficacy and Immunogenicity

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

The immunogenicity data presented in the applicant's previous sBLA for prevention of genital warts in males has been updated to include the Month 36 time point. See Section 8.1.8.9 above.

A full assessment of immunogenicity in males from studies V501-016, -018, and -020 is documented in the clinical review of the applicant's previous sBLA for the prevention of genital warts in males, including duration of immune response, comparison with females, and rationale and justification for bridging efficacy from 16-26 year old males to 9-15 year old males based on immunogenicity data. That clinical review is published on the FDA website under the October 19, 2009 approval package, here: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm. All those analyses and assessments have not changed. This includes, most importantly, the conclusion regarding immuno-bridging of efficacy for the indication.

Similar to the indication of prevention of genital warts in males, the clinical reviewer has determined that it is reasonable to bridge efficacy to 9-15 year old males and females for the prevention of AIN and anal cancer based on the efficacy and immunogenicity data in older study subjects.

9.2 Safety

The safety data presented in the original Study 020 CSR (finalized 05-Dec-2008) were assessed in the review of the original application for an indication of prevention of genital warts in males. In this dataset, there were no new reported serious adverse events, deaths, or new subject discontinuations due to adverse experiences.

In addition, because study subjects were well beyond the vaccination phase (Day 1 to Month 7), there were very minor changes to the data overall. These included revisions due to such things as data entry errors and changes to encoding of terms. Thus, the safety data submitted to this sBLA are nearly identical to the original males sBLA submission. For details of the CBER assessment, please refer to the clinical review of the males sBLA published on the FDA website under the October 19, 2009 approval package, here: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm.

CBER's overall assessment of the safety data has not changed. Gardasil appears to have an acceptable safety profile. No safety signals were identified.

10 Additional Clinical Issues

10.1 Directions for Use

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

10.2 Dose Regimens and Administration

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

10.3 Special Populations

10.3.1 Pregnancy

No new data were submitted with this application regarding use in pregnancy.

10.3.2 Geriatric Use

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

10.3.3 Immunocompromised Patients

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

10.3.4 Pediatrics

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 through 8 years of age. The review team agreed to grant the partial 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 this BLA supplement, Gardasil has been adequately studied and labeled for use in children 9 years of age and older for the prevention of AIN and anal cancer; and the PREA requirement to study Gardasil for the prevention of AIN and anal cancer in children 8 years of age and younger is waived.

11 Conclusions - Overall

Data submitted to the sBLA demonstrate that Gardasil is efficacious in the prevention of AIN caused by HPV 6/11/16/18 in males 16-26 years of age.

The data linking anal hrHPV infection to AIN and subsequent anal cancer are persuasive. AIN (particularly AIN2+) is a reasonable correlate endpoint for evaluating an intervention for the prevention of anal cancer.

Based on the available epidemiological, histological, and pathophysiological data, it is reasonable to extrapolate from the efficacy data in males in order to grant the indication of prevention of AIN and anal cancer in females.

Immunogenicity bridging data provides a basis for inferring protection of 9 to 15 year old individuals against AIN and anal cancer.

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. No revisions to the pharmacovigilance program are recommended at this time.

During the review of the applicant's previous sBLA for prevention of genital warts in males, the applicant agreed to extend Study 020 to 10 years of follow-up. The study extension will provide data on long term safety, immunogenicity, and efficacy on the endpoints of persistent infection, external genital lesions, AIN and anal cancer. The proposed protocol revision is adequate to evaluate long term follow-up on these outcomes.

The available data support the approval of Gardasil for use in males and females 9-26 years of age for the prevention of AIN and anal cancer caused by HPV types 6, 11, 16, and 18.

12 Recommendations

12.1 Approval Recommendations

Gardasil is recommended for approval for use in males and females 9 through 26 years of age for the prevention of AIN and anal cancer caused by HPV types 6, 11, 16, and 18.

12.2 Recommendations on Postmarketing Actions

The applicant's pharmacovigilance plan is adequate. No further regulatory action for postmarketing safety surveillance are recommended.

12.3 Labeling

The package insert (PI) and the patient package insert (PPI) were submitted by the applicant with proposed changes to reflect the additional indication in males and females. Both documents were evaluated by a reviewer in the Advertising and Promotional Labeling Branch (APLB). In addition, each review team member contributed to internal discussions. The most

substantial labeling issue involved the consideration of the indication in females based on efficacy data in males. In consultation with the VRBPAC, the review team concluded that it is reasonable to bridge the efficacy data in males to females.

After several minor revisions to the PI and PPI were agreed to in a series of discussions with the applicant, the review committee determined that the prescribing information as it pertains to the new indication is acceptable.