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

VRBPAC Briefing Document for the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Subject: Male indication for Gardasil

Product: Gardasil® (Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant)

BLA Supplement: #125126/1297

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Sponsor: Merck Research Laboratories

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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 sponsor 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 alum control was unremarkable, with similar rates of overall adverse events (AE) - 69% vs. 64%, respectively, and serious adverse events (SAE) – 0.4% vs. 0.6%, respectively.

Because the incidence of HPV-related genital lesions is very low before the onset of sexual relations, a placebo-controlled efficacy trial in subjects <16 years of age would be impractical. Therefore, in order to demonstrate protection, the sponsor conducted bridging studies to compare antibody responses to HPV in male subjects from the pivotal trial to males 9-15 years of age. Antibody responses to each of the 4 virus like particle (VLP) types in the adolescent population were non-inferior to those of older subjects.

The sponsor has proposed a post-marketing plan, but it was submitted too late in the cycle to be included in this briefing document. It will be presented at the VRBPAC.

CBER is seeking input from the VRBPAC regarding the overall risk/benefit ratio of administering Gardasil to males for the indication of prevention of genital warts considering the data presented to the sBLA. Questions for the VRBPAC to consider are:

1. Given the efficacy and safety data included in the sBLA, is the overall risk/benefit ratio favorable for the licensure of Gardasil in males for the indication of prevention of genital warts?

2. Given the safety data presented to the sBLA, is the post-marketing plan (to be presented at VRBPAC) adequate to address safety in the male population targeted in the indication?

Introduction and Background

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, 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 sponsor is specific for genital warts. Therefore, CBER has focused primarily on the topic of genital warts in its presentation to, and its request for guidance from, the VRBPAC.

Disease Burden of Genital Warts in Men

Condyloma acuminata, or genital warts (GW), are the most common presenting complaint in both males and females with HPV infection (Dempsey et al). Overall 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).

Merck's Clinical Development Program in Males

In the pivotal efficacy studies, Gardasil was evaluated among women 16 to 26 years of age. Efficacy was bridged to adolescent females by demonstrating non-inferiority of antibody responses among female adolescents 9 to 15 years of age compared to female adults. Generally, the sponsor took the same approach in the clinical development of the vaccine for males.

The data submitted to the sBLA come primarily from the pivotal efficacy and safety study in males, Protocol V501-020 (referred to hereafter, for the most part,

simply as “020”). That study was reviewed in detail and the highlights are covered in this document.

Two smaller immunogenicity bridging studies, V501-016 and -018, were submitted in support of extending the labeled indication to the 9-15 years age group. Those studies are covered under the topic of immunobridging and are also discussed regarding their contribution to the overall safety database in males. See Table 1 for a summary of the relevant studies.

Table 1: Studies Submitted in Support of Licensure of Gardasil for Males

Study Identifier	Type of Study	Primary Efficaacy 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 sponsor’s clinical development program in which vaccine was compared to unadjuvanted placebo.

Regulatory History

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)

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

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, 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.

Pivotal Study in Males: V501-020

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 a 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.

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.

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 was not submitted to the sBLA and because the efficacy objective of the MSM substudy has no bearing on the indication sought by the sponsor at this time, the MSM substudy data are not the subject of VRBPAC discussion and are not addressed in this briefing document.

Secondary Efficacy Objectives:

(1) 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

(2) 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.

Endpoints

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 acuminata (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 heterosexual men (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. 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. What became clear in examining the data was that the vast majority of endpoint cases defined as "external genital lesions" were in fact genital warts. Very few cases of PIN occurred. Therefore, the sponsor and CBER agreed to reconsider the originally requested indication of prevention of external genital lesions and evaluate a less broad indication focusing only on genital warts.

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 polymerase chain reaction (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.

Results

Populations Enrolled/Analyzed

See Appendix A for definitions of analysis populations and for tables documenting populations enrolled, subject disposition, and demographic characteristics by vaccination group.

Efficacy – Primary Endpoint: Prevention of Genital Warts

The results of the primary efficacy endpoint of prevention of genital warts for the major analysis populations are displayed in Table 2.

Table 2: Efficacy Against Genital Warts in Different Analysis Populations

Analysis Population	Gardasil		Alum control		Efficacy % (95%CI)
	n	Number of cases	n	Number of cases	
Per-Protocol Efficacy (PPE)	1397	3	1408	28	89.4% (65.5, 97.9)
Naïve to Relevant HPV Type (HNRT)	1775	10	1770	48	79.6% (59.1, 90.8)
Full Analysis Set (FAS)	1943	24	1937	72	67.2% (47.3, 80.3)

n = Number of subjects in the respective population eligible for analysis
Source: Adapted from - original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.195-205

Other Efficacy Analyses

Efficacy was analyzed in subpopulations according to subject characteristics (Table 3). 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 small number of cases among MSM's results in a wide confidence interval. Generally, subject characteristics, including sexual demographics seemed to have limited effect on efficacy. See Table 3.

Table 3: Efficacy Against HPV 6/11/16/18-Related EGL Stratified by Subject Characteristics (PPE Population)

Subject Characteristic	Gardasil (N=2025)		Alum control (N=2030)		Efficacy % (95%CI)
	n	# of cases	n	# of cases	
HPV 6/11/16/18-Related EGL overall	1397	3	1408	31	90.4% (69.2, 98.1)
15-20 years old	701	1	763	19	94.3% (63.9, 99.9)
21-27 years old	696	2	645	12	85.1% (33.2, 98.4)
Sexual Orientation - HM	1,200	2	1,198	26	92.4% (69.6, 99.1)
Sexual Orientation - MSM	197	1	210	5	79% (-87.9, 99.6)
Lifetime # of Sexual Partners: 0	10	0	9	0	NA
Lifetime # of Sexual Partners: 1	303	1	306	4	74.3% (-159, 99.5)
Lifetime # of Sexual Partners: 2	256	0	291	2	100% (-485, 100)
Lifetime # of Sexual Partners: 3	290	1	298	4	75.2% (-150, 99.5)
Lifetime # of Sexual Partners: 4	277	0	255	12	100% (67.5, 100)
Lifetime # of Sexual Partners: 5	260	1	245	9	89.8% (26.1, 99.8)
Circumcised	470	1	473	8	87.6% (7.4, 99.7)
Not Circumcised	927	2	935	23	91.4% (65.0, 99.0)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Month 7.
CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HM = Heterosexual men; MSM = Men having sex with men
Source: Adapted from - original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.195, 208-210

Because the vast majority of Gardasil recipients in the general population would not be screened prior to vaccination, an important question in the assessment of this data is what effect, if any, the vaccine will have in subjects with pre-existing HPV infection. Table 4 displays efficacy estimates in subjects PCR+ for vaccine-type HPV on the day of first vaccination. A marked reduction in efficacy was seen in the setting of pre-existing infection.

Table 4: Efficacy Against HPV 6/11/16/18-Related EGL Among Subjects Who Were Seronegative and PCR Positive for the Relevant Vaccine HPV Type(s) at Day 1

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	177	15	183	20	23.2% (-57.8, 63.4)
HPV 6-Related EGL	70	11	55	11	30.3% (-77.3, 72.6)
HPV 11-Related EGL	16	2	18	4	28.5% (-398, 93.5)
HPV 16-Related EGL	68	2	91	7	62.4% (-97.4, 96.2)
HPV 18-Related EGL	45	0	49	2	100% (-480, 100)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Day 1.
EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer
Source: Adapted from - original BLA 125126.1297.0, 5.3.5.1.3 - Clinical Study Report V503-020, p.267

The efficacy against EGL due to any HPV type was analyzed in the Full Analysis Set to best approximate the possible impact of Gardasil as it will be used in a broader population of males. There were 36 cases in 1943 subjects in the Gardasil group compared to 89 cases in 1937 subjects in the placebo group; the efficacy point estimate was 60.2%, with a 95%CI of (40.8, 73.8).

Clinical Reviewer Note: The analyses discussed above under the heading, "*Other Efficacy Analyses*", were considered in the overall assessment of effectiveness in the sBLA. It should be noted that the endpoint in these analyses is external genital lesions (EGL), which includes PIN. Because these analyses were not decisive in the evaluation of the sought-after indication specifically and because the vast majority of EGL are in fact genital warts, CBER did not repeat these analyses limiting the endpoint to genital warts.

Efficacy – Secondary Endpoints: Prevention of Persistent Infection

Persistent infection, defined as PCR detection of the same HPV type on two occasions at least 4 months apart, was one of the secondary endpoints. Table 5 displays efficacy against persistent infection in the PPE population.

Table 5: Efficacy Against HPV 6/11/16/18-Related Persistent Infection (PI) 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 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

Safety

Safety Assessments were performed at each vaccination visit and every 3 months post-dose 3.

All subjects were given a Vaccine Report Card (VRC) to record:

- Oral temperatures out to 4 days
- Injection-site adverse events (AE) out to 14 days
- Systemic AE's out to 14 days

No routine laboratory tests were conducted within the context of the study.

Standard criteria were used for defining AE's in terms of severity, causality, and non-serious vs. serious.

Adverse Events

The summary analysis of AE's was unremarkable. Similar percentages of subjects in Gardasil group compared to the placebo group experienced any AE during the study (69.2% vs. 64.2%, respectively), discontinued participation in the study due to an AE (0.3% vs. 0.7%, respectively), or reported a new medical condition (24.2% vs. 22.8%, respectively).

Analysis of the most common systemic AE's was similarly unremarkable. The case splits of systemic AE's in the Gardasil group compared to the placebo group by system organ class (SOC) were similar. Table 6 displays the most common systemic AE's reported.

Table 6: Number (%) of Subjects Who Reported Systemic AE's With ≥ 1% Incidence (Days 1 to 15 Following Any Vaccination Visit)

Adverse Event Term	Gardasil (N=1945)	Alum control (N=1950)
	n (%)	n (%)
With one or more systemic AE's	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

Injection Site Adverse Events

Gardasil recipients experienced a somewhat higher rate of injection site AE's 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 7.

Table 7: Subjects Reporting Specific Injection-Site Adverse Experiences With ≥ 1% Incidence (Days 1 to 5 Days Following Any Vaccination Visit)

	Gardasil (N=1945)		**Alum control** (N=1950)		**Risk Difference** qHPV – control (95%CI)	**p-Value***
	n	(%)	n	(%)		
One or more injection-site AE's	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 AE's, 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.

Serious Adverse Events

A total of 6 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 SAE's was assessed by the Investigator as being related to treatment.

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 SAE's and 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.

Immunogenicity in Males Across Studies

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 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 Table 8 for anti-HPV GMT's and SCR's in males from Protocol 020.

Immunobridging to Males Aged 9-15 years

Anti-HPV responses (Month 7 GMT's and SCR's) 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. GMT's were non-inferior in the younger male subjects and SCR's were uniformly high and comparable across age groups. See Table 8.

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 8: Month 7 Anti-HPV cLIA GMT's and SCR's 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)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
**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

Immunogenicity in Males Compared to Females

In response to a CBER request, the sponsor 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 GMT's were lower in males compared to females, particularly for types 6, 11, and 18. The differences persisted at month 24. See Table 9.

Table 9: 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 - original BLA 125126.1297.0, 5.4, Reference 2272 – Integrated immunogenicity analyses in support of Gardasil™ men's filing, p.14

Duration of Efficacy

In females, no correlate of protection has yet been established for prevention of HPV infection and disease, primarily because the low number of 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.

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

Safety Across Studies

The total safety database of male subjects vaccinated in the clinical development program is displayed in Table 10.

Table 10: 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 exception is that the overall rate of AE's was slightly higher in the younger population. To a large degree, this was driven by a higher rate of injection site AE's 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.

One analysis of particular interest that was performed on the combined males dataset was an evaluation of potential autoimmune disorder signaling. No substantial differences were noted between Gardasil and placebo groups. See Table 11.

Table 11: 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

Postmarketing

Based on literature that indicates that male and female immune responses differ, including differences in reactogenicity to vaccines (Cook), CBER has requested that the sponsor submit a plan for Phase IV studies and pharmacovigilance plans. There are no specific safety signals identified at this time; however, given the limited number of participants in safety trials, CBER believes that post-marketing surveillance and studies will be essential. The sponsor has agreed to submit preliminary protocols by Friday, July 31. Thus CBER will not be able to include our review of the sponsor's proposal for post-marketing surveillance in this briefing document. The sponsor and CBER will present the post-licensure surveillance plan at the VRBPAC meeting.

Because Gardasil is already licensed for males in many countries, CBER requested post-licensure international safety data as part of the BLA review process. A review of the limited numbers of international safety reports for Gardasil in males did not reveal other predicted or identified safety signals.

CBER Conclusions

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

- 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 GMT's against each of the 4 VLP types in 9-15 year old males are non-inferior to those in 16-26 year old males.

- In the limited safety database in males, no safety signals have been identified. The adequacy of the post-marketing plan to address safety in males in a broader population is being reviewed.

Questions for the Committee

1. Given the efficacy and safety data included in the sBLA, is the overall risk/benefit ratio favorable for the licensure of Gardasil in males for the indication of prevention of genital warts?

2. Given the safety data presented to the sBLA, is the post-marketing plan (to be presented at VRBPAC) adequate to address safety in the male population targeted in the indication?

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Appendix A

Analysis Population Definitions

Efficacy Analysis Populations:

1) 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 (1 month after 3rd vaccine dose).
2) 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)
3) Full analysis set (**FAS**), consisting of subjects who received at least 1 dose of vaccine or placebo
4) 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.
5) 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 the protocol in ways that could interfere with the evaluation of immune response to injections of qHPV.

* "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 Populations:

1) 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.

Population Characteristics, Disposition and Demographics

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

Table 12 displays the number of subjects eligible for the PPE analysis. Table 13 summarizes the disposition of all the subjects enrolled.

Table 12: 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 13: 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

Table 14 summarizes the subject demographics. The two vaccination groups were well-balanced with regard to each demographic characteristic.

Table 14: 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 15 summarizes the sexual history of subjects at enrollment.

Table 15: 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

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.