VRBPAC Background Document

Gardasil™ HPV Quadrivalent Vaccine
May 18, 2006 VRBPAC Meeting

Introduction and Background:

Cervical cancer is an important public health problem in the United States, with 9,710 new cervical cancer cases and 3,700 deaths due to cervical cancer projected for 2006.[1] Cervical cancer has been associated with human papilloma virus (HPV) infection. The applicant, Merck, Inc., began a clinical development program in 1997 with a recombinant HPV virus-like particle (VLP) vaccine for the prevention of cervical cancer. The applicant's clinical development program proceeded using a quadrivalent VLP vaccine, Gardasil™ that contains the major capsid protein (L1 protein) from four types of HPV: types 6, 11, 16, and 18. HPV types 16 and 18 are thought to be responsible for more than 50% of cervical cancer, but more than 15 different types of HPV are considered to be "oncogenic" and are associated with development of cervical cancer. Cervical intraepithelial neoplasia grade 2/3 (CIN 2/3) and adenocarcinoma in situ (AIS) are considered to be precursors to cervical cancer. Condyloma acuminata results from infection with many different types of HPV, but HPV 6 and 11 are thought to be responsible for a majority of these cases. Therefore, a vaccine that is highly efficacious in providing protection against HPV types 6, 11, 16, and 18, based on available epidemiological data, might be capable having a significant impact in preventing cervical cancer and condyloma acuminata. The Vaccine and Related Biological Products Advisory Committee (VRBPAC) discussion will focus on the results submitted to the biologics license application (BLA) from the clinical development program of Gardasil™ for prevention of HPV disease in females.

Regulatory Milestones:

1997 Submission of the original investigational new drug application (IND) for monovalent VLP vaccine containing the L1 protein from HPV 11. Subsequent INDs were submitted for monovalent VLP vaccines containing L1 proteins from HPV 16 and 18, respectively. Phase 1 and phase 2 evaluations were conducted under these INDs.

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)

[1] Jemal A, et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56:106-130.

by histology (with virology to determine the associated HPV type) as the primary endpoint in the evaluation of a vaccine to prevent cervical cancer.

2002 CBER granted fast track designation to Merck's development program for the HPV quadrivalent vaccine for prevention of cervical cancer. Merck initiated phase 3 clinical trials of the HPV quadrivalent vaccine.

2005 May: Pre-BLA meeting. CBER agreed that the efficacy data limited to the first 24 weeks of the phase 3 studies could be submitted to the BLA in order to support efficacy. CBER encouraged early (rolling) submission of CMC, pre-clinical and phase 1 and 2 clinical data. CBER agreed to grant a priority review of the BLA.

November: CBER determined that clinical efficacy, immune response, and safety data from studies conducted in females would be considered for licensure for use in females. Immune response studies conducted in males might contribute important safety data but would not provide data to be considered for licensure in males. (A separate clinical development program is ongoing for men and boys.)

December: Completion of the "rolling" BLA submission with receipt of the efficacy data from the phase 3 studies.

Summary of Clinical Data:

Table 1: Clinical studies

Study Number	Vaccine HPV type	Phase	Total sample size (Gardasil™ plus placebo)	Geographic Distribution of Study Populations
001	11	1	140	North America
002	16	1	109	North America
004	16	1	480	North America
005	16	2*	2409	North America
006	18	1	40	North America
007	6/11/16/18	2*	1106^	North America, Latin America, Europe
013 (011 + 012) (FUTURE I)	6/11/16/18	3*	5455[#]	North America, Latin America, South America, Europe, Asia, Australia
015 (FUTURE II)	6/11/16/18	3*	12167	North America, South America, Europe, Asia
016	6/11/16/18	2	1529^	North America, Latin America, South America, Europe, Asia, Australia
018	6/11/16/18	2*	939	North America, Latin America, Europe, Asia

* Double-blind, randomized, placebo-controlled studies
^ Includes subjects randomized to different doses of HPV quadrivalent VLP
[#] Does not include 304 subjects who received HPV monovalent VLP vaccine in a bridging substudy.

Phase 1 and Phase 2 Studies

Merck conducted six phase 1 and phase 2 clinical studies between 1997 and 2004. Four smaller phase 1 or early phase 2 studies evaluated monovalent HPV VLP vaccines, serotypes 11, 16, or 18, in order to characterize safety and immune responses among different doses. Two larger phase 2 studies were conducted between 2000 and 2004 that included clinical endpoints in addition to the safety and immune response endpoints. The results of these studies were used to identify appropriate dose and endpoints to be used in the phase 3 pivotal studies. The studies suggested an acceptable safety profile for further clinical development. The larger phase 2 studies provided supportive evidence of vaccine activity. The applicant's clinical development program focused on a three-dose regimen at months 0, 2, and 6 based on previous clinical and immunological experiences with their hepatitis B vaccine product.

Studies 001, 002, and 006 were small phase 1 safety studies that evaluated the monovalent HPV VLP serotypes 11, 16, and 18, respectively. Studies 001 and 002 enrolled 249 subjects, and approximately 200 received the vaccine. The results demonstrated a "dose response", where higher doses generally resulted in larger post-vaccination geometric mean titers. Overall, the immune responses in subjects who received the 20 µg, 40 µg, or 50µg dose were better than the immune responses in subjects who received the 10 µg dose. There appeared to be no advantage in immune responses to an 80 µg dose, or to the administration of a fourth dose.

Study 005 began to demonstrate initial evidence of activity of a 40 µg monovalent HPV 16 VLP vaccine against HPV disease due to HPV type 16. For subjects in study 005 without evidence of infection with HPV 16 at baseline, the applicant reported no cases of CIN due to HPV 16 out of of 753 subjects in the vaccine group and nine cases of CIN due to HPV 16 out of 750 subjects in the placebo group.

Study 007 evaluated different doses of each antigen, characterized by "low, medium, and high" dose groups. The study also incorporated clinical HPV endpoints. The study enrolled just over 1,000 women. Of note, the secondary efficacy analysis included only women who were seronegative for HPV at baseline with a secondary endpoint of detection of HPV 6/11/16/18 DNA on two or more consecutive cervicovaginal samples by PCR ("persistent HPV cases"). In this analysis, the following number of persistent HPV cases were recorded: 4 out of 235 subjects randomized to receive the "low" dose, 7 out of 232 randomized to receive the "medium" dose, 3 out of 234 randomized to receive the "high" dose, and 35 out of 233 randomized to receive placebo. In general, subjects randomized to receive the higher doses had greater proportions of adverse events. Therefore, the lower dose group (20/40/40/20 µg for HPV types 6, 11, 16, and 18, respectively) appeared to have comparable activity to the higher dose groups and had a better safety profile. The 20/40/40/20 µg dose was brought forward for clinical development in the phase 3 studies.

Phase 3 Studies

Two randomized, double-blinded, placebo-controlled phase III studies evaluated the clinical efficacy and safety of Gardasil™. The two studies, the FUTURE I and FUTURE II studies, evaluated the clinical endpoints of CIN 2/3 or worse and external genital lesions due to HPV. The Future II study, which was the larger of the two studies and had a straightforward design, will be presented first.

Study 015: The FUTURE II Study

The sponsor provided the results from the phase 3 study, "A randomized, worldwide, placebo controlled, double blind study to investigate the safety, immunogenicity, and efficacy on the incidence of HPV 16/18 related CIN 2/3 or worse of the quadrivalent HPV (types 6, 11, 16, 18) L1 virus like particle (VLP) vaccine in 16-23 year old women – The FUTURE II Study." The study's primary objective was the determination of safety and efficacy in the prevention of cervical carcinoma due to HPV type 16 or 18 following administration of a three-dose regimen among women who had no evidence of previous infection with HPV.

Female subjects 16-23 years of age who had normal baseline pelvic examinations were eligible for enrollment and were not prescreened for HPV prior to randomization. Subjects were randomized 1:1 to receive Gardasil™ or placebo intramuscularly, at months 0, 2, and 6. Subjects returned on study at months 7, 12, 24, 36, and 48 for review of serious adverse events, complete physical examination including examination of external genitalia, and Pap test for cytology. Cytology specimens were evaluated using the Bethesda System-2001.[2] Subjects were referred to colposcopy based on a mandatory Pap test triage algorithm (see appendix A for colposcopy algorithm). An expert pathology panel, consisting of four pathologists, reviewed the slides prepared from cervical biopsy/definitive therapy specimens (see Appendix B for Pathology Panel). The consensus diagnosis of this panel represented the final diagnosis for purposes of the study's efficacy endpoints. A lot consistency substudy and an enhanced safety substudy were incorporated into the study design.

The study began enrollment on June 24, 2002 and ultimately screened approximately 12,700 subjects. In total, 12,167 subjects were enrolled in the study. Of the 540 subjects who were screened but not enrolled, most were found to have met exclusion criteria before study entry, for example, reporting greater than 4 lifetime sexual partners or having a condition that in the opinion of the investigator would interfere with study participation. The study's database in preparation for BLA submission was locked on June 10, 2005. The study is still ongoing. Overall 228 subjects discontinued participation during the vaccination period, which represented approximately 2% of the overall study population. The mean duration of clinical endpoint follow-up for this study after the month 7 study visit was approximately 1.4 years.

[2] Wright TC, et al. Am J Obstet Gynecol, 2003 Jul;189(1):295-304.

A total of 10,585 subjects, or 87% of all enrolled subjects, met the criteria for the per protocol population for the primary HPV 16/18 efficacy analysis. (See appendix C for definitions of the populations for the analyses) The results of the study demonstrated a vaccine efficacy of 100% for the per protocol primary analysis of efficacy for HPV 16/18, as shown in the table below:

Table 2. Study 015: Analysis of efficacy, per protocol population, against vaccine-relevant HPV types 16 and 18 CIN 2/3 or worse, and against HPV types 6, 11, 16, and 18 CIN 2/3 or worse.
[From original BLA, Tables 7-2 and 7-9, complete study report (CSR) for study 015, pp. 229 and 246, respectively.]

	Gardasil™ N=6082				**Placebo N=6075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 years at risk	Observed Efficacy	95% CI
HPV 16/18 CIN 2/3 or Worse	5301	**0**	7435.1	0	5258	**21**	7385.5	0.3	100%	75.8, 100%
HPV 6/11/16/18 CIN 2/3 or Worse*	5383	**0**	7545.7	0	5370	**22**	7541.5	0.3	100%	81.1, 100%

*Secondary endpoint

It is important to note here that **the applicant's analyses were specific to the HPV type.** For example, from the efficacy datasets submitted with the BLA subject number AN47906 is a 21 year old subject randomized to receive Gardasil™. She had evidence of HPV infection type 16 by PCR detection of HPV 16 DNA at the baseline visit and was excluded from the efficacy analysis for HPV type 16. She met the colposcopy algorithm during the study and received a panel diagnosis of CIN 3 disease with virologic evidence of HPV 16 from her biopsy. However, she was included in the per protocol efficacy analysis for HPV 18 because she did not meet exclusion criteria for the per protocol population for HPV 18. Therefore, because she contributed favorable efficacy data for HPV 18 "incidence rate per 100 years at risk", she ultimately contributed favorable primary endpoint efficacy data for the overall per protocol population for HPV 16/18. The applicant's modified intent to treat population 2 (MITT-2) included subjects who were negative at baseline for the vaccine-relevant HPV types 6, 11, 16, or 18 and received at least one vaccine.

Table 3. Study 015: Analysis of efficacy, MITT-2 population, against vaccine-relevant HPV types 16 and 18 CIN 2/3 or worse.
[From original BLA, Table 7-4, CSR for study 015, p. 235.]

	Gardasil™ N=6082				**Placebo N=6075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 years at risk	Observed Efficacy	95% CI
HPV 16/18 CIN 2/3 or Worse	5736	**1**	10797.2	<0.001	5766	**36**	10881.5	0.3	97.2%	83.4, 99.9%

Table 4 presents the analysis of all subjects who received at least one vaccine regardless of baseline HPV serostatus or PCR results and had documentation of follow up at least once after the one month study visit (MITT-3 population):

Table 4. Study 015: Analysis of efficacy, MITT-3 population, against vaccine-relevant HPV 16 and 18 CIN 2/3 or worse.
[From original BLA, Table 11-86, CSR for study 015, p. 657.]

	Gardasil™ N=6082				**Placebo N=6075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 years at risk	Observed Efficacy	95% CI
HPV 16/18 CIN 2/3 or Worse	5947	**68**	11159.5	0.6	5973	**116**	11242.9	1.0	40.9%	19.7, 56.9%

Secondary endpoints of study 015 included the presence of external genital lesions. The following tables demonstrate the observations of genital lesions (EGL) due to vaccine-associated HPV types in the per protocol population and the observations of genital lesions due to any type of HPV in the MITT-3 population.

Table 5. Study 015: Analysis of efficacy, per protocol population, against EGL due to HPV type 6, 11, 16, or 18. [From original BLA, Table 7-11, CSR for study 015, p. 251.]

	Gardasil™ N=6082				**Placebo N=6075**					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 EGL	5401	**1**	7545.8	<0.001	5387	**70**	7513.7	0.9	98.6%	91.8, 100%

Table 6. Study 015: Analysis of efficacy, MITT-3 population, against EGL due to any type HPV.
[From original BLA, CSR for study 015, Table 11-99, p. 673.]

	Gardasil™ N=6082				**Placebo N=6075**					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 years at risk	Observed Efficacy	95% CI
HPV any type EGL	6016	**96**	11,116.4	0.9	6027	**177**	11,153.6	1.6	45.6%	29.8, 58.0%

Study 013: The FUTURE I Study

The BLA contained results from the phase 3 study, "A study to evaluate the efficacy of the quadrivalent HPV (types 6, 11, 16, 18) L1 virus like particle (VLP) vaccine in reducing the incidence of HPV 6, 11, 16, and 18 related external genital warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer in 16-23 year old women." The study's co-primary objectives included the determination of vaccine efficacy based on incidence of CIN, adenocarcinoma in situ, or cervical cancer due to all four HPV types (6, 11, 16, and 18) following administration of a three-dose regimen among women who had no evidence of previous infection with HPV. The study was designed to provide evidence of safety and efficacy for the prevention of cervical cancer in a population of adolescent and young adult females.

This multi-center and multinational study enrolled healthy female subjects 16-23 years of age who had normal baseline pelvic examinations. Subjects were not prescreened for HPV prior to randomization. Subjects received vaccine formulation or placebo intramuscularly at months 0, 2, and 6. Subjects returned on study at months 3, 7, 12, 18, 24, 30, 36, and 48 for review of safety and complete physical examination including examination of external genitalia. Pap tests were performed at day 1 and months 7, 12, 18, 24, 30, and 36. Sera for immunogenicity were obtained at day 1 and at months 7, 12, 24 and 48. Subjects were first evaluated in one of two embedded substudies: either concomitant administration with hepatitis B vaccine (study 011) or a comparative arm with a monovalent HPV 16 (study 012). Therefore, randomization schemes differed as to whether subjects were first enrolled in study 011 or study 012. After administration of three doses of study vaccines or placebo, subjects were followed for the primary clinical outcomes (study 013). For study 013, approximately the same proportions were randomly assigned to Gardasil™ or placebo. Cytology specimens were evaluated using the Bethesda System-2001.[2] The study included an algorithm for referral to colposcopy, which differed slightly from that used in study 015 (see Appendix A). Subjects in study 015 who had atypical squamous cells of undetermined significance (ASC-US) were not referred to colposcopy, but had a Pap test repeated sooner at 6 months instead of scheduled 12 months. In this study, subjects with ASC-US received an HPV probe, and if positive were referred to colposcopy. An expert pathology panel, consisting of four

pathologists, reviewed the slides prepared from cervical biopsy/definitive therapy specimens (see Appendix B). The consensus diagnosis of this panel represented the final diagnosis for purposes of the study's primary efficacy endpoint. This study's co-primary endpoint was CIN 1 or worse.

The study began enrollment on December 28, 2001 and ultimately screened 6767 subjects. In total, 5759 subjects were enrolled in the study and had a mean duration of follow-up of 1.7 years. For the 1008 subjects who screened for the study but did not enroll, most were found to have met exclusion criteria before study entry, for example, reporting greater than 4 lifetime sexual partners or having a condition that in the opinion of the investigator would interfere with study participation. The study database was locked on November 4, 2005 for evaluation of the efficacy endpoints. The study is still ongoing. Overall 274 subjects discontinued participation during the vaccination period, which represented approximately 5% of the overall study population. The 304 subjects randomized to receive monovalent HPV 16 VLP vaccine in the substudy 012 were not evaluated for the longer term efficacy and safety follow up in study 013. An additional 246 (4.5%) of subjects did not complete the longer term follow up after the vaccination. The demographic characteristics between the Gardasil™ vaccine group and the placebo group were well balanced. Approximately 78% of subjects were included in the per protocol efficacy population for HPV 6/11/16/18; 22% were excluded from per protocol population. About 27% of subjects were either seropositive to a vaccine-relevant HPV type or had positive PCR at baseline. This difference in proportions reflects the HPV type-specific analyses of the data, where a subject could be excluded from one HPV type-specific per protocol efficacy population but be included in other HPV type-specific efficacy populations as illustrated above by the subject in study 015. The following tables outline the applicant's analyses similar to the above descriptions for study 015, although for study 013 the primary endpoint was CIN 1 or worse:

Table 7. Study 013: Analysis of efficacy, per protocol population, against vaccine-relevant HPV 6, 11, 16 or 18 CIN 1 or worse.
[From original BLA, Table 7-4, CSR for study 013, p. 242.]

	Gardasil™ N=2717				**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 CIN 1 or worse	2240	**0**	3779.8	0	2258	**37**	3787.4	1.0	100%	87.4, 100.0%

The applicant's analysis of the subjects who were negative at baseline for all four HPV types and received at least one vaccine (MITT-2 population) was an approach to evaluate vaccine efficacy on a modified intent-to-treat basis.

Table 8. Study 013: Analysis of efficacy, MITT-2 population, against vaccine-relevant HPV 6, 11, 16 or 18 CIN 1 or worse.
[From original BLA, Table 7-7, CSR for study 013, p. 249.]

	Gardasil™ N=2717				**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 CIN 1 or worse	2557	**2*** (both CIN 1)	5490.1	<0.001	2573	**57**	5489.0	1.0	96.5%	86.7, 99.6%

Similar to study 015, the applicant provided an analysis of all study subjects who received at least one vaccine and had follow up data collected at least one month after receipt of vaccine in the study (MITT-3 population). Table 9 presents data for the endpoint CIN 2/3 or worse, which was not the primary endpoint for study 013; however, these data are provided for comparison to study 015.

Table 9. Study 013: Analysis of efficacy, MITT-3 population, against vaccine-relevant HPV types 6, 11, 16 or 18 CIN 1 or worse, and CIN 2/3 or worse.
[From original BLA, Table 7-8, CSR for study 013, p. 250.]

	Gardasil™ N=2717				**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 CIN 1 or worse	2607	**65**	5566.5	1.2	2611	**113**	5525.4	2.0	42.9%	21.9, 58.6%
HPV 6/11/16/18 CIN 2/3 or worse	2607	**48**	5585.0	0.9	2611	**62**	5570.4	1.1	22.8%	<0, 48.2%

The study's co-primary endpoint was the presence of external genital lesions (EGL). The results of the per protocol population for vaccine-relevant EGL and the MITT-3 population for EGL due to any type of HPV are presented below.

Table 10. Study 013: Analysis of efficacy, per protocol population, against external genital lesions EGL due to HPV types 6, 11, 16, and 18.
[From original BLA, Table 7-14, CSR for study 013, p. 264.]

	Gardasil™ N=2717				**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 Related EGL	2261	**0**	3865.2	<0.001	2279	**40**	3868.4	1.0	100.0%	88.4, 100.0%

Table 11. Study 013: Analysis of efficacy, MITT-3 population, against EGL due to any type HPV.
[From original BLA, Table 11-82, CSR for study 013, p. 626.]

	Gardasil™ N=2717				**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
EGL due to any HPV type	2671	**87**	5641.9	1.5	2668	**126**	5598.5	2.3	31.5%	9.2, 48.5%

Combined Efficacy Analyses

The following tables demonstrate efficacy analyses that were provided by the applicant. Efficacy data from studies 007, 013, and 015 where subjects were randomized to receive either Gardasil™ or placebo were included. Please refer to Appendix C for definitions of the efficacy analysis populations.

Table 12. Studies 007, 013 and 015: Combined analysis of efficacy against the incidence of CIN 2/3 or worse due to vaccine-relevant HPV 6, 11, 16, or 18.
[From original BLA, Summary of Clinical Efficacy, Table 2.7.3-cervixcancer: 27].

	Gardasil™ N=9075				**Placebo N=9075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 CIN 2/3 or worse	MITT-2 8625	**1***	17139.1	<0.001	MITT-2 8673	**69**	17231.2	0.4	98.5%	91.6, 100%
HPV 6/11/16/18 CIN 2/3 or worse	MITT-3 8814	**118**	17467.0	0.7	MITT-3 8846	**186**	17527.5	1.1	36.3%	19.4, 49.9%

* There were no cases of CIN 2/3 or worse in this analysis among Gardasil™ recipients in study 013

Table 13. Studies 007, 013 and 015: Combined analysis of efficacy against incidence of CIN 2/3 or worse due to any type HPV.
[From additional efficacy analyses requested by CBER and submitted March 15, 2006, Table 2-2 p. 21.]

	Gardasil™ N=9075				**Placebo N=9075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV any type CIN 2/3 or worse	RMITT-2* 5638	**59**	11333.4	0.5	RMITT-2 5701	**96**	11454.4	0.8	37.9%	13.2, 55.9%
HPV any type CIN 2/3 or worse	MITT-3 8814	**287**	17409.5	1.6	MITT-3 8846	**328**	17469.4	1.9	12.2%	<0.0, 25.3%

*****Here the applicant provided integrated efficacy analyses due to any type HPV for the RMITT-2 population and did not submit integrated efficacy analyses for the MITT-2 population.

Table 14. Studies 007, 013 and 015: Combined analysis of efficacy against EGL due to vaccine-relevant HPV 6, 11, 16, 18 in MITT-2 and MITT-3 populations.
[From original BLA, Summary of Clinical Efficacy, Appendix 2.7.3 exgenlesions-8, p.63.]

	Gardasil™ N=9075				**Placebo N=9075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
EGL due to HPV 6/11/16/18	MITT-2 8760	**9**	17300.4	0.1	MITT-2 8786	**174**	17297.5	1.0	94.8%	90.0, 97.7%
EGL due to HPV 6/11/16/18	MITT-3 8954	**68**	17595.0	0.4	MITT-3 8962	**229**	17560.1	1.3	70.4%	61.0, 77.7%

Table 15. Studies 007, 013 and 015: Combined analysis of efficacy against EGL due to any type HPV among RMITT-2 and MITT-3 populations.
[From original BLA, Summary of Clinical Efficacy, Appendix 2.7.3 exgenlesions-9, p. 46.]

	Gardasil™ N=9075				**Placebo N=9075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
EGL due to any HPV type	RMITT-2* 5734	**57**	11298.0	0.5	RMITT-2 5769	**167**	11345.6	1.5	65.7%	53.4, 75.1%
EGL due to any HPV type	MITT-3 8954	**185**	17487.4	1.1	MITT-3 8962	**307**	17480.0	1.8	39.8%	27.5, 50.1%

*****As with the integrated analyses for CIN 2/3 or worse, the applicant provided integrated efficacy analyses due to any type HPV for the RMITT-2 population and did not submit integrated efficacy analyses for the MITT-2 population.

In addition, the applicant provided the results of study 005, in which subjects were clinically evaluated for a mean duration of 3.1 years following the administration of a monovalent HPV 16 VLP or placebo. The results from this study were based on longer-term follow up compared to the results from the other studies that provided efficacy data.

Table 16. Study 005: Analysis of efficacy, MITT-3 population, against the incidence of CIN 2/3 or worse due to any HPV type.
[From original BLA, CSR for study 005, Table 11-33.]

	Monovalent HPV 16 VLP N=1193				**Placebo N=1198**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV any type CIN 2/3 or worse	MITT-3 1017	**27**	3635	0.7	MITT-3 1050	**50**	3683	1.4	45.3%	10.9, 67.1%
HPV any type CIN 3	MITT-3 1017	**6**	3638	0.2	MITT-3 1050	**21**	3700	0.6	70.9%	25.6, 90.4%

Concerns Regarding Primary Endpoint Analyses among Subgroups

There were two important concerns that were identified during the course of the efficacy review of this BLA. One was the potential for Gardasil™ to enhance disease among a subgroup of subjects who had evidence of persistent infection with vaccine-relevant HPV types at baseline. The other concern was the observations of CIN 2/3 or worse cases due to HPV types not contained in the vaccine. These cases of disease due to other HPV types have the potential to counter the efficacy results of Gardasil™ for the HPV types contained in the vaccine.

1. **Evaluation of the potential of Gardasil™ to enhance cervical disease in subjects who had evidence of persistent infection with vaccine-relevant HPV types prior to vaccination.**

The results of exploratory subgroup analyses for study 013 suggested a concern that subjects who were seropositive and PCR-positive for the vaccine-relevant HPV types had a greater number of CIN 2/3 or worse cases as demonstrated in the following table:

Table 17. Study 013: Applicant's analysis of efficacy against vaccine-relevant HPV types CIN 2/3 or worse among subjects who were PCR positive and seropositive for relevant HPV types at day 1. [From original BLA, study 013 CSR, Table 11-88, p. 636]

	Gardasil™ N=2717				**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 CIN 2/3 or worse	156	**31**	278.9	11.1	137	**19**	247.1	7.7	-44.6%	<0.0, 8.5%

CBER further evaluated this subgroup by looking at potential imbalances in the baseline demographic characteristics:

Table 18; Study 013: Selected characteristics for subgroup of PCR positive and seropositive for vaccine-relevant HPV types at day 1.
[From additional efficacy analyses requested by CBER and submitted March 15, 2006, table 1e-2, p. 13.]

Study 013 subgroup	Gardasil™	Placebo
Subgroup population	156	137
Current smoker	34.6%	31.4%
History of cervicovaginal infection or STD	35.9%	32.1%
Pap test with HSIL	6.5%	3.7%

The applicant also provided an analysis of the subgroup of subjects who were PCR positive and/or seropositive for the relevant vaccine HPV type at day 1. In this subgroup, subjects were included if they were PCR positive and seropositive, PCR positive and seronegative, or PCR negative and seropositive at the day 1 evaluation.

Table 19. Study 013: Analysis of efficacy against vaccine-relevant HPV types CIN 2/3 or worse among subjects who were PCR positive <u>and/or</u> seropositive for the relevant HPV type at day 1.
[From additional efficacy analyses requested by CBER and submitted March 15, 2006, table 1e-2, p. 13.]

	Gardasil™ N=2717				**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 CIN 2/3 or worse	685	**48**	1385.6	3.5	664	**35**	1350.3	2.6	-33.7%	<0.0, 15.3%

This demonstrated a limitation of the evaluation of small subgroups, where subgroups might have imbalances in baseline demographic characteristics. In this case, it appeared that subjects in this subgroup of study 013 who received Gardasil™ might have had enhanced risk factors for development of CIN 2/3 or worse compared to placebo recipients. In study 015, the applicant conducted a subgroup primary efficacy analyses for HPV 16/18. Here, the evaluation of this subgroup did not raise a concern about enhancement of cervical disease due to HPV:

Table 20. Study 015: Analysis of efficacy against vaccine-relevant HPV types CIN 2/3 or worse among subjects who were PCR positive and seropositive for the relevant HPV type at day 1.
[From additional efficacy analyses requested by CBER and submitted March 15, 2006, Table 1a-1, p. 2.]

	Gardasil™ N=6082				**Placebo N=6075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed reduction	95% CI
HPV 6/11/16/18 CIN 2/3 or worse	398	**42**	703.0	6.0	430	**48**	760	6.3	5.4	<0.0, 39.0%

The baseline demographic data appeared to be more balanced in this subgroup in study 015. Furthermore, evaluation of the subgroups of subjects who were PCR positive and seropositive for relevant HPV type at day 1 across studies and for HPV 6, 11, 16 and 18 types tempered evidence of disease enhancement.

Table 21. Combined analysis studies 007, 013 and 015: Analysis of efficacy against vaccine HPV related CIN among subjects who were PCR positive and seropositive for the relevant HPV type at day 1.
[From additional efficacy analyses requested by CBER and submitted March 15, 2006, Table 1b-1, p. 4.]

	Gardasil™ N=9075				**Placebo N=9075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed reduction	95% CI
HPV 6/11/16/18 CIN 2/3 or worse	568	**75**	1016.2	7.4	580	**69**	1044.0	6.6	-11.7	<0.0, 20.6%

Therefore, while the subgroup from study 013 remains a concern of the clinical review team, there is some evidence that this represented an unbalanced subgroup where Gardasil™ recipients at baseline had more risk factors for development of CIN 2/3 or worse. Furthermore, when the subgroups from three studies are combined, these groups appear to be more similar. Finally, there is compelling evidence that the vaccine lacks therapeutic efficacy among women who have had prior exposure to HPV and have not cleared previous infection (PCR positive and seropositive), which represented approximately 6% of the overall study populations.

2. Cases of CIN 2/3 or worse due to HPV types not associated with Gardasil™

The second concern was the observations of CIN 2/3 or worse cases due to HPV types not associated with Gardasil™.

Table 22. Study 015: Analysis of efficacy against CIN 2/3 or worse due to any HPV type, restricted MITT-2 population.
[From original BLA, CSR for study 015, Table 7-12, p. 256.]

	Gardasil™ N=6082				**Placebo N=6075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed efficacy	95% CI
HPV any type CIN 2/3 or worse	3789	**32**	7,186.6	0.4	3826	**51**	7272.7	0.7	36.5%	<0.0, 60.5%

The applicant's analyses primarily focused on vaccine-relevant HPV analyses. Therefore, at CBER's request the applicant provided an additional analysis of the subgroup of subjects who met the "per protocol" definition for all four vaccine-relevant HPV types:

Table 23. Study 015: Analysis of efficacy against CIN 2/3 or worse due to any type HPV, subgroup of subjects meeting the "per protocol" population for all four vaccine-relevant HPV types.
[From the applicant's response to CBER questions to MRL sent via secure email on March 1, 2006, Table 1-2, p. 17.]

	Gardasil™ N=6082				**Placebo N=6075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed reduction	95% CI
HPV any type CIN 2/3 or worse	3899	**44**	5470.2	0.8	3703	**49**	5214.4	0.9	14.4%	<0.0, 44.3%

Table 24. Study 013: Analysis of efficacy against CIN 2/3 or worse due to any HPV type, restricted MITT-2 population.
[From original BLA, CSR for study 013, Table 7-24, p. 290.]

	Gardasil™ N=2717				**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed reduction	95% CI
HPV any type CIN 1 or worse	1683	**102**	3635.8	2.8	1697	**135**	3613.1	3.7	24.9%	2.2, 42.5%
HPV type 6/11/16/18 CIN 1 or worse	1683	**0**	3685.7	0	1697	**39**	3689.9	1.1	100%	90.1, 100%
HPV not related to 6/11/16/18 CIN 1 or worse	1683	**102**	3635.8	2.8	1697	**107**	3627.2	2.9	4.9%	<0, 28.2%

*The applicant did not provide an analysis for this study of CIN 2/3 or worse.

Finally, the applicant provided analyses across all studies using Gardasil™.

Table 25. Studies 007, 013, and 015: Analysis of efficacy against CIN 2/3 or worse due to any HPV type among subgroup of subjects meeting the "per protocol" population for all four vaccine-relevant HPV types.
[From the applicant's response to CBER questions to MRL sent via secure email on March 1, 2006, Table 1-2 p. 19.]

	Gardasil™ N=9075				**Placebo N=9075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed reduction	95% CI
HPV any type CIN 2/3 or worse	5685	**75**	8631.5	0.9	5457	**87**	8315.7	1.0	16.9%	<0, 39.8%

Table 26. Studies 007, 013, and 015: **Analysis of efficacy against CIN 2/3 or worse due to any HPV type among subgroup of subjects meeting the "per protocol" population for all four vaccine-relevant HPV types, and who had normal Pap smears at day 1**.
[From the applicant's response to CBER questions to MRL sent via secure email on March 1, 2006, Table 1-2 p. 20.]

	Gardasil™ N=9075				**Placebo N=9075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed reduction	95% CI
HPV any type CIN 2/3 or worse	5051	**54**	7680.9	0.7	4887	**66**	7465.8	0.9	20.5%	<0, 45.5%

The applicant also provided an analysis of efficacy against CIN 2/3 due to any type HPV in the population that is considered to cover nearly all subjects enrolled in studies 007, 013, and 015, the MITT-3 population.

Table 27. Studies 007, 013, and 015: **Analysis of efficacy against CIN 2/3 or worse due to any HPV type, MITT-3 population**.
[From the applicant's responses to CBER questions submitted March 15, 2006, Table on p. 17.]

	Gardasil™ N=9075				**Placebo N=9075**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed reduction	95% CI
HPV any type CIN 2/3 or worse	8814	**287**	17409.5	1.6	8846	**328**	17469	1.9	12.2%	<0, 25.3%
HPV not 6/11/16/18 CIN 2/3 or worse	8814	**169**	--	--	8846	**142**	--	--	--	--

Therefore, CIN 2/3 or worse due to HPV types not contained in Gardasil™ were identified among subjects randomized to receive Gardasil™ as well as in subjects randomized to receive placebo. In the subgroup of subjects that did not have prior exposure to vaccine-relevant HPV and had normal baseline Pap tests, there appeared to be a modest efficacy of approximately 20% against CIN 2/3 or worse due to any type HPV. We again note the important limitations of a subgroup analysis where imbalances

in baseline demographics could account for differences in the subgroup efficacy determinations. The degree to which cases of CIN 2/3 or worse due to HPV types not associated with Gardasil™ might offset its efficacy against vaccine-relevant HPV types has not been fully elucidated in these studies. The BLA contained virologic characterization of disease due to HPV types 6, 11, 16 or 18 and did not characterize other HPV types. The applicant proposed a plan to identify the HPV types other than 6, 11, 16, or 18 from the studies' clinical specimens.

Studies in Younger Age Groups

Study 016: "Bridging" immune response study and "End-expiry" study

Study 016, "A study to demonstrate immunogenicity and tolerability of the quadrivalent HPB (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine in preadolescents and adolescents, and to demonstrate end-expiry specifications for the vaccine", was a phase 2 study of the safety and immunogenicity of Gardasil™ when administered to approximately 2,500 healthy children 10 to 15 years of age and healthy adolescent and adult females 16 to 23 years of age. In addition to the primary objective of safety, the study contained two "substudies" that were designed to evaluate immune responses following partial doses and to compare immune responses in children 10 to 15 years of age to the immune responses in adolescent and young adult females 16 to 23 years of age. Therefore, the study was intended to serve as an immune response "bridging study" to support the use of Gardasil™ in girls ages 10 to 15 years. The table below illustrates the immune response analyses by comparison of GMT between 10-15 year old females and 16-23 year old females.

Table 28. Protocol 016: Statistical Analysis of Non-Inferiority of Month 7 HPV cLIA GMTs Comparing 10-15 year old females to 16-23 year old females.
[From original BLA, CSR synopsis, protocol 016, p. 127.]

Assay	**10-15 year old females N=506**		**16-23 year old females N=511**		**Estimated Fold Difference Group A/Group B (95% CI)**	**p-value for non-inferiority**
	N	Estimated GMT (mmU/mL)	N	Estimated GMT (mmU/mL)		
Anti-HPV 6	426	**960.0**	320	**574.9**	**1.67** (1.46, 1.91)	< 0.001
Anti-HPV 11	426	**1224.8**	320	**705.9**	**1.74** (1.50, 2.00)	< 0.001
Anti-HPV 16	427	**4713.3**	306	**2548.0**	**1.85** (1.55, 2.21)	< 0.001
Anti-HPV 18	429	**918.4**	340	**452.9**	**2.03** (1.72, 2.39)	< 0.001

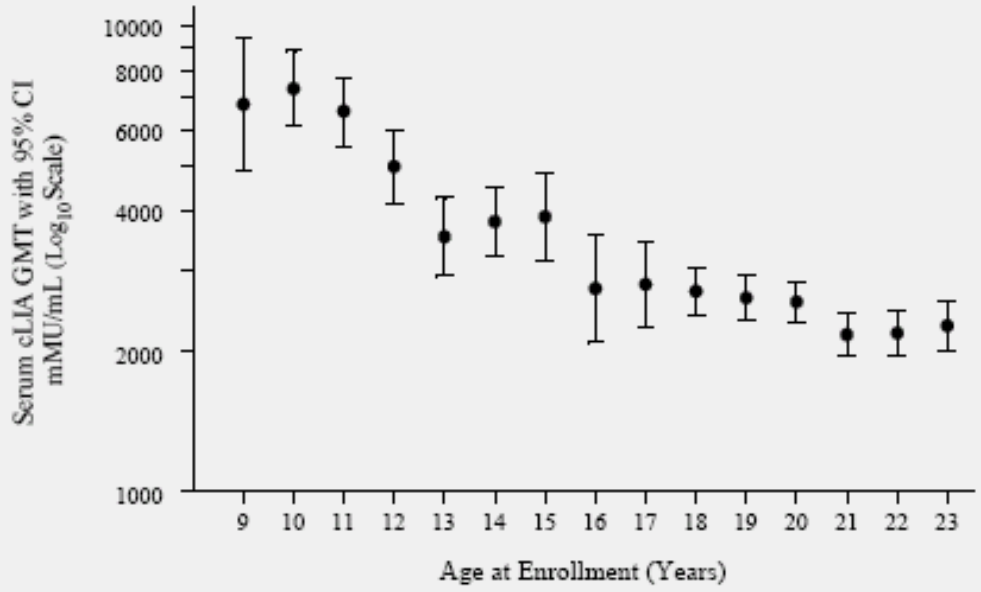
The end expiry substudy enrolled approximately 500 subjects to receive a 20% formulation (2/8/8/4), approximately 500 subjects to receive a 40% formulation

(8/16/16/8), approximately 500 subjects to receive a 60% formulation (12/24/24/12), and approximately 1500 subjects to receive the full dose formulation. The subjects receiving different dose formulations were from one of each of the three age/gender groups. There appeared to be a dose response with increasing dose formulations in this study.

Study 018: Safety and immune response younger children

Study 018, "A safety and immunogenicity study of quadrivalent HPV (types 6, 11, 16, 18) L1 virus-like particle (VLP) in preadolescents and adolescents", was designed to demonstrate non-inferiority of immune responses between males and females 9 to 15 years of age. Over 1700 children, one-half boys and one-half girls were randomized in a 2:1 fashion to receive Gardasil™ or placebo. The primary objective was the collection of safety data, which contributed to the overall safety database discussed below. The following figure represents an immune response analysis across all studies and all age groups of female subjects for HPV 16. In general, immune responses to HPV types 6, 11, and 18 appeared to be similar to this figure:

Month 7 HPV 16 cLIA Geometric Mean Titers and 95% CI by Age at Enrollment—
9- to 26-Year-Old Female Recipients of GARDASIL™
(Per-Protocol Immunogenicity Population)



Number of Subjects Evaluable (n)															
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	67	131	165	142	165	150	109	80	135	423	506	594	550	527	375

HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Safety

The safety data from all clinical studies were reviewed. These data across all protocols, in which subjects received Gardasil™ (studies 007, 013, 015, 016 and 018), are summarized here. Serious adverse events (SAEs) or deaths appeared to be reported with equal frequencies between Gardasil™ groups and placebo groups and are outlined in the tables below.

Table 29. Number (%) of SAEs and deaths combined from studies 007, 013, 015, 016, and 018.
[From March 8, 2006 safety update tables 2.7.4: 20 and 2.7.4: 21.]

Serious adverse event	**Gardasil™ N=11778**	**Placebo N=9680**
SAE over study period	101 (0.9%)	97 (1.0%)
SAE reported 1-15 days	53 (0.5%)	42 (0.4%)
Deaths [Table 2.7.4:20]	11	7

There were eleven deaths in subjects who received Gardasil™: six were attributed to traumatic injuries or drug overdose, one death attributed to pancreatic cancer, one death attributed to cardiac arrhythmia, one death attributed to DVT/PE, one death attributed to DIC with possible sepsis, and one death attributed to pneumonia and sepsis. Of the seven deaths in subjects who received placebo, five were attributed to traumatic injuries or suicide, one death attributed to complications of labor and delivery, and one death attributed to pulmonary embolism. Most deaths occurred months or years after the third vaccination and thus there were no obvious temporal associations between deaths and administration of study vaccine. A review of the serious adverse events that were observed in subjects randomized to receive Gardasil™ did not demonstrate a safety signal of concern.

Table 30. Review of SAEs by organ system in studies 007, 013, 015, 016 and 018.
[From March 8, 2006 safety update submitted to BLA, Table 2.7.4:21]

Serious adverse event	**Gardasil™ N=11778**	**Placebo N=9680**
Gynecological or obstetrical	42	41
Gastrointestinal	11	6
*Appendicitis	4	1
Injury	6	6
Neurological	4	7
Immune mediated	2	4
Coagulation/DVT	2	1
Pulmonary	2	5
Genitourinary	6	3
Endocrine	1	0
Injection site reaction	1	0
Psychiatric	5	2
Cardiovascular	1	1
Musculoskeletal	1	1
ENT	1	0
Administration of excess study vaccine	16	20
Total	101	97

Local and systemic reactogenicity data from the subjects who kept more intensive diary cards (Detailed Safety Population) in the several days following vaccination demonstrated that subjects randomized to receive Gardasil™ had a greater proportion with mild to moderate injection site reactions. Severe injection site reactions were very infrequently reported but higher in the subjects randomized to receive Gardasil™.

Table 31. Detailed Safety Population: Number (%) of subjects who reported injection site adverse event experiences by maximum intensity rating following any vaccination in studies 007, 013, 015, 016 and 018.
[From original BLA, safety summary, Table 2.7.4:45.]

Injection site adverse reactions	**Gardasil™ N=6160**	**Placebo N=4064**
Subjects with injection site experiences	5030 (82.9%)	2927 (73.3%)
Mild	3162 (52.1%)	2125 (53.2%)
Moderate	1586 (26.1%)	724 (18.1%)
Severe	271 (4.5%)	76 (1.9%)

Table 32. Detailed Safety Population: Number (%) of subjects who reported systemic adverse reactions of 2% or greater in the 15 days following receipt of study vaccine.
[From original BLA, safety summary, Table 2.7.4:14.]

Systemic adverse reaction	**Gardasil™ N=6160**	**Placebo N=4064**
Subjects reporting systemic adverse reaction	3591 (59.2%)	2414 (60.4%)
Headache	1602 (26.4%)	1101 (27.6%)
Pyrexia	782 (12.9%)	440 (11.0%)
Nausea	370 (6.1%)	251 (6.3%)
Diarrhea	224 (3.7%)	144 (3.6%)
Nasopharyngitis	353 (5.8%)	245 (6.1%)
Pharyngolaryngeal pain	266 (4.4%)	190 (4.8%)
Dizziness	214 (3.5%)	142 (3.6%)
Skin disorder	210 (3.5%)	143 (3.6%)
Abdominal pain upper	193 (3.2%)	136 3.4%)
Influenza	192 (3.2%)	154 (3.9%)
Dysmenorrheal	178 (2/9%)	152 (3.8%)
Abdominal pain	157 (2.6%)	82 (3.2%)
Fatigue	156 (2.6%)	85 (2.1%)
Vomiting	147 (2.4%)	81 (2.0%)
Injury, poisoning, procedural complications	143 (2.4%)	85 (2.1%)
Myalgias	119 (2.0%)	81 (2.0%)
Pain in extremity	118 (1.9%)	95 (2.4%)

The following table outlines the reports of new medical problems that were collected during the vaccination schedule and following the vaccination schedule. The organ systems that are bolded indicate differences between the Gardasil™ and placebo groups.

Table 33. New Medical Conditions (number and percent) during the vaccination period (day 0 through month 7) and after month 7, selected organ system evaluations where proportions differed between Gardasil™ and placebo groups. [From March 8, 2006 safety update submitted to BLA, Appendix 2.4.7:31.]

	During vaccination period		**Post month 7**	
Organ System	Gardasil™ N= 11778 (%)	Placebo N= 9868 (%)	Gardasil™ N= 10452 (%)	Placebo N= 9385 (%)
Eye disorders	118 (1.0)	72 (0.7)	82 (0.8)	78 (0.8)
Conjunctivitis	61 (0.5)	36 (0.4)	45 (0.4)	54 (0.6)
Respiratory, thoracic, mediastinal disorders	379 (3.2)	234 (2.4)	172 (1.6)	154 (1.6)
Cough	104 (0.9)	70 (0.7)	42 (0.4)	41 (0.4)
Nasal congestion	31 (0.3)	21 (0.2)	3 (<0.1)	3 (<0.1)
Pharyngeolaryngeal pain	119 (1.0)	64 (0.7)	30 (0.3)	36 (0.4)
Allergic rhinitis	46 (0.4)	18 (0.2)	15 (0.1)	12 (0.1)
Surgical or medical procedures	384 (3.3)	296 (3.1)	477 (4.6)	495 (5.3)
Appendectomy	19 (0.2)	4 (<0.1)	17 (0.2)	26 (0.3)

One potential safety signal in the BLA was reports of congenital anomalies among women who became pregnant and gave birth during the study period. When limited to receipt of vaccine within 30 days of becoming pregnant, there were five reports of congenital anomalies among women who received Gardasil™ and no reports of congenital anomalies among women who received placebo. However, the five congenital anomalies were widely varied and did not fit a particular pattern. The following table outlined pregnancies and pregnancy outcomes that were observed in all clinical studies of Gardasil™.

Table 34. Pregnancy outcomes from studies 013, 105, 016 and 018.
[From March 8, 2006 safety update submitted to BLA, table 2.7.4:24.]

	Gardasil™ N=10418	Placebo N=9120
Number of pregnancies	1115 (10.7%)	1151 (12.6%)
Live births	621 (62.3%)*	611 (60%)*
Vaginal delivery	467 (75.2%)	462 (75.6%)
Infant outcome = normal	570 (91.8%)	569 (93.1%)
Infant outcome = abnormal	49 (7.9%)	40 (6.5%)
Congenital anomaly: live births	14 (2.3%)	12 (2.0%)
Other medical condition	39 (6.3%)	28 (4.6%)
Congenital anomaly infant or fetus [#]	15	16
Abdominal wall defect	0	5
Cardiac	8	5
Chromosomal abnormality	2	0
Craniofacial/ENT	4	2
Gastrointestinal	3	0
Hematological	0	1
Orthopedic/musculoskeletal	3	5
Renal	0	1

* Percent based on known pregnancy outcome
[#] Some infants had more than one reported congenital anomaly

The applicant further evaluated congenital anomalies by the timing of the administration of study vaccine. Here, infant/fetus congenital anomalies are summarized by the estimated date of conception within or beyond 30 days of receipt of study vaccine.

Table 35. Distribution of congenital anomaly cases. [From March 8, 2006 safety update submitted to BLA, table 2.7.4:26.]

	Gardasil™	Placebo
Congenital anomaly infant or fetus	15	16
EDC within 30 days	**5**	0
EDC beyond 30 days	10	16

Summary of the five cases of congenital anomalies in the Gardasil™ group:

1. Hip dysplasia
2. Pyloric stenosis, ankyloglossia
3. Congenital hydronephrosis
4. Congenital megacolon
5. Left talipes equinovarus

Items for VRBPAC Discussion

The discussion and voting items for the committee will focus on whether the data submitted in the BLA support the safety and efficacy of Gardasil™ for prevention of HPV-related disease. If the data support the safety and efficacy of Gardasil™, an additional item for discussion will be the finding in the baseline PCR positive and seropositive subgroup of study 013 of an increased rate of CIN 2/3 or worse due to the relevant HPV vaccine types among Gardasil™ recipients. The review team found CIN 2/3 or worse cases among recipients of Gardasil™. Another item for discussion will be the degree to which HVP types not contained in the vaccine might offset the overall clinical effectiveness of the vaccine, or whether the findings of CIN 2/3 or worse among Gardasil™ recipients might represent the impact of prevalent HPV disease. The committee should also discuss the observation of five congenital anomalies among infants born to recipients of Gardasil™ who were vaccinated near the time of conception. Although questions will not focus specifically on labeling recommendations, the committee should be prepared to discuss how the product label should display important efficacy and safety information about subgroup intention-to-treat analyses.

Appendix A

Colposcopy algorithm for study 015:

Mandatory Regimen for Triage of Abnormal Pap Tests to Colposcopy

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

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

‡ Subjects with a diagnosis of LSIL at Day 1 were referred immediately for colposcopy.

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

NOS = Not otherwise specified; HPV = Human papillomavirus; ASC-US = Atypical squamous cells of undetermined significance; ASC-H = Atypical squamous cells, cannot rule out HSIL; LSIL = Low-grade squamous intraepithelial lesions; HSIL = High-grade squamous intraepithelial lesions.

Appendix A, cont.

Colposcopy algorithm for study 013

Mandatory Regimen for Triage of Abnormal Pap Tests to Colposcopy

ThinPrep™ Pap Result	Action
Negative for intraepithelial lesion or malignancy (includes reactive, reparative, inflammatory, etc.)	Routine visit interval as specified by the protocol.
Atypical Squamous Cells of Undetermined Significance (ASC-US)	Central laboratory performed reflex HPV testing on residual ThinPrep™ material (High-Risk and Low-Risk Probe, Hybrid Capture II, DIGENE™). If at least 1 probe was positive, the subject was to be referred for colposcopy. If both probes were negative, then the subject returned for Pap screening at the routine visit interval.
Atypical Squamous Cells, cannot rule out HSIL (ASC-H)	Referral to colposcopy.
Low-grade Squamous Intraepithelial Lesion (LSIL)	Referral to colposcopy.
High-grade Squamous Intraepithelial Lesion (HSIL)	Referral to colposcopy.
Atypical Glandular Cells (to include atypical endocervical, endometrial, NOS; adenocarcinoma in situ, adenocarcinoma, etc.)	Referral to colposcopy.
Inadequate specimen	Repeat Pap test as soon as possible. The interval between the rescheduled Pap test and the Pap test that had the unsatisfactory finding must have been at least 4 weeks.
Subjects with any abnormal Pap test result at Month 48 were referred immediately for colposcopy. This colposcopy must have been performed within 2 months of the Month 48 visit. All specimens collected during this colposcopy were handled through the Sponsor central laboratory. A diagnosis of an HPV-related external genital lesion (e.g., VIN, VaIN, and genital warts), as confirmed by the Sponsor central laboratory ALSO constituted a reason for referral to colposcopy. If a histologically confirmed HPV-related vaginal lesion was diagnosed as a consequence of a colposcopic examination of the cervix, then the subject did not require another referral to colposcopy. Any cervical/vaginal lesion suspected to be HPV-related (e.g., CIN, VaIN, cancer, or condylomata) was to be biopsied. Colposcopy should have only been performed according to the guidelines in this table. HPV = Human papillomavirus; VIN = Vulvar intraepithelial neoplasia; VaIN = Vaginal intraepithelial neoplasia; CIN = Cervical intraepithelial neoplasia; NOS = Not otherwise specified.	

Subjects in study 015 who had atypical squamous cells of undetermined significance (ASC-US) were not referred to colposcopy, but had a Pap test repeated sooner at 6 months instead of scheduled 12 months. In study 013, subjects with ASC-US received an HPV probe, and if positive were referred to colposcopy.

Appendix B

For all studies included in the efficacy composite (Studies 005, 007, 013, and 015), these procedures were used for cervical biopsy/definitive therapy specimens, from original BLA Summary of Clinical Efficacy – cervixcancer section 2.7.3, p. 42:

> Slides of tissue specimens were prepared by the program central laboratory. The laboratory reviewed the slides and provided a diagnosis for the purpose of management of the subject. The diagnosis from the laboratory was not included in the endpoint definition because studies have shown that pathologists who read histologic slides for the purpose of medical management tend to over-diagnosis CIN 1 lesions due to medicolegal pressure. The slides prepared by the central laboratory from the cervical biopsy/definitive therapy specimens were submitted to an expert Pathology Panel. This panel, consisting of four pathologists, reviewed these slides for the purpose of providing the official diagnosis for the primary analysis of vaccine efficacy. The Pathology Panel was blinded to the results of the PCR analysis of the cervical biopsy/definitive therapy specimen and HPV PCR swabs obtained during routine visits. The consensus diagnosis of the panel represented the final diagnosis for study purposes.

Table 1. Members of the Pathology Panel

Name/Title	Address
Robert Kurman, M.D.	Department of Pathology Johns Hopkins University 401 North Broadway Weinberg Building, Room 2242 Baltimore, MD 21231 Telephone: (410) 955-2804 / FAX: (410) 614-1287
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Mark Stoler, M.D.	Department of Surgical Pathology UVA Health Systems P.O. Box 800214 Charlottesville, VA 22908 Telephone: (434) 982-0284 / FAX: (434) 924-0217
Alexander Ferenczy, M.D.	Department of Pathology Sir Mortimer B. Davis Jewish General Hospital 3755 Cote Sainte-Catherine Road, Room G-102 Montreal, Quebec, CANADA, H3T 1E2 Telephone: (514) 340-7526 / FAX: (514) 340-7542

Appendix B, cont.

The panel will be blinded to each subject's study treatment, subject PCR status, and Central Laboratory pathologist diagnosis, and will not be directly involved in subject management. Additionally, in order to minimize potential bias, cervical specimens and external specimens (including external genital lesion and vaginal lesion biopsies) from a single subject-visit will be separated and assigned to different review cycles (see Section I.C.2. Merck Coordinating Center and Section II.C. Procedures).

The panelists' classifications will also be used for providing "Safety Net notifications". The SPONSOR will notify the Principal Investigator and study site for any of the following circumstances:

- Histological classification of any carcinoma, including CIN 3 (squamous cell carcinoma in-situ), adenocarcinoma in situ or adenocarcinoma, during any review stage which was NOT reported previously by the Central Laboratory pathologist;
- Histological classification of anogenital cancer, vulvar intraepithelial neoplasia (VIN) 2/3, or vaginal intraepithelial neoplasia (VaIN) 2/3 during any review stage which was NOT reported previously by the Central Laboratory pathologist;
- Consensus classification of CIN 2/3 or worse for any cervical specimen (cervical biopsy, ECC, or definitive therapy specimen) which is more severe than the worst diagnosis reported by the Central Laboratory pathologist for any cervical specimen from that subject-visit (see hierarchies given in Section II.E, Table 4);
- Consensus classification for any vaginal biopsy or external genital lesion biopsy specimen of VIN 2/3, VaIN 2/3, or any more severe diagnosis which was NOT reported previously by the Central Laboratory pathologist (see hierarchies given in Section II.E, Table 5).

Appendix C:

Applicant's definitions of the populations used in efficacy analyses.

Per Protocol:
- Received all three vaccinations
- Seronegative at day 1 and PCR-negative at day 1 and at month 7 to the appropriate HPV types
- Did not deviate from the protocol
- Clinical endpoints were counted beginning one month after the third dose (month 7)

Modified Intent-to-treat population 1 (MITT-1):
- Received all three vaccinations
- Seronegative at day 1 and PCR-negative at day 1 and at month 7 to the appropriate HPV types
- Clinical endpoints were counted beginning one month after the third dose (month 7)

Modified Intent-to-treat population 2 (MITT-2):
- Received at least one vaccine
- Seronegative at day 1 and PCR-negative at day 1 to the appropriate HPV types
- Had any follow-up visit after one month following the first injection
- Clinical endpoints were counted beginning one month after the first dose (month 1)

Modified Intent-to-treat population 2, restricted (RMITT-2):
- Received at least one vaccine
- Seronegative at day 1 and PCR-negative at day 1 to the appropriate HPV types
- Had any follow-up visit after one month following the first injection
- Pap test results normal at day 1
- Clinical endpoints were counted beginning one month after the first dose (month 1)

Modified Intent-to-treat population 3 (MITT-3)
- Received at least one vaccine
- Had any follow-up visit after one month following the first injection
- Clinical endpoints were counted beginning one month after the first dose (month 1)