September 11, 2008

From: Nancy B. Miller, M.D.
Medical Officer
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Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Subject: Clinical Review of Biologics License Application Supplement for Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant (Gardasil®) to extend indication for prevention of vaginal and vulvar cancers related to HPV types 16 and 18.

To: BLA STN# 125126/419

Through: Joseph Toerner, M.D., M.P.H., Team Leader
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1. Title and General Information

1.1 Title: Medical Officer's Review

1.1.1 STN BLA 125126

1.1.2 Related INDs: ---------(b)(4)----------

1.1.3 Reviewer's Name: Nancy B. Miller, M.D., DVRPA, HFM-485

1.1.4 Submission Date: 4/2/07

1.1.5 Review Completed: 9/10//08

1.2 Product

1.2.1 Proper Name: Human Papillomavirus Quadrivalent [Types 6, 11, 16, 18] Vaccine, Recombinant

1.2.2 Trade Name: GARDASIL®

1.2.3 Product Formulation: Each 0.5 mL dose of the vaccine contains:

20 mcg of HPV 6 L1 protein
40 mcg of HPV 11 L1 protein
40 mcg of HPV 16 L1 protein
20 mcg of HPV 18 L1 protein
225 mcg aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant)
9.56 mg of sodium chloride
0.78 mg of L-histidine
50 mcg of polysorbate 80
35 mcg of sodium borate
< 7 mcg yeast protein
water for injection

1.3 Applicant: Merck, Inc.

1.4 Pharmacologic Category: Vaccine

1.5 Proposed Licensed Indication: Prevention of the following diseases:

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

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

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

1.6 Population: Females 9-26 years of age

1.7 Dosage Form and Routes of Administration: The vaccine is administered by intramuscular injection as a three dose series at 0, 2, and 6 months. It will be supplied in cartons of one and ten 0.5 mL single dose vials and one and six pre-filled syringes.

2. TABLE OF CONTENTS

3. Executive Summary

Merck submitted a Biologics License Application (BLA) Supplement for Gardasil®, a quadrivalent HPV 6/11/16/18 L1 VLP vaccine adjuvanted with aluminum hydroxide, on April 2, 2007 to support additional indications to prevent vulvar and vaginal cancer related to HPV 16 and 18. The supplement BLA should be approved, granting the additional indications to be included in product labeling as well as updated safety and efficacy data to be included in product labeling. These new indications were sought on the basis of close-out data from the pivotal Phase IIB and III efficacy studies for Gardasil, in which subjects were followed in a blinded manner (subject blinded, investigator blinded, and lab and pathology personnel blinded to allocation) in a pre-specified manner after the time of original licensure (June 8, 2006 in the U.S.). The conclusions, which follow below, are derived from the review of the additional data from Phase IIb and III trials (Studies 007, 013, and 015) submitted to the BLA supplement. At the time of original licensure, the sponsor had committed to submit final Clinical Study Reports (CSRs) for Protocols 013 and 015 when completed. In these studies, subjects were followed for development of additional cervical and external genital disease endpoints related to vaccine HPV types, as well as development genital disease endpoints related to non-vaccine HPV types. Protocol 007 was originally submitted in May, 2000; Protocol 013 was initially submitted in December 2001; and Protocol 015 was initially submitted in May 2002. As specified in a post-marketing commitment, these analyses were to be completed by April 30, 2007. The final reports for these studies (i.e., Clinical Study Reports) to include the results of these analyses were to be submitted by June 30, 2007.

The data submitted to the BLA supplement are considered supportive of the additional indications of Gardasil efficacy in the prevention of HPV 16 and/or 18 related vulvar and vaginal squamous cell cancers due to prevention of HPV 16 and/or 18 related VIN 2/3 and VaIN 2/3. VIN 2/3 and VaIN 2/3 were considered acceptable surrogates for HPV 16 and/or 18 related vulvar and vaginal squamous cell cancers, respectively, in females 9-26 years of age who are naïve for the relevant HPV type.

With the approval of this supplement, the package insert was revised to conform to the Physician's Labeling Rule format. The most up-to-date efficacy, safety, and immunogenicity data were included in supplement 125126/-(b)(4)- (which contained final close out data from studies HPV-013 and HPV-015), and these data were reviewed and considered in the revision of the package insert approved 9/12/08. In addition, safety data from study HPV-019 (Gardasil use in women 24-45 years of age) were also reviewed and included in this document and package insert to provide complete information available from clinical studies on serious adverse events, deaths, pregnancy outcomes, and reports of congenital anomalies which occurred in older women. New medical conditions which have been reported since vaccination, as well as follow-up safety data for study HPV-018 out to Month 30, the saline placebo controlled study in children 9-15 years of age, were included in this review and the lackage insert.

In the original application for licensure, indications to prevent HPV 6-, 11-, 16-, or 18 related Vulvar Intraepithelial Neoplasia (VIN) Grades 2/3 or Vaginal Intraepithelial Neoplasia (VaIN) Grades 2/3 were approved. A co-primary endpoint for Study 013,

included in the composite endpoint "External Genital Lesions," was diagnosis of VIN 2/3 and VaIN 2/3 with evidence of HPV 6, 11, 16, or 18 in the specimen. Data to support these indications also came from an analysis of combined data from Studies 007, 013, and 015. In the original analysis of Study 013 (case event driven), the efficacy of Gardasil against HPV related 6, 11, 16, and/or 18 related VIN 2/3 or VaIN 2/3 was 100% [95%: 30.2, 100%] for the PPE population. In the analysis of combined studies data, efficacy was 100% [95% CI: 67.2, 100%]. Analysis of the ability of Gardasil to prevent 6, 11, 16, and/or 18 related VIN 2/3 was provided for the combined studies and in the PPE population, efficacy of Gardasil was 100% [95% CI: 41.4, 100%]. Similarly, the ability of Gardasil to prevent HPV 6, 11, 16, and/or 18 related VaIN 2/3 was presented for the combined Studies 007, 013, and 015. Although the point estimates for efficacy were 100% for the PPE population, the number of VaIN 2/3 cases was small and therefore the lower bound of the 95% CI for this estimate was less than zero. The numbers of cases of VIN 2/3 and VaIN 2/3 related to the oncogenic HPV types 16 and 18 individually did not reach statistical significance, although the point estimate of efficacy for each of these endpoints were also 100%. As the subjects were followed in the combined studies (pre-specified in a blinded manner for subject, investigator, and personnel involved in the ascertainment of endpoints), only subjects in the control group developed additional cases associated with HPV 16 or 18, and the point estimates for HPV 16 and/or 18 related VIN 2/3 and VaIN 2/3 in subjects previously unexposed to the relevant HPV type (per-protocol population) were 100% when considered together [95% CI: 72.3, 100%] and individually (VIN 2/3 [95% CI: 41.7, 100%] and VaIN 2/3 [95% CI: 30.9%, 100%]). These data are further discussed in the overview of efficacy across trials in this review. The original clinical review is located on the FDA website at the following URL: http://www.fda.gov/cber/review/hpvmer060806r.pdf. It is important to note that, unlike cervical cancer, in which approximately 99% of cases have been reported to be associated with ANY HPV infection, not all vulvar and vaginal cancers are related to HPV infection. Further, these cancers are rare.

Vaccine estimates of efficacy in the Modified Intent to Treat-3 (MITT-3) population, which includes naïve (seronegative Day 1 and PCR negative through Month 1 for the relevant HPV type) and non-naïve (seropositive and/or PCR positive at Day 1 for the relevant HPV type) subjects with cases counted after day 1 of Month 1 visit, remain lower than the point estimates of vaccine efficacy calculated in the per-protocol population. In the final close-out data, for vaccine efficacy in the prevention of HPV 16 and/or 18 related VIN 2/3 and VaIN 2/3 in the MITT-3 population is 84.2% [95% CI: 46.2, 97.0%]. The point estimate of efficacy in prevention of HPV 16 and/or 18 related VIN 2/3 is 69.1% [95% CI: 29.8, 87.9%], and for HPV 16 and/or 18 related VaIN 2/3 is 84.6% [95% CI: 31.8, 98.3%].

At the time of CBER's VRBPAC presentation in May, 2006, (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm), the role of baseline HPV status and endpoint counting for prophylactic vaccine efficacy was discussed. If a subject was naïve (that is, did not have evidence of previous exposure to all 4 of the vaccine HPV types [was seronegative at baseline and PCR negative for each type Day 1 through Month 7], that subject would be eligible for the per protocol population for each of the types. However, if a subject was naïve to HPV 6, 11, and 18

(that is, did not have evidence of prior exposure to HPV 6, 11, and 18 by virtue of serongativity and PCR negativity through Month 7), but had evidence of prior exposure to HPV 16 (that is, the subject was seropositive at Day 1 and/or PCR positive for HPV 16 Day 1 through Month 7) , that subject would be eligible for the per protocol populations for HPV 6, 11, and 18, but not for HPV 16. Therefore, it was possible that this subject would develop HPV 16 related disease despite protection against the other vaccine HPV types for which the subject was naïve through Month 7.

Another important point is that in the Vaccines and Related Biological Products Advisory Committee in May 2006, CBER noted that the sponsor's per-protocol HPV type-specific analyses that indicated a high level of efficacy in naïve subjects may not reflect the efficacy of Gardasil for all HPV related disease on a population basis, because of prevalent infection with vaccine and non-vaccine HPV types at the time of vaccination, and because of lack of meaningful prevention of non-vaccine HPV type related disease in subjects naïve (PCR negative) for the non-vaccine HPV types. In this review, CBER has included a table including all VIN 2/3 and VaIN 2/3 cases detected throughout the studies, with subjects counted after Day 1. These tables include those subjects who developed lesions related to vaccine HPV types, non-vaccine HPV types, and those not associated with detected HPV. Of note, a case of well-differentiated vulvar cancer was detected in the Gardasil group at Month 24 in a subject in whom HPV was never detected, and who never had an abnormal Pap test during the study period. The lesion did not contain one of the 10 oncogenic HPV types for which the specimen was tested. As noted in the package insert under warnings and precautions: "Not all vulvar and vaginal cancers are caused by HPV and Gardasil protects only against those vulvar and vaginal cancers caused by HPV 16 and 18." Another related warning and precaution states: "Gardasil has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a woman has previously been exposed through sexual activity."

Follow-up data were also presented within the supplements to the BLA and continue to support the originally approved indications, including prevention of HPV 16 and 18 related cervical cancer, HPV 6 and 11 related condyloma acuminata or genital warts, and HPV 6, 11, 16, and 18 related Cervical Intraepthelial Neoplasia (CIN) grade 2/3, Adenocarcinoma in situ (AIS) or worse, CIN 1, VIN 2/3 and VaIN 2/3. These additional analyses are also presented in the overview of efficacy. Analyses of these endpoints in women who were previously exposed to vaccine and non-vaccine HPV type infection are included within the review, as well as analyses of women who were naïve for non-vaccine HPV types. At the time of the original review and licensure, testing for specific non-vaccine HPV types had not yet been conducted. A discussion of impact on non-vaccine HPV types as they relate to development of CIN 2/3 or worse is also included in this review.

The additional safety data provided in the clinical studies is discussed in the overview of safety across trials. Additional post-marketing safety events are discussed. Review of updated safety data within the clinical trials demonstrates similar findings reported at the time of the original review. Analyses of serious post-marketing events are ongoing by CBER staff of Vaccine Adverse Event Reporting System (VAERS). As noted in the

article by Zhou et al[1], VAERS is a passive surveillance system, and reports of events are voluntarily submitted by those who experience them, their caregivers, or others. As the authors note, passive surveillance systems are subject to multiple limitations, including underreporting, reporting of temporal associations or unconfirmed diagnoses, and lack of denominator data and unbiased comparison groups. The authors also note that because of these limitations, determining causal associations between vaccines and adverse events from VAERS reports is usually not possible, and that vaccine safety concerns identified through adverse event monitoring nearly always require confirmation using an epidemiologic or other study. At the time of this reviw, the incidences of adverse events in the post-marketing period after receipt of Gardasil have not exceeded the expected background rates for certain conditions. However, because of the stated limitations that exist for reporting to VAERS, continuing analyses in a post-marketing safety surveillance study is ongoing.

Also included in supplement 125126/419 is an updated report of immunogenicity of Gardasil out to Month 60 (in Phase IIb study HPV-007), and presentation of immune responses at the time of completion of studies HPV-013 and HPV-015.

As already noted, the package insert has been revised to conform with the Physician's Labeling Rule. Limitations of vaccine efficacy have been included in the warnings and precautions section, and efficacy and safety sections of the package insert have been updated as well to include additional efficacy and safety data. Adverse events reported in the post-marketing period have been updated. The information regarding anti-HPV 6, 11, 16, and 18 antibodies Geometric Mean Titers and seropositivity rates at Month 60, and their similarity to those measured at Month 24, has been included in the package insert as well. The major changes are noted in the labeling section of this review.

4. Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls – No CMC information is included in this supplement, although communications regarding resolution of general sponsor compliance issues resolved on July 10, 2008 are included in the supplement.

4.2 Animal Pharmacology/Toxicology –No toxicology data included in this supplement.

CLINICAL REVIEW

5. Clinical and Regulatory Background

5.1 Disease Studied and Available Interventions: Cervical cancer is an important public health problem in the United States, with 9710 new cervical cancer cases and 3700 death due to cervical cancer projected for 2006.[2] Cervical cancer has been associated with Human Papillomavirus (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,

[1] Zhou W et al. MMWR Surveillance Summary 2003 Jan 24;52(1):1-24.
[2] Jemal A et al. Cancer Statistics, 2006. *CA: A Cancer Journal for Clinicians* 2006;56:106-30.

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 the 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 HPV 11 are thought to be responsible for > 90% of these cases.[3] A vaccine that is efficacious in providing protection against HPV types 6, 11, 16, and 18, based on available epidemiological data, might be capable of having an impact in preventing cervical cancer, condyloma acuminata, and other HPV associated diseases related to the vaccine HPV types.

Similarly, vulvar and vaginal dysplasias, vulvar intraepithelial neoplasias grade 2/3 (VIN 2/3) and vaginal intraepithelial neoplasias grades 2/3 (VaIN 2/3) associated with HPV 16 and/or 18 are considered to be precursors of some vulvar and vaginal cancers. It is noted that vulvar cancer is not always associated with HPV infection, although the incidence of VIN has nearly doubled in the past few decades and is being found in younger women, and some of this increase may be related to increased exposure to HPV infection over this time. Dr. Gerald Willett, M.D., Division of Reproductive and Urologic Products, Center for Drugs, provided a consultation to discuss the etiology of VIN and VaIN and the appropriateness of their use as precursors of vulvar and vaginal cancer, respectively. (Please see separate review document.) In his review, the following citation is included from a recent article by Dr. M. Srodon et al[4]: "VIN 3 and VaIN 3 are often found immediately adjacent to their respective carcinomas and it is generally acknowledged that these intraepithelial lesions are the precursors of vulvar and vaginal carcinomas." Analyses conducted on the original data were supportive of including an indication that Gardasil prevents VIN 2/3 and VaIN 2/3 related to vaccine HPV types for which the subjects were naive.

In the original data sets, the point estimate of vaccine efficacy (VE) in reduction of HPV 16 and/or 18 related VIN 2/3 and VaIN 2/3 in the per protocol population[5] was noted to be 100% [95% CI: 55.5, 100%], but did not reach statistical significance for the endpoints individually due to the small number of cases. In the data submitted to supplement 125126/419, the VE for the combined endpoint of HPV 16 and/or 18 related VIN 2/3 and VaIN 2/3 was 100% [95% CI: 72.3, 100%]. Individually, the VE for HPV 16 and/or 18 related VIN 2/3 was 100% [95% CI: 41.7, 100%], and the VE against HPV 16 and/or 18 related VaIN 2/3 was 100% [95% CI: 30.9, 100%]. In the final close-out report, for studies HPV-007, -013 and -015, in the same per protocol population, the combined efficacy in reduction of HPV 16 and/or 18 related VIN 2/3 and/or VaIN 2/3 related to HPV 16 and/or 18 was 100% [95% CI: 78.6, 100%], for HPV 16 and/or 18 related VIN 2/3 100% [95% CI: 55.5, 100%], and for HPV 16

[3] vanKrogh G et al. *Sex Transm Inf* 2000; 76: 162-8.
[4] Srodon M et al. *Am J Surg Pathol* 2006; 30(12): 1513-8.
[5] Per Protocol Population for Efficacy: subjects were naïve (seronegative Day 1 and PCR negative for the relevant HPV type Day 1 through Month 7, received all 3 doses of study material, and were not protocol violators.

and/or 18 related VaIN 2/3 100% [95% CI: 49.5, 100%]. As noted at the time of original licensure, efficacy is lower when all subjects are included in the analysis (includes subjects who are naïve and non-naïve at baseline, with cases counted starting 1 day after Month 1). CBER has tabulated the case splits from the time of vaccine administration, and in the entire population, Gardasil does not prevent cases of VIN 2/3 and VaIN 2/3 related to HPV types present at baseline, nor those related to non-vaccine HPV types for which a subject is naive, nor those which are unrelated to HPV.

In addition to the planned statistical review and analyses by the sponsor, CBER also reviewed the impact of incidence of VIN 2/3 and VaIN 2/3 lesions related to vaccine HPV types and non-vaccine HPV types, and this discussion is included in the overview of efficacy section.

Other issues discussed in this review include: immunogenicity data out to Month 60 from study HPV-007, updated safety data from available studies, final efficacy estimates for HPV 16/18 related CIN 2/3, HPV 6/11 related genital warts and external genital lesions) and CIN 1 from close-out data for studies HPV-013 and -015 (approximately 42 months duration). The datasets from the final study reports for studies HPV-013 and HPV-015 permitted an analysis of the impact of Gardasil on non-vaccine HPV types. These data were included in supplement 125126/419 as well as STN 125126/-(b)(4)-. In order to provide the most comprehensive safety data available to date, it was considered important to include safety data submitted to supplement -(b)(4)- (serious adverse events, pregnancy outcomes, and congenital anomaly information) and supplement -(b)(4)- (updated safety follow-up, serious adverse event totals, pregnancy outcomes) within this review document and in the updated Physician's Labeling Rule package insert (label).

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

Gardasil was licensed in the U.S. for the prevention of HPV 6, 11, 16, 18 related CIN 2/3 or worse, CIN 1, condyloma, VIN 2/3 and VaIN 2/3 in June 2006. A related product, Cervarix, manufactured by GlaxoSmithKline, which contains HPV 16/18 L1 VLP adjuvanted with aluminum hydroxide and monophosphoryl lipid A, is approved for marketing in Australia (May 2007) and the European Union (September 2007), [total of 66 foreign countries as of 6/24/08].

5.3 Previous human experience with the product or related products as well as foreign experience

As of February 2008, there have been app. ---(b)(4)-- doses distributed in the US, and app. --(b)(4)-- doses distributed worldwide. Post-marketing studies for Gardasil are underway worldwide (safety and efficacy), and results of these trials are still pending. The results of initial safety data are included in the original review of Gardasil at the following FDA website (http://www.fda.gov/cber/review/hpvmer060806r.pdf). Additional safety experience has been reported in supplement 419, as well as supplements -(b)(4)- and -(b)(4)-. This information has been included within the

safety overview within this document. Some update information is included for the post-marketing commitments, and status of completed commitments. In addition, this document includes events which have occurred in the post-marketing period and were reported to VAERS (Vaccine Adverse Events Reporting System). For Cervarix, the vaccine is available as noted in a large number of foreign countries.

5.4 Regulatory Background Information

TABLE 1
Regulatory Background Information – 125126/419

Date	Action
4/2/07 (received)	Submission of supplement 125126/419.0 This supplement included indication for cross-protection
5/21/07	CBER requests additional safety data for potentially autoimmune events included in revised Table 5 of the proposed package insert.
6/8/07	Request for resubmission labeling for /419 and /-(b)(4)- as appropriate with removal of cross-protection from both
7/6/07	Revised submission for prevention of vulvar/vaginal cancer (/419.1)
7/13/07	Additional safety data submitted as requested for potentially autoimmune events included in revised package insert Table 5. (/419.2)
8/2/07	CBER requests meta-analysis of potentially autoimmune events in clinical trials, and requests that Merck submit a meta-analysis methodology proposal; if proposal OK, Merck to then submit the conducted meta-analysis.
9/12/07	Merck submits meta-analysis of auto-immune events within Table 5. (/419.3)
9/12/07	CBER requests line numbered package insert.
9/13/07	Discussion of Merck's reply to CBER's request for additional data on potential autoimmune events and meta-analysis plan
9/19/07	Submission of line numbered package insert. (/419.4)
9/21/07	Discussion of meta-analysis for autoimmune disorders in non-IND studies.
10/4/07	Response to information on auto-immune events and requested meta-analysis. (/419.5)
10/16/07	Additional requested narrative on subjects with auto-immune events, (/419.6)
	CBER requests methodology for multiplicity adjustment.
12/17/07	Submission of requested methodology for multiplicity adjustment details. (/419.7)
1/11/08	Supplement issued complete response because of compliance issues.
7/10/08	Office of Compliance sends letter to Merck indicating the compliance issues were resolved.
7/11/08	Compliance issues resolved, and /419 review re-starts as a class I re-submission, with a 2-month review clock
7/25/08	CBER - revised PLR package insert [PI 2/22/08 used as template] sent to Merck for their review, with deadline for first response 8/8/08.
8/1/08	CBER request for additional information on subject with myocarditis.
8/5/08	Merck submitted revised label in response to the one sent to them on 7/25/08 (submitted to -(b)(4)-).
8/10/08	CBER holds internal PI meeting to revise from Merck's PI sent 8/5/08.
8/25/08	CBER –revised PLR package insert sent to Merck with additional revisions, with deadline for response of 8/29/08.
8/29/08	Merck submitted label with points to discuss in response to label sent 8/25/08.
9/5/08	CBER and Merck discuss PI in telecon.
9/12/08	Approval of indication to prevent HPV 16 and 18 related vulvar and vaginal cancers

From a regulatory view, the submission of this supplement was complicated by the fact that when initially submitted, the supplement included data to support two indications: the indication that the vaccine prevents vulvar and vaginal cancer related to HPV 16 and/or 18, as well as the indication that the vaccine provides -----(b)(4)----------. The Prescription Drug User Fee Act (PDUFA) stipulated that a separate supplement was required to be submitted for each proposed new indication. Because of these PDUFA regulations, the supplement was re-submitted in two parts. Supplement 419.1 was submitted and included the

indication to prevent HPV 16 and/or 18 related vulvar and vaginal cancers on 7/6/07. The same data was submitted to supplement -(b)(4)- on 6/10/07. That supplement also contained an updated safety report at Month 24 for study HPV-018 (safety and immunogenicity profile) in pre-adolescent girls and boys as compared to a true saline placebo. In supplement 125126/-(b)(4)-, Month 30 data was submitted to the BLA as well, and noted in the review. A subsequent amendment, -(b)(4)-, which was submitted 2/6/08, contained the final close out efficacy and safety data for all subjects in studies HPV-013 and -015. In addition, this amendment also included the Post-marketing Safety Update Report (12/1/06 to 5/31/07). Given the need to review the most complete data and then include it in the revised package insert, the final study reports for studies HPV-013 and HPV-015 were reviewed and included in this document and the revised package insert.

The additional supplement -(b)(4)- includes an important document for safety (congenital anomaly and pregnancy outcome follow-up report). In addition, safety data including deaths, serious adverse events, and discontinuations due to adverse events were reviewed and included in this review.

Updated safety and close-out efficacy data from supplement -(b)(4)- and safety data from supplement -(b)(4)- were considered important and required inclusion in the label. Since a major revision of the label to PLR format was completed with approval of supplement 419, this review includes the updated safety and close-out efficacy data from supplements 419 and -(b)(4)-, and important safety data from supplement -(b)(4)-.

All clinical studies submitted to the BLA were conducted under IND. Studies were reviewed and found to be safe to proceed. Studies that enrolled pediatric subjects included Parent/Guardian consent as well as subject assent.

It is noted that some adverse events identified in post-marketing reports to VAERS have been included within the post-marketing section of the revised label. Although causality has not been definitively associated with the vaccine, the seriousness of these adverse events dictated that these events be included within that section.

6 Clinical Data Sources, Review Strategy, and Data Integrity

6.1 Material Reviewed

BLA 125126/419 contained the sponsor's clinical study reports which supported the indications for prevention of vulvar/vaginal cancer related to HPV 16/18. These clinical studies are included in Table 2 below.

6.2 Tables of Clinical Studies

TABLE 2

Quadrivalent HPV 6, 11, 16, 18 L1 VLP Vaccine Summary of Pivotal Phase IIb-III Trials

Study Protocol	Description	Study Population	Planned Subjects	Vaccine: Control	Number of subject who received Gardasil	Dosing Vaccine	Placebo or Control	Dates
007-10 Multicenter (23 sites in 5 countries: US, Brazil, Finland, Norway, Sweden) (Revised 2/26/07)	Phase 2b + dose range (Part A and B)	16-23 yo women	Part A: 45 Part B: 1000	alum 225: 135, alum 450: 140 20/40/40/20: 276 40/40/40/40: 272 80/80/40/80: 280	276	3 doses @ 0,2,6,M	Alum control @ 0,2,6,M	5/26/00 – 5/10/04; Extension study ended 9/16/06 for safety, efficacy & immunogenicity; [Gardasil given then at M 60, 62, & 66 to control subjects, and Gardasil to vaccine recipients at M60.]
013-10 Multicenter (62 centers in 16 countries in North America, Latin America, Europe and Asia) (3/20/07 & 11/9/07 versions)	Phase 3 Efficacy Internal and External Genital Disease	16-23 yo women	5700	2717:2725 +304 HPV16	2717	3 doses @ 0,2,6M	Alum @0,2,6M	12/28/01-7/15/05; follow-up analyses conducted at 6/15/06 and 7/31/07.
015-10 Multicenter (90 centers in 14 countries in 4 geographic areas) (3/9/07 & 11/13/07 versions)	Phase 3 Safety +Immunogenicity+Efficacy Consistency Lot substudy NSAE substudy Long-term follow-up study	16-23 yo women (16-26 yo in Singapore)	11500	6082:6075 (459:457 NSAE) (1514:1513 consistency lot) (uncertain number in long term)	6082	3 doses @ 0,2,6M	Alum @0,2,6M	6/24/02-6/10/05; follow-up analyses conducted 6/15/06 & 7/31/07.
018 Multicenter (47 sites in 10 countries) M24 follow-up for safety (2/23/07)	Phase 3 Safety + Immunogenicity	9-15 yo girls and boys	1650	1179:596	1775 (615 girls 564 boys)	3 doses @ 0,2,6M	Saline @ 0,2,6M	10/8/03-1/19/05

N: number of subjects who received at least one dose of 20/40/40/20 dose vaccine

Updated overall analyses reports were submitted and reviewed. These included the following:

- Updated Analyses of Efficacy of Gardasil in the Reduction of CIN 2/3 or worse in young women (reports dated 3/15/07 & 11/9/07).
- Impact of Gardasil on Incidence of cervical or External Genital Disease Related to HPV Types not included in Gardasil in Young Women (Cross-Protection) (reports

dated 3/27/07 and 12/4/07). The 12/4/07 report contains the final close out data for studies 013 and 015 and supercedes the one sent 3/27/07.

- Updated Statistical Integrated Summary of Efficacy (report dated 3/2/07)
- Risk Management Plan (report dated 3/14/07) [This details the previously agreed to post-marketing commitments, with additional details for some.]
- Requested clinical narratives and meta-analyses for autoimmune events included in revised Table 5 of the Packaging Insert. These data were submitted as supplements 419.2 (sent 7/13/07); 419.3 (proposed meta-analysis methodology – 9/12/07); 419.5 (actual meta-analysis of potentially autoimmune events in Gardasil clinical trials-10/4/07); and 419.6 (additional clinical narratives – 10/16/07).
- Pregnancy history update JMP dataset for 007 (contained in 125126/-(b)(4)-) [1/11/08]
- Updated evaluation of congenital anomalies in pregnancy outcomes of subjects enrolled in Gardasil trials (report dated 12/3/07)
- Updated safety and efficacy tables to include close out data for studies HPV-013 and 015 (sent 2/22/08)
- Updated safety and immunogenicity reports for study HPV-018 (Months 24 and 30).

In addition, the sponsor provided the synopsis reports for studies HPV-002 (9/2/04); HPV-004 (10/1/04); HPV-006 (12/1/04); HPV-007 (2/28/05); HPV-005 (8/17/05); HPV-016 (7/13/05); HPV-016 (8/5/05); HPV-018 (8/8/05 & 9/15/05); HPV-011 [substudy HPV-013] (9/22/05); HPV-012 [substudy of HPV-013] (10/13/05); HPV-013 (11/10/05); HPV-015 (9/27/05) and HPV-015-03 (10/13/05). Also, the original analysis reports for efficacy of the vaccine in prevention of HPV 16/18 related CIN 2/3 (10/18/05) were included in the submission, as well as the original evaluation of congenital anomalies (11/17/05); and integrated summary of pathology panel performance (10/28/05). These reports and data were reviewed at the time of the original BLA, so were not re-reviewed. Also included in the BLA were interim analysis reports for study HPV-007 (6/7/01) and the protocol for study HPV-015-10 (7/12/06).

6.3 Review Strategy

The individual clinical study reports containing additional efficacy, safety and immunogenicity data were initially reviewed (Studies 007-10, 013-10, 015-10 and 018 Month 24 data). This was followed by review of SAS datasets with JMP software for review of efficacy (histopathological endpoints as per Merck Pathology Panel) for each treatment group and safety. The summary of clinical efficacy (cervical lesions, external genital lesions), the summary of safety, and the integrated analysis of efficacy were also reviewed. Separate reports for updated congenital anomalies, post-marketing safety update report were also reviewed. In addition, requests for additional analyses were made in several communications and the responses from the sponsor were reviewed as well.

6.4 Good Clinical Practice and Data Integrity – No additional studies were reviewed for supplements 419 and -(b)(4)-, and the data reviewed were from close-out data from studies conducted at previously inspected clinical sites. For study sites involved in studies HPV-013 and HPV-015, one site (Site 0029) was found to have violated the protocol and agreements with study subjects, Merck Research Laboratories (MRL),

and the IRB. The site failed to correct these violations. In view of the circumstances, MRL, in consultation with the IRB, closed the site, and set a cut-off of 6/15/06, after which data from the site were not to be included in the final data presented. This was detailed in a memo dated 8/13/07 which was included as part of the final study report for study HPV-013-010. The latest visit date for this site for which data were included was 5/22/06. Site 0029 was the subject of an audit by the Department of Health and Human Services of the Food and Drug Administration of the United States, which issued a Form 483 Inspectional Observations to the site, in which it confirmed that serious violations had taken place, date stamped 10/10/07. Violations included (as per the FDA letter): several subjects' study visits were not conducted within protocol-mandated timeframes; not all dates on source documents matched the corresponding case report forms; one subject did not meet inclusion criteria; required follow-up tests were not performed within specified timeframes; assent was not obtained for one 17 year old subject; and test article storage temperatures were not logged on multiple occasions. All tables, summaries, and figures in this study (and all integrated summaries presented in this Supplemental Application) include data from Site 0029 up to 22-May-2006. The clinical responsibilities for subjects at this site were transferred to another investigator at another site. It is noted that ----------(b)(4), (b)(5)----------.

6.5 Financial Disclosures – There were no new financial reports submitted because the efficacy data presented in the supplements were close out data from already ongoing studies which were reported in the original BLA submission.

7 Human Immunogenicity

The vaccine was shown to be immunogenic for all 4 vaccine HPV types (HPV 6, 11, 16, 18) as measured by Merck's competitive Luminex immunoassay, which was used for Protocols 007, 013, 015, 016 and 018. An immune correlate of protection was not identified. The immune response at 1 month after dose 3 of the vaccine was higher than that seen in subjects who were previously PCR positive and/or seropositive for that specific HPV subtype. In this supplement, the immune response has been demonstrated at Month 60 in study HPV-007, which is similar to the immune response previously reported for Month 24. A subset of subjects who received Gardasil in the original trial received a fourth dose of vaccine at Month 60, with an increase in immune response (GMTs) that was higher than the immune response (GMTs) in subjects who initially received alum control and received dose 1 of Gardasil at Month 60. Immune response was reported within the close-out data for studies HPV-013 and HPV-015.

8 Clinical Studies: The follow-up reports for the following four (4) Phase IIb and Phase III studies were reviewed. More extensive reviews of the original study reports for these four studies are included in the clinical review on the FDA website: http://www.fda.gov/cber/review/hpvmer060806r.pdf.

8.1 Study HPV- 007: A Placebo Controlled Dose-Ranging Study of Quadrivalent HPV Virus Like Particle (VLP) Vaccine in 16 to 23 Year Old Women

Efficacy: Efficacy estimates were calculated for all subjects in Protocol 007, according to their original vaccination group, based on cumulative data from the main study and the extension, through 5 years. The endpoints included persistent infection (defined as detection of the same HPV DNA by PCR on two samples at least four months apart or HPV related genital disease (in the Per Protocol Efficacy [PPE] population). These subjects received 3 doses of vaccine on schedule, were not protocol violators, and most importantly, were naïve (seronegative at Day 1 and HPV PCR negative through Month 7). Vaccine efficacy against the combined incidence of persistent HPV 6, 11, 16, or 18 infection or HPV 6, 11, 16, or 18-related cervical or genital disease in the PPE population was 95.8% [95% Confidence Intervals (CI): 83.8% to 99.5%], based on follow-up through Month 60 for subjects in the extension and through Month 36 for subjects who did not participate in the extension. The sponsor notes that two subjects in the Gardasil group developed persistent infection (one for HPV 18 and one for HPV 16 at Month 36). None of the Gardasil recipients in the PPE population developed HPV 6, 11, 16, or 18 related genital disease. Efficacy against the composite endpoint of persistent HPV 6, 11, 16, or 18 infection or HPV 6, 11, 16, or 18-related cervical or genital disease was 73.2.% (95% CI: 56% to 84.3%) in the Modified Intent to Treat (MITT-3) Population. These subjects were either naïve or non-naïve for the relevant HPV type at baseline. The sponsor notes that the efficacy estimates in both populations were higher than those reported in the original Protocol 007 clinical study report (CSR) which reported follow-up only through Month 36 for all subjects.

TABLE 3
Study HPV-007: Analysis of Efficacy Against HPV 6, 11, 16, or 18 Related Persistent Infection or Disease (Per Protocol Efficacy Population [PPE])

	Gardasil N=276				Control 225 mcg and 450 mcg alum* N=275					
HPV 6, 11, 16, or 18 related infection or disease	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Original submission	235	4	566.8	0.7	233	36	536.5	6.7	**89.5%**	70.7, 97.3%
Analysis 9/16/06: combined subjects through M36 and those followed through M60.	235	2	767.8	0.3	233	46	748.2	6.1	**95.8%**	83.8, 99.5%
Analysis 9/16/06: subjects followed through Month 60	104	1	465.5	0.2	120	22	497.7	4.4	**95.0%**	69.3, 99.9%

Source: 125126/0, Table 7-4, CSR 007, p. 222-3; 125126/419Tables 4-3, 4-6, 4-8, CSR 007-10, p. 47-48, p.53-4
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted starting 1 day after Month 7.
*Two doses of alum control were used in study 007, and subjects were combined in the efficacy analyses.

TABLE 4
Study HPV-007: Analysis of Efficacy Against HPV 6, 11, 16, or 18 Related Disease (EGL and CIN*) (Per Protocol Efficacy Population [PPE])

	Gardasil N=276				Control 225 mcg and 450 mcg alum** N=275					
HPV 6, 11, 16, or 18 related infection or disease	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Original submission	235	0	568.8	0.0	233	6 (3 EGL, 3 CIN)	563	1.1	**100.0%**	15.9, 100%
Analysis 9/16/06: combined subjects through M36 and those followed through M60.	235	0	771.7	0.0	233	6 3 EGL 3 CIN – (2 CIN 1; 1 CIN 2)	797/1	0.8	**100.0%**	12.3, 100%
Analysis 9/16/06: subjects followed through Month 60	104	0	460.5	0.0	120	1 (1 EGL)	531.8	0.2	**100.0%**	-4403.5, 100.0%)

Source: STN 125126.0, CSR 007, Table 7-12, p. 243; STN 125126.419.0, Table 4-3 (p. 47-48); Table 4-6 (p. 53-54.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted starting 1 day after Month 7.
*EGL=External Genital Lesions; CIN = Cervical Intraepithelial Neoplasia
**Two doses of alum control were used in study 007, and subjects were combined in the efficacy analyses.

TABLE 5
Study HPV- 007: Secondary Analysis of Efficacy Against HPV 6, 11, 16, 18 Related Persistent Infection or Disease (Modified Intent to Treat-3 Population [MITT-3])

	Gardasil N=276				Control 225 mcg and 450 mcg alum* N=275					
HPV 6, 11, 16, or 18 related infection or disease	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Original submission	268	23	690.6	3.3	269	61	650.9	9.4	**64.5%**	41.7, 79%
Analysis 9/16/06: combined subjects through M36 and those followed through M60.	268	21	901.8	2.3	269	74	851.4	8.7	**73.2%**	56, 84.3%
Analysis 9/16/06: subjects followed through Month 60	114	6	532.3	1.1	127	38	531.6	7.1	**84.2%**	62.4, 94.6%

Source: STN 125126/0, CSR 007, Table 7-4, p. 222-3; and STN 125126/419.0, CST 007-10, Table 4-5 (p. 51-52); Table 4-8 (p. 57-58)
Modified Intent to Treat Population 3 (MITT-3): Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted starting 1 day after Month 1.
*Two doses of alum control were used in study 007, and subjects were combined in the efficacy analyses.

TABLE 6
Study HPV- 007: Analysis of Efficacy Against HPV 6, 11, 16, or 18 Related Disease (EGL and CIN*) (Modified Intent To Treat-3 Population [MITT-3])

	Gardasil N=276				Control 225 mcg and 450 mcg alum** N=275					
HPV 6, 11, 16, or 18 related infection or disease	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Original submission	268	3 (3 CIN)	732.9	0.4	269	15 (4 EGL, 12 CIN)	722.1	2.1	**80.3%**	30.3, 96.3%
Analysis 9/16/06: combined subjects through M36 and those followed through M60.	268	3 (1 CIN 1 2 CIN 2 or worse)	954.2	0.3	269	14 (11 CIN 1 or worse-5 CIN 1, 6 CIN 2, 4 CIN 3; 4 EGL)	965.1	1.5	**78.3%**	22.3, 96.0%
Analysis 9/16/06: subjects followed through Month 60	114	1	555.9	0.2	127	6 (5 CIN 1 or worse, 1 CIN 1, 4 CIN 2, 4 CIN 3; 1 EGL)	609.1	1.0	**81.7%**	-50.5, 99.6%

Source: STN 125126.0, CSR 007, Table 11-68, p. 50-51; STN 125126/419/0, CSR 007-10, Table 4-5, p. 51-52; Table 4-8, p. 57-58.
One subject may have had more than one endpoint.
Modified Intent to Treat Population 3 [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted starting 1 day after Month 1.
*EGL=External Genital Lesions; CIN = Cervical Intraepithelial Neoplasia
**Two doses of alum control were used in study 007, and subjects were combined in the efficacy analyses.

Reviewer's Comment:
It is noted that the subjects followed for 36 months and those followed for the extension study were combined. It is understood that a subject would contribute to the combined analysis once (i.e., combined groups followed for 36 months and 60 months), but it was also important to look at the point estimates of efficacy for the group which was followed for 60 months alone. This group is smaller, but point estimates of efficacy remain high in this group as well.

In the Per Protocol Efficacy Population (PPE), there are two (2) subjects in the Gardasil group with persistent infection in the updated analyses instead of four (4) as in the original analysis because the definition of persistent infection included subjects who were noted to be HPV DNA positive for a vaccine HPV type at the last visit without confirmation (and 2 cases were detected at Month 36 in the original analysis.) In the

extension study results, these 2 cases did not have another HPV DNA detected in the follow-up visits, so the number of subjects was lower and point estimates of efficacy were somewhat higher. The analysis for the Modified Intent to Treat 3 (MITT-3) population includes subjects regardless of baseline HPV status (could have been naïve or non-naïve).

The sponsor notes that subjects who were followed out to Month 36 and those out to Month 60 were included in the primary analysis. When they count only subjects who were followed for the entire 60 months (because not all participated in the extension study), the point estimates of efficacy were very close to those seen in the primary analysis. It is noted that none of the Gardasil subjects in the PPE group developed a vaccine type HPV related genital lesion.

One other factor which would impact the number of cases of persistent infection in both groups was the fact that there was an 18 month gap in collection of cases (from Month 36 to Month 54). This would result in missing a number of cases of 4-month persistent infection(s) that may have come and gone in that time period. However, these events would be expected to be noted in both treatment groups. The sponsor did conduct a sensitivity analysis and found that the point estimates of efficacy remained similar to those seen in the primary analysis.

One additional exploratory analysis of interest was assessment of persistent infection with the same HPV DNA at an interval $\geq$ 1 year. This analysis was conducted in the combined group (those followed for 36 months and those followed for 60 months) as well as those followed for 60 months. Although the number of subjects was small, and only the point estimate of efficacy in the PPE combined analysis reached statistical significance, no subject in the Gardasil PPE cohort group developed a persistent infection $\geq$ 1 year in duration in either the combined group or in the extension study only analyses (Table 7). In the MITT-3 population, the sponsor notes that 11/12 of the Gardasil subjects with a persistent infection $\geq$ 1 year duration were related to HPV infection noted at baseline (see Table 8). As noted in the original review, and confirmed with additional data submitted to the Biological Supplemental Application, there is no impact on prevalent infection, i.e., Gardasil does not prevent vaccine HPV infection which was already present at the time of vaccination, but also does not appear to have a negative impact on long-term persistent infection with the relevant vaccine HPV type.

TABLE 7

Study HPV- 007: Subjects with Persistent Infections ≥ 1 year duration in the Per Protocol Efficacy population [PPE] (combined analysis and those followed alone through Month 60)

	Gardasil N=276				Alum Control 225 mcg and 450 mcg alum* N=275					
HPV 6, 11, 16, or 18 related infection or disease	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Analysis 9/16/06: combined subjects through M36 and those followed through M60.	232	0	766.7	0.0	231	9	780.1	1.2	**100.0%**	48.4, 100%
Analysis 9/16/06: subjects followed through Month 60	104	0	457.2	0.0	120	5	519.9	1.0	**100.0%**	-24.1, 100%

Source: CSR 007-10, STN125126/419, Tables 4-9 and 4-12, p. 59, 62

Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted starting 1 day after Month 7.

*Two doses of alum control were used in study 007, and subjects were combined in the efficacy analyses.

TABLE 8

Study HPV- 007: Subjects with Persistent Infections ≥ 1 year duration in the Modified Intent to Treat-3 population [MITT-3] (combined analysis and those followed alone through Month 60)

	Gardasil N=276				Control 225 mcg and 450 mcg alum* N=275					
HPV 6, 11, 16, or 18 related infection or disease	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Analysis 9/16/06: combined subjects through M36 and those followed through M60.	254	12	912.1	1.3	254	22	915.5	2.4	**45.2%**	-15.5, 75.3%
Analysis 9/16/06: subjects followed through Month 60	114	4	537.5	0.7	127	11	582.1	1.9	**60.6%**	-32.9, 90.9%

Source: CSR 007-10, STN125126/419, Tables 4-11 and 4-14, p. 61, 64

Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted starting 1 day after Month 1.

*Two doses of alum control were used in study 007, and subjects were combined in the efficacy analyses.

In conclusion, the vaccine efficacy in preventing persistent infection (4 month definition) reached statistical significance in both analyses groups for the Per Protocol Efficacy population in the extension part of study HPV-007. For persistent infections of ≥ 12 months, the point estimates efficacy in preventing these infections related to a vaccine HPV type were 100% in both analyses groups, although statistical significance was not reached in the treatment group followed for 60 months. It is noted that no new cases of vaccine related HPV disease for which a subject was naïve occurred in either analysis population over the additional time period of follow-up.

Immunogenicity following 4th dose: Subjects who received Gardasil in the original Protocol 007 dose-ranging study were eligible to participate in a study extension, which was designed to investigate whether a fourth dose of Gardasil, administered approximately 4.5 years following completion of a 3-dose regimen, induced anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses that were higher than subjects who received their first dose of Gardasil at day 1. Subjects in the extension received an injection of Gardasil at Month 60 and immune responses (anti-HPV 6, 11, 16, and 18 GMTs) were collected at Month 60, 1 week following Month 60, and Month 61. Study sites in the Nordic region and Brazil were chosen for evaluation of the fourth dose due to good subject retention. Of the 1,158 subjects who enrolled in Protocol 007,

551 received either Gardasil (276 subjects) or control (275 subjects) in the dose-ranging phase of the study, a subset of those 551 subjects (all subjects who were enrolled in Brazil, Norway, Sweden, or Finland) were eligible to participate in the extension phase of the study starting at Month 54. Overall, 241 subjects entered the extension phase at Month 54, 224 of whom received an injection of Gardasil at Month 60. For subjects who received a primary series of Gardasil in the main study, the Month 60 vaccination was a fourth dose. For subjects who received control in the main study, the Month 60 vaccination represented their first dose of Gardasil (120 subjects). This dose was followed by a second and a third dose of Gardasil at Months 62 and 66, respectively. The analysis was based on data for study extension visits through 9/19/06. The results showed that the observed anti-HPV 16 and anti-HPV 18 Geometric Mean Titers (GMTs) one month following a fourth dose of Gardasil, among subjects who received 3 primary doses of Gardasil were higher than those 1 month following a first dose of Gardasil among subjects who received 3 primary doses of control.

TABLE 9
Study HPV-007: Analysis of Anti-HPV 16 and Anti-HPV 18 Levels 1 Month Postdose 4 (Month 61) (Extension Per-Protocol Immunogenicity Population [PPE])

cLIA Assay	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™		Control Primary Series + GARDASIL™	
	Pre-Dose 4 (Month 60) n/GMTs	Postdose 4 (Month 61) n/GMTs	Pre-Dose 4 (Month 60) n/GMTs	Postdose 4 (Month 61) n/GMTs
Anti-HPV 16	**82/404.2**	**81/5714.0**	**71/< 12**	**73/104.5**
Anti-HPV 18	**85/44.7**	**86/1230.0**	**89/< 8**	**92/20.3**

Source: STN 125126/419, CSR 007-10, Table 4-19, p. 73

Reviewer Comment: The GMTs were higher prior to dose 4 in the Gardasil group as compared to those who originally received control. The GMTs were noted to increase in the control group, but GMTs were similar to the GMTs noted in the Gardasil group after receipt of dose 1 (not dose 4). The sponsor has conducted a statistical comparison and report that the response in the Gardasil group was higher. The sponsor assessed this comparison as evidence of an anamnestic response to Gardasil. It is not clear if and when a booster dose would be required to maintain an immune response and expected efficacy, since at this time, the duration of protective immune response has not been established. ----------(b)(4), (b)(5)----------. These data are not included in the updated package insert, but are of interest. Further data regarding immune responses are presented in the section of immunogenicity across trials.

Safety: All subjects received a vaccination report card (VRC) on which to record all adverse experiences that occurred during the 15-day period (day of vaccination plus 14 calendar days) after each injection. All local (injection-site) and systemic reactions were reported, regardless of severity, on the appropriate case report forms (CRFs).

The proportion of subjects who reported one or more adverse experiences Days 1 to 15 following vaccination Visit 4 during the extension phase (88.5%) was similar to the proportion of the same subjects (subset of subjects who participated in the extension and received a primary series of Gardasil) who reported one or more adverse experiences Days 1 to 15 Postdose 3 in the main study (76.1%). The proportions of subjects in the Gardasil group who received Dose 4 of Gardasil (88.5%) with any adverse event in Days 1-15 postdose 4 were similar to those who received Dose 1 of the original control recipients (90.8%).

The maximum intensity of clinical adverse experiences for most subjects in both treatment groups was mild or moderate and were similar in the two groups. The proportions of subjects with severe adverse events were also similar in both groups (10.1% [dose 1 Gardasil] as compared to 8.7% [dose 4 Gardasil]. There was no evidence of increased severity in overall adverse events in those who received dose 4 as compared to those who received dose 1.

79.8% of subjects who received dose 4 Gardasil had one or more injection-site adverse experiences, as compared to 85.7% in those who received dose 1 of Gardasil.

41.3% of subjects who received dose 4 of Gardasil had one or more systemic adverse events as compared to 54.6% of subjects who received dose 1.

3% of subjects who received dose 4 of Gardasil had elevated temperature as compared to 9% of subjects who received dose 1.

In the group who received Gardasil after receipt of control as the primary series, the proportions of subjects with one or more systemic adverse experiences were higher Postdose 1 than Postdose 2 or Postdose 3. The maximum intensity of clinical adverse experiences for most subjects was mild or moderate. These safety findings are consistent with data collected in the main clinical studies, and already reflected in the package insert.

Serious Adverse Events: Two additional SAEs were reported during the extension phase.

AN 8415 <u>"Drug Intoxication"</u>: a 23-year-old White female, was vaccinated with her first, second, and third doses of Gardasil on 12/27/00, 2/23/01, and 6/6/01. The subject completed the main study (through Month 36) and continued in the extension. On 6/7/05, the subject was included in the extension phase of the study. On 12/8/05, the subject was vaccinated with her fourth dose of Gardasil. On 12/12/05, the subject experienced severe leg pain and took approximately 7.5 g (10 tab, 750 mg) of acetaminophen to treat the pain. On --(b)(6)--, the subject was hospitalized due to nausea, tachycardia, and dizziness due to drug intoxication. The subject was treated with IV medication and released the same day. The subject recovered from the drug intoxication. The investigator determined that the drug intoxication was definitely not related to study vaccine/control.

AN 9043 <u>"Hospitalization following procedural complication"</u>: a 27-year-old White female, was vaccinated with her first, second, and third doses of control (450 mcg) on 12/6/00, 2/19/01, and 5/31/01. The subject completed the main study (through Month 36) and continued in the extension. The subject completed her first extension visit (Month 54) on 6/13/05. -(b)(6)-, the subject experienced moderate cervix bleeding following a loop electrosurgical excision procedure (LEEP) procedure. The subject was admitted to the hospital for re-suture and released. On -(b)(6)-, the subject again experienced moderate cervix bleeding and was re-admitted to the hospital. The subject was released from the hospital the same day. The subject recovered from both episodes of cervix bleeding. The subject continued in the study and on 11/29/05, the subject completed her Month 60 visit and vaccination. The investigator determined that the cervix bleeding was definitely not related to study vaccine/control. However, cervix bleeding was related to a study procedure (LEEP).

In review of the safety for systemic events, one case of myocarditis was noted in the 15 days after dose 4 of Gardasil, and was assessed as related to the vaccine. This case was considered a non-serious adverse event, and further information regarding was requested from the sponsor. The sponsor reported that the 20 year old subject in Finland received a 4th dose of Gardasil on 12/2/05 (@ Month (M) 60. Concomitant medications included NUVARING (for contraception) and esomperazole (for gastric pain). The subject felt feverish from the day of vaccination through 12/31/05, and noted an increased heart rate and 'arrhythmia' 12/15/05-12/31/05. The subject saw a specialist and a diagnosis of myocarditis was made. An EKG was taken and it was reportedly normal. The specialist assessed the event as viral myocarditis, non-serious, related to influenza. The subject was not hospitalized and received no other treatment. She completed the study on 1/16/06 and had no reported complaints at that time.

In regards to new medical history, the proportions of subjects in both treatment groups with a new medical conditions was 36.0% in the dose 4 group as compared to 38.6% in the dose 1 group.

Reviewer's Comment: Conclusions for overall efficacy, safety, and immunogenicity will be discussed in Sections 9, 10, and 11.

8.2 Protocol 013: A Study to Evaluate the Efficacy of Quadrivalent HPV (Types 6, 11, 16, and 18) L1 Virus-Like Particles (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 (FUTURE I)

This was a randomized, double-blind (operating under in-house blinding procedures), control-controlled, multicenter efficacy study in 5455 subjects. Each subject was also enrolled in 1 of 2 immunogenicity substudies (Protocol 011, Protocol 012). Subjects were randomized in a 1:1 ratio to receive a 3-dose regimen of either Gardasil or control at Day 1, Month 2, and Month. Immunogenicity and safety data from Day 1 through 1 month Postdose 3 (Month 7) for each of the substudies were summarized in separate clinical study reports (CSRs). The first analysis was the study's primary analysis. Data from this analysis were summarized in the Protocol

013 CSR included in the Original Application. The second analysis updated the initially documented results for Protocol 013 with data collected at visits conducted over an additional 11 calendar months. Those analyses included data from all visits conducted on or before 6/15/06. The report of that analysis was submitted as the first close-out of study HPV-013. The final version of the CSR presented all data from the enrollment of study subjects until the completion of the last study visit, 4/6/07, inclusive. These data were reviewed along with the final efficacy analysis of study 015 (see below). Overall safety update will also be discussed in conjunction with those of study HPV-015 as well. The efficacy, safety, and immunogenicity data will be discussed in conjunction with the discussion of overall efficacy, safety and immunogenicity.

8.3 Protocol 015: 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 (Females United to Unilaterally Reduce Endo/Ectocervical Disease)

This is a large, randomized, double-blind (operating under in-house blinding procedures), placebo-controlled, multicenter, multinational efficacy study in app. 11,500 subjects. Within this study, subjects may have also been enrolled in any of 3 separate substudies; one that prospectively assessed the tolerability of the quadrivalent HPV vaccine (Non-Serious Adverse Experience Substudy; NSAE), one that demonstrated the consistency of manufacture of the Gardasil (Consistency Lot Substudy), and a third that confirmed complete ascertainment of cytology and pathology specimens (Registry Substudy). Subjects were randomized in a 1:1 ratio to receive either Gardasil or control. To assess efficacy Papanicolaou (Pap) testing was to be done at Day 1, Month 7, Month 12, Month 24, Month 36, and Month 48 and Pap test abnormalities were followed up according to a pre-defined mandatory triage algorithm. The results from the NSAE substudy and Consistency Lot substudy were reported in previous P015 CSRs.

This review includes data through approximately 3.5 years of follow-up in Protocols 013 and 015, an additional 7 months beyond the initial follow-up data, allowing for greater precision in point estimates of efficacy. Safety will be discussed in conjunction with reports from study HPV-013 as well in the overall safety assessment.

8.4 Protocol 018: A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents (Month 24 report)

The follow-up report provides safety and immunogenicity through Month 24 and Month 30. These follow-up data will be discussed in the sections of overall safety and immunogenicity.

Please see original review for details on the original clinical study report (FDA website as referenced above).

9. Overall Efficacy

Efficacy against HPV 16 and/or 18 Related Vulvar and Vaginal Cancer – Prophylactic Efficacy and Overall Efficacy in the study population

The analyses presented in the close out data of studies HPV 007, 013, and 015 were considered supportive of the new indication that Gardasil prevents vulvar and vaginal cancer related to HPV 16 and/or 18. This assessment is based on the prevention of the histopathological endpoints HPV 16 and/or 18 related Vulvar Intraepithelial Neoplasia (VIN) grades 2/3 and (VaIN) Vaginal Intraepithelial Neoplasia grades 2/3. In the original analysis, there was a positive point estimate which reached statistical significance for HPV 6, 11, 16, or 18 related VIN 2/3, but not VaIN 2/3. Also in the original analysis, the point estimate for prevention of combined HPV 16 and/or 18 related VIN 2/3 and VaIN 2/3 reached statistical significance, although the point estimates for HPV 16 and/or 18 related VIN 2/3 and VaIN 2/3 did not reach statistical significance individually. In the close out data, analyses for each of these latter endpoints reached statistical significance because additional cases accrued in the control group, but not in the Gardasil group in the per protocol population.

Populations Analyzed:

- **Per Protocol Efficacy Population (PPE)** subjects were naïve for the relevant vaccine HPV type at baseline (seronegative and PCR negative), remained PCR negative through Month 7 (1 month after the vaccine series was completed), were not protocol violators, with cases being counted 1 days after 30 days after Dose 3. Subjects were sexually active (vast majority) and may or may not have had a normal Pap smear.
- **The Modified Intent to Treat Population-3 (MITT-3)** included all subjects in the study, regardless of baseline status for the relevant HPV types, could have included protocol violators, with cases counted 30 days after Dose 1.

Reviewer's Comment: The drawback with these populations is that counting of cases does not start after Day 1. In the CBER observational review of cases provided below, cases are counted in all subjects after Day 1. In all analyses, there is a positive impact in prevention of these dysplasias in those who have not been exposed to the relevant HPV type even after counting of cases after Day 1.

The following tables first present the analyses of efficacy in prevention of HPV 6, 11, 16, or and/or 18 related VIN 2/3 and VaIN 2/3 at the time of original licensure, and in the initial and final close study reports. The analyses of efficacy in prevention of the oncogenic vaccine HPV type related VIN 2/3 and VaIN 2/3 are presented second. Efficacy in prevention of VIN 2/3 and VaIN 2/3 related to HPV 16 and/or 18 are those of primary interest in supporting the indication for prevention of some vulvar and vaginal squamous cell cancers related to HPV 16 and/or 18.

TABLE 10
Studies HPV-007, -013, and -015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related VIN 2/3 and VaIN 2/3: Per Protocol Efficacy Population [PPE] and Modified Intent to Treat Population 3 [MITT-3] (Original Analysis and Close Out Data)

	Gardasil N=9075				Control N=9075					
HPV 6, 11, 16, 18 related VIN 2/3	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE (Original)	7897	0	11979.2	0.0	7899	13	11986.9	0.1	**100%**	**67.2, 100%**
PPE (close-out data #1)	7899	0	19333.2	0.0	7899	19	19311.0	0.1	**100%**	**78.6, 100%**
PPE (final close-out data)	7900	0	23609.8	0.0	7902	23	23600.8	0.1	**100%**	**82.6, 100%**
MITT-3 (Original)	8954	8	17672.3	0.0	8962	30	17722.6	0.2	**73.3%**	**40.3, 89.4%**
MITT-3 (final close-out data)	8955	9	30489.7	0.0	8968	43	30563.9	0.1	**79.0%**	**56.4, 91.0%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.;
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, Table 1-1 and 1-3, Efficacy Information Amendment, 5/17/06; STN 125126/419.0, Table 2.7.3:exgenlesions:10, p. 45, 47; STN 125126/-(b)(4)-, p. 21, 23;

TABLE 11
Studies HPV-007, -013, and -015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related VIN 2/3: Per Protocol Efficacy Population [PPE] and Modified Intent to Treat Population 3 [MITT-3] (Original Analysis and Close Out Data)

	Gardasil N=9075				Control N=9075					
HPV 6, 11, 16, 18 related VIN 2/3	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE (Original)	7897	0	11979.2	0.0	7899	8	11988.3	0.1	**100%**	**41.4, 100.0%**
PPE (close-out data #1)	7899	0	19373.2	0.0	7900	11	19316.3	0.1	**100%**	**60.2, 100%**
PPE (final close-out data)	7900	0	23609.8	0.0	7902	13	23611.4	0.1	**100%**	**67.2, 100%**
MITT-3 (Original)	8954	7	11673.1	0.0	8962	22	17726.6	0.1	**68.1%**	**22.7, 88.5%**
MITT-3 (final close-out data)	8955	8	30491.8	0.0	8968	30	30508.9	0.1	**73.3%**	**40.3, 89.4%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.;
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, Table 1-1 and 1-3, Efficacy Information Amendment, 5/17/06; STN 125126/419.0, Table 2.7.3:exgenlesions:10, p. 45, 47; STN 125126/-(b)(4)-, p. 21, 23;

TABLE 12

Studies HPV-007, -013, and -015: Analysis of Efficacy Against HPV 6, 11, 16, 18 related VaIN 2/3 – Per Protocol Efficacy Population [PPE] and Modified Intent to Treat-3 Population [MITT-3] (Original Analysis and Close-out data)

	Gardasil N=9075				Control N=9075					
HPV 6, 11, 16, 18 related VIN 2/3	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE (original)	7897	0	11979.2	0.0	7899	5	11989.9	0.0	**100%**	**<0.0, 100%**
PPE (close-out data #1)	7899	0	19333.2	0.0	7900	8	19322.4	0.0	**100%**	**41.4, 100%**
PPE (final close out data)	7900	0	23609.8	0.0	7902	10	23618.2	0.0	**100%**	**55.4, 100%**
MITT-3 (original)	8954	2	17678.4	0.0	8962	9	17734.5	0.1	**77.7%**	**<0.0, 97,7%**
MITT-3 (final close-out data)	8955	2	30503.9	0.0	8968	14	30609.7	0.0	**85.7%**	**37.6, 98.4%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, Table 1-1 and 1-3, Efficacy Information Amendment, 5/17/06; STN 125126/419.0, Table 2.7.3:exgenlesions:10, p.45,47; STN 125126/-(b)(4)-, p. 21, 23

TABLE 13

Studies HPV-007, -013, and -015: Analysis of Efficacy Against HPV 16/18 Related VIN 2/3 and VaIN 2/3: Per Protocol Efficacy Population [PPE] and Modified Intent to Treat-3 Population [MITT-3] (Original Analysis and Close Out Data)

	Gardasil N=9075				Control N=9075					
HPV 16/18 related VIN 2/3 and VaIN 2/3	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE (Original)	7769	0	11786.6	0.0	7741	10	11752.8	0.1	**100%**	**55.5, 100%**
PPE (close-out data #1)	7771	0	19204.6	0.0	7742	15	18931.9	0.1	**100%**	**72.3, 100%**
PPE (final close-out data)	7772	0	23228.1	0.0	7744	19	23143.7	0.1	**100%**	**78.6, 100%**
MITT-3 (Original)	8954	8	17672.3	0.0	8962	26	17726.0	0.1	**69.1%**	**29.8, 87.9%**
MITT-3 (final close-out data)	8955	9	30489.7	0.0	8968	38	30573/2	0.1	**84.2%**	**46.2, 97.0%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow- up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, Table 1-1 and 1-3, Efficacy Information Amendment, 5/17/06; STN 125126/419.0, Table 2.7.3:exgenlesions:13, p.53,55; STN 125126/-(b)(4)-, p. 24

TABLE 14
Studies HPV-007, -013, and -015: Analysis of Efficacy Against HPV 16/18 Related VIN 2/3: Per Protocol Efficacy population [PPE] and Modified Intent to Treat -3 Population [MITT-3] (Original Analysis and Close Out Data)

	Gardasil N=9075				Control N=9075					
HPV 6, 11, 16, 18 related VIN 2/3	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE (Original)	7769	0	11786.6	0.0	7741	5	11754.3	0.0	**100%**	**<0.0, 100%**
PPE (close-out data #1)	7771	0	19024.6	0.0	7742	8	18937.7	0.0	**100%**	**41.7, 100%**
PPE (final close-out data)	7772	0	23228.1	0.0	7744	10	23154.0	0.0	**100%**	**55.5, 100%**
MITT-3 (Original)	8954	7	17673/1	0.0	8962	18	17730.0	0.1	**61.0%**	**2.1, 86.2%**
MITT-3 (final close-out data)	8955	8	30491.8	0.0	8968	26	30590.0	0.1	**69.1%**	**29.8, 87.9%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
N = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow- up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, Table 1-4, Efficacy Information Amendment, 5/17/06; STN 125126/419.0, Table 2.7.3:exgenlesions:13, p.53, 55; STN 125126/-(b)(4)-, p. 26

TABLE 15
Studies HPV-007, -013, and -015: Analysis of Efficacy Against HPV 16/18 Related VaIN 2/3: Per Protocol Efficacy population [PPE] and Modified Intent to Treat -3 Population [MITT-3] (Original Analysis and Close Out Data)

	Gardasil N=9075				Control N=9075					
HPV 6, 11, 16, 18 related VIN 2/3	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE (Original)	7769	0	11786.6	0.0	7741	5	11754.2	0.0	**100%**	**<0.0, 100%**
PPE (close-out data #1)	7771	0	19024.6	0.0	7742	7	18937.7	0.0	**100%**	**30.9, 100%**
PPE (final close-out data)	7772	0	23228.1	0.0	7744	9	23155.4	0.0	**100%**	**49.5, 100%**
MITT-3 (Original)	8951	2	17678.4	0.0	8962	9	17734.5	0.1	**77.7%**	**<0.0, 97.7%**
MITT-3 (final close-out data)	8955	2	30503.8	0.0	8968	13	306100.0	0.0	**84.6%**	**31.8, 98.3%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow- up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, Table 1-1 and 1-3, Efficacy Information Amendment, 5/17/06; STN 125126/419.0, Table 2.7.3:exgenlesions:13, p.53,55; STN 125126/-(b)(4)-, p. 26

Reviewer's Comment: The point estimates of efficacy for prevention of VIN 2/3 and VaIN 2/3 individually as related to vaccine HPV types in both the PPE and MITT-3 populations are statistically significant, as well as in the analyses of vaccine efficacy for prevention of VIN 2/3 and VaIN 2/3 related to HPV 16 and/or 18, individually. These latter analyses pertain to prevention of VIN 2/3 and VaIN 2/3 related to the oncogenic HPV types in Gardasil, which are related to development of vulvar and vaginal cancers that are related to HPV 16 and/or 18. From review of the tables, the point estimates remain at 100% in the per protocol populations for each of the endpoints. As time has progressed, additional cases develop in the control subjects who are naïve for the relevant vaccine HPV type. In the entire population (or MITT-3 cohort), which includes subjects who are naïve and non-naïve for the relevant vaccine HPV type, the overall point estimates of efficacy have increased, and the 95% CIs have narrowed, and all have reached statistical significance.

The sponsor also assessed the efficacy in the prevention of VIN 2/3 and VaIN 2/3 related to ANY HPV type. The sponsor reported these in another subgroup, the **Restricted Modified Intent To Treat – population (MITT-2),** in which subjects were naïve for the 14 vaccine HPV types at baseline, had a negative Pap test at baseline, and had cases counted after Day 30). The results are provided for the final close-out analyses. The point estimates of efficacy for prevention of both VIN 2/3 and VaIN 2/3 were highly

positive, although the point estimate for prevention of VaIN 2/3 does not reach statistical significance. It is noted that this is a subgroup of a subgroup, and although most closely mimics a truly "naïve" population, it still does not exclude subjects who may have been previously exposed to one of 4 non-vaccine oncogenic HPV types, since the subjects in the studies were for the most part sexually active, and since Pap tests have < 100% sensitivity (as low as 53% in one review article), a negative Pap test does not definitively rule out presence of dysplasia or HPV infection. In these analyses assessing efficacy in prevention of vulvar or vaginal cancer related to ANY vaccine HPV type, The revised label indicates that only vulvar and vaginal cancers related to HPV 16 and/or 18 will be prevented by Gardasil in subjects not previously exposed to HPV 16 and/or 18, nor those lesions which are unrelated to HPV, nor those which are related to a non-vaccine HPV type.

One Gardasil recipient, AN 33082, developed a vulvar cancer unrelated to any HPV type. She participated in study HPV-013: 20 year old female with a negative Pap test at enrollment, was negative for evidence of exposure to HPV 6, 11, 16, and 18 at baseline. Sexual activity was reported at 17 years of age. Genital examinations were negative through Month 24, at which time a perineal lesion was detected. Concomitant medications included hormonal contraceptives. Her Pap tests remained normal throughout M24, and no vaccine or non-vaccine HPV type by PCR (10 other oncogenic types) was detected through Month 24. No HPV DNA by PCR was detected in the lesion. In addition, disagreement was noted in the path report among the 3 pathologists, in that 1/3 diagnosed the lesion as reactive and 2/3 diagnosed the lesion as well differentiated carcinoma. She was reported to recover with no reported recurrence. The revised label indicates that only vulvar and vaginal cancers related to HPV 16 and/or 18 will be prevented by Gardasil in subjects not previously exposed to HPV 16 and/or 18. Gardasil does not prevent vulvar and vaginal cancers or precursors which are unrelated to HPV, nor those which are related to a non-vaccine HPV type.

TABLE 16
Studies HPV-013 and -015: Analysis of Efficacy Against VIN 2/3 and VaIN 2/3 Related to ANY HPV – Restricted Modified Intent to Treat-2 [MITT-2] and Modified Intent to Treat Population [MITT-3] (Close-out data)

	Gardasil N=9075				Control N=9075					
Population/Lesion	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
RMITT-2 VIN 2/3&VaIN 2/3	4688	7	16088.1	0.0	4735	31	16284.3	0.2	**77.1%**	**47.1, 91.5%**
RMITT-2 VIN 2/3	4688	3	16090.7	0.0	4735	18	16296.1	0.2	**83.1%**	**42.2, 96.8%**
RMITT-2 VaIN 2/3	4688	5	16089.5	0.0	4735	13	16312.3	0.1	**61.0%**	**-16.6, 89.1%**
MITT-3 VIN 2/3&VaIN 2/3	8688	30	29730.2	0.1	8701	61	29798.8	0.2	**50.7%**	**22.5, 69.3%**
MITT-3 VIN 2/3	8688	18	29743.3	0.1	8701	36	29834.9	0.1	**49.8%**	**9.3, 73.2%**
MITT-3 VaIN 2/3	8688	14	29761.3	0.0	8701	26	29858.0	0.1	**46.0%**	**-7.3, 73.9%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Restricted Modified Intent to Treat-2 population [RMITT-2]: subjects who are naïve for all tested HPV types at baseline with negative Pap tests, with cases counted 1 day after Month 1.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, efficacy amendment 2/22/08, p. 29-30

CBER Review of Data

To characterize all VIN 2/3 and VaIN 2/3 cases, clinical datasets were searched in the following manner:

- Labbx.xpt dataset for studies 007, 013, and 015 were searched for histopathological diagnoses (as per MRL Pathology Panel) of Vulvar Intraepithelial Neoplasia Grades 2 and 3 (VIN 2/3) and Vaginal Intraepithelial Neoplasia Grades 2 and 3 (VaIN 2/3) by treatment group. Time to event was noted.
- For each lesion identified, serostatus and Pap test at baseline was recorded, as well as PCR status at baseline, HPV PCR in the lesion. (Location of the lesion identified was noted so as to identify HPV PCR in that exact location).

Number of lesions was tabulated for each diagnosis according to the following classifications:

- Subject naïve (seronegative and PCR negative) for the vaccine HPV type at baseline and PCR negative through Month 7 and cases counted after Month 7 (similar to PPE, includes protocol violators).
- Subject naïve (seronegative and PCR negative) for the vaccine HPV type at baseline and cases counted after day 1. (Similar to the Naïve to Relevant HPV type).
- Subject naïve (PCR negative) for non-vaccine HPV type at Day 1 and developed case related to that type. (Cases counted after Day 1).
- Subject non-naïve for vaccine or non-vaccine HPV type at baseline and developed case related to the HPV type with which they were originally infected; cases counted after Day 1.
- Subjects who developed a lesion without associated HPV identified in specific location, but may have been non-naïve for other HPV types at baseline.

CBER acknowledges that these listings do not take into consideration the differing time to event analyses as conducted by the sponsor. CBER counted cases starting after Day 1. Nonetheless, these reviews are believed to be helpful to assist in understanding the full impact of Gardasil, and what benefits can be expected and in which subjects. Summary tables were prepared from the tables which listed individual histopathological lesions. The tables which list VIN 2/3 and VaIN 2/3 lesions in subjects which were reported at the time of the final close-out submission, and are included in **Appendix 1**. Numbers of cases may not match those in the Merck analyses because in CBER's review, protocol violators were included, and all subjects were counted from Day 1 (compared to Month 7 for the PPE population and compared to 1 day after Day 30 as in the MITT-3 population calculations).

For VIN 2/3 lesions identified from Day 1 in the datasets, there were 37 such cases in the alum control group and 21 in the Gardasil group.

Four (4) of these cases were detected before or during the vaccination period in the Gardasil group as compared to none (0) in the control group.

Prophylactic Efficacy for Vaccine HPV related VIN 2/3:

- There were 17 VIN 2/3 cases related to a vaccine HPV type for which the subject was naïve through Month 7 in the control group as compared to 0 cases in the Gardasil group (analogous to the per protocol group).
- If all subjects are considered as to baseline vaccine HPV status from Day 1, there were 25 VIN 2/3 cases related to a vaccine HPV type for which a subject was naïve at baseline in the control group as compared to 1 such case in the Gardasil group (although this one subject in the Gardasil subject, HPV 16 was first detected at the time of Month 3, at the time of the vaccination 2 visit.) HPV 16 was detected in 24 of the lesions in the alum control group who were naïve for HPV 16 at baseline.

Efficacy Not Demonstrated for VIN 2/3 related to HPV in subjects already infected with HPV type at baseline:

- There were 6 lesions related to a vaccine HPV type with which the subject was infected at baseline in the control group as compared to 8 in the Gardasil group, although 3/8 of these lesions in the Gardasil group were detected by the time of vaccination 2.

Prophylactic Efficacy Not Demonstrated for Prevention VIN 2/3 associated with Non-Vaccine HPV Types:

- For subject who were naïve to a non-vaccine HPV type and developed a VIN 2/3 case related to a non-vaccine HPV type, there were 3 cases in the alum control group and 6 in the Gardasil group.

VIN 2/3 Lesions Negative for HPV:

- For subjects in whom no HPV type was identified in the lesion, there were 3 in the control group and 6 in the Gardasil group (one of these were detected prevaccination). One case in the Gardasil group was a well-differentiated squamous cell carcinoma of the posterior introitus. at Month 24. This subject was noted above. AN 33082 (study HPV-013), a 20 year old female with a negative Pap test at enrollment, was negative for evidence of exposure to HPV 6, 11, 16, and 18 at baseline. Sexual activity was reported at 17 years of age. Genital examinations were negative through Month 24, at which time a perineal lesion was detected. Concomitant medications included hormonal contraceptives. Her Pap tests remained normal throughout M24, and no vaccine or non-vaccine HPV type by PCR (10 other oncogenic types) was detected through Month 24. No HPV DNA by PCR was detected in the lesion. In addition, disagreement was noted in the path report among the 3 pathologists, in that 1/3 diagnosed the lesion as reactive and 2/3 diagnosed the lesion as well differentiated carcinoma. She was reported to recover with no reported recurrence. See further discussions following Table 17

Overall Impact on VIN 2/3 in Women 16-26 years of age who participated in studies HPV-013 and HPV-015:

- In this population of females 16-26 years of age participating in studies HPV-007, HPV-013 and HPV-015, with a maximum of 4 or 5 sexual partners, with no history of cervical disease or external genital, but who may or may not have had an abnormal Pap test at baseline, there was an impact on the number of subjects who developed VIN 2/3 during the study (37 in the control group as compared to 21 subjects in the Gardasil group). The cases of VIN 2/3 which occurred in Gardasil recipients were women with evidence of exposure to HPV 16 and/or 18 or a non-vaccine HPV type prior to vaccination, as well as several non-vaccine HPV types to which they had not been exposed. To maximize benefit in prevention of vaccine related lesions, testing for specific high-risk HPV types in sexually active females in this age group prior to vaccination may prove helpful in deciding who among sexually active subjects would potentially benefit the most from vaccination. However, such HPV type specific testing is not available for public use, so at the present time, would not be feasible except in perhaps special circumstances. In addition, there is no evidence of cross-

protection against non-vaccine HPV types not included in the vaccine (see discussion of efficacy in prevention of CIN 2/3. Both treatment groups developed lesions related to non-vaccine HPV types to which they were naïve, as well as developed lesions without and identified HPV type. The anogenital cancer that was diagnosed in a Gardasil recipient at Month 24 was naïve for all tested HPV types.

A summary table of the total lesions identified in each group is provided below.

TABLE 17

Summary Table of VIN 2/3 lesions detected at time of close-out studies HPV-007, HPV-013, and HPV-015 (CBER generated)

LESIONS IDENTIFIED IN DATASETS 007, 013, 015 AT CLOSE-OUT – VIN 2/3						
	Gardasil	Times to development	HPV type(s)	Alum control	Times to development	HPV type(s)
Total number of cases	21			37		
Number of cases (Naïve for relevant HPV type through M7)	**0**	NA	NA	**17**	Postvax 3-1 M12-4 M18-2 M24-5 M30-1 M36-1 M48-3	2 w/HPV 6 (6-1; 6,31-1) 15 w/HPV 16 (6,16-1; 6,16,31-1; 6,16,52,56-1; 6,16, 56-1; *11,16,39-1; 16 alone-7; *16,18,31-1; 16,58-1; 16,59-1)
Number of cases (Naïve for relevant HPV type at baseline)	*1*	M36 (infected by Vax 2)	16-1	*25*	Above + Postvax 3-1 M12-3 M18-1 M24-2 M30-1	8 with HPV 16 (11, 16-1; 16 alone-7)
Number of cases (Infected with relevant HPV type @ baseline)	8	Vax 1-1 Vax 2-2 M12-3 M18-1 M19-1	8 with HPV 16(6, 16-1; 16 alone-5; 16, 35-1; 16, new 51-1.	6	Postvax 3-2 M12-2 M18, 24, 48-1 M48-1	2 w/ HPV 6 (6, new 31-1; 6,52-1; 16 alone -1; 16,33-1; 16,new 56-1; 16,51-1 (also w/new 31, 56, 58, 59)
Number of cases (Non-vaccine HPV type related cases, negative @ baseline for relevant non-vaccine HPV type)	6	M12-1 M18-1 M19-1 M24-1 M48-1	31-1 45,33-1 33, 58, 59-1 35-1 51-1 56-1	3	Postvax 3-1 M19-1 M36-1	31-3
Number of cases (Negative HPV DNA in lesion)	5	Prevax-1 Postvax 3-1 M12-2 M30-1		3	M12-2 M36-1	
Case of external well-differentiated vulvar cancer	1	M18	Negative	0		

Source: From datasets labbx.xpt, labxpcr 1-13.xpt, labxpap 1-5.xpt, sero1-2.xpt, study HPV-007, 013, and 015.**Bolded numbers:** Subjects naïve through Month 7 (sero- and PCR negative at baseline, and PCR negative at Month 7 for relevant vaccine HPV type at baseline); *Italic numbers:* Subjects naïve at baseline (sero- and PCR-negative for relevant vaccine HPV type); Numbers highlighted in yellow: Lesions in subjects infected with relevant HPV type at baseline; Numbers highlighted in teal: Lesions in subjects naïve (PCR negative) for relevant non-vaccine HPV type associated with lesion; Numbers highlighted in green: Subjects with lesions negative for any of the 14 HPV types tested (regardless of baseline sero- and/or PCR status); *Cases noted – HPV 16 detected by M7, subjects Naïve for HPV 11 or HPV 18 through Month 7)

Reviewer's Comment: Overall, there was prevention of the VIN 2/3 lesions related to vaccine HPV types (HPV 16 in the majority) in subjects who were naïve for the relevant vaccine HPV type. Please see CDER consultation for further review. As noted in our consultant's review, not all vulvar cancers are related to HPV, and the revised package insert indicates that not all vulvar cancers are associated with HPV 16 or 18, and this vaccine would be expected to prevent only those related to those vaccine HPV types. In addition, vulvar cancers are rare, and the impact of Gardasil will be small due to the low prevalence of these diseases, and will be greater on the high prevalence condition, i.e., vulvar dysplasias. Based on prevention of VIN 2/3 lesions which are reported to precede vulvar cancers which are HPV related, the indication to prevent vulvar cancer is being added as an indication to the package insert. As noted by our consultant, progression from VIN 2/3 to vulvar cancer has been noted in several studies, and pathology results have demonstrated these intraepithelial lesions adjacent to invasive lesions. As the CDER consultant notes, the incidence of VIN has nearly doubled in the past few decades and the disease is being found in younger women. This increase is postulated to perhaps be due to HIV infection as well as increased exposure to HPV. VIN tends to be multicentric, and tends to have a chronic course, and may be difficult to treat. One study is cited in which the overall prevalence of HPV DNA in VIN as 91.2% in one study by Carter et al.[6] The CDER consultant also notes that practically all HPV-related vulvar cancers are squamous cell carcinomas, but not all squamous cell carcinomas of the vulva are HPV related. The subject who did develop the well –differentiated squamous cell carcinoma in the study had no abnormal Pap tests, and no HPV was detected on any smears throughout the study. In summary, Gardasil can be expected to prevent HPV 16 and 18 related VIN 2/3, but cannot be expected to prevent VIN 2/3 or vulvar cancer related to non-vaccine HPV types, nor to VIN 2/3 or vulvar cancers not associated with HPV.

[6] Carter JJ et al. Cancer Res 2001; 61(5) : 1934-40.

For VaIN 2/3 lesions which were identified from Day 1 in the datasets, there were 26 such cases in the alum control group and 15 in the Gardasil group. See Appendix 1 for a complete listing of individual subjects who developed VaIN 2/3 lesions during the studies.

Three (3) subjects in the control group developed two lesions – one within the vaccination period and later in the trial due to an acquired HPV type, and one additional 1 subject had the lesion detected at vaccination 2 (associated with an HPV type present at baseline.

Prophylactic Efficacy for Vaccine HPV related VaIN 2/3:

- There were 10 VaIN 2/3 cases related to a vaccine HPV type for which the subject was naïve through Month 7 in the control group as compared to 0 such cases in the Gardasil group (analogous to the per protocol group).
- If all subjects are considered as to baseline vaccine HPV status from Day 1, there were a total of 12 VaIN 2/3 cases related to a vaccine HPV type for which a subject was naïve at baseline in the control group as compared to 0 in the Gardasil group.

Efficacy Not Demonstrated for Prevention of VaIN 2/3 related to HPV in subjects already infected with that HPV type at baseline:

- There were 2 lesions related to a vaccine or non-vaccine HPV type with which the subject was infected at baseline in the control group as compared to 4 in the Gardasil group.

Prophylactic Efficacy Not Demonstrated for Prevention of VaIN 2/3 associated with Non-Vaccine HPV Types:

- For subjects who were naïve to a non-vaccine HPV type and developed a VIN 2/3 case related to a non-vaccine HPV type, there were 4 cases in the alum control group and 10 in the Gardasil group. In the Gardasil group, 3/10 had an abnormal Pap test (≥ LSIL) at baseline, 4/10 had other HPV types present at baseline and 1 additional subject had other HPV types detected by the time of Vaccination 2. In the control group, 2/4 had an abnormal Pap test at baseline (LSIL) and 3/4 had another HPV type detected at baseline. More detailed analysis of non-vaccine HPV types is included in the section about efficacy in the prevention of all CIN 2/3 in the close-out data for studies HPV-013 and HPV-015, given the larger number of CIN 2/3 lesions diagnosed.

VaIN 2/3 Lesions Negative for HPV:

- For subjects in whom no HPV type was detected in the lesion, there were 8 VaIN lesions in the control group and 1 in the Gardasil group. 3/8 subjects in the control group with a normal Pap test and naïve for any tested HPV type at baseline developed a lesion without identified HPV. It is noted that 3/8 subjects in the control group acquired HPV 16 after vaccination, 1/8 control subjects was infected with HPV 16 at baseline, and 3/8 control subjects were infected with a non-vaccine HPV type at baseline. The one subject in the Gardasil group who developed VaIN without a

detectable HPV type had detectable antibodies to ant HPV 18 and HPV 6 at baseline (although both were below cutoff for seropositvity.)

Overall Impact on VaIN 2/3 in Women 16-26 years of age who participated in studies HPV-007, HPV-013 and HPV-015:

- In this population of females 16-26 years of age participating in studies HPV-007, HPV-013 and HPV-015, with a maximum of 4 or 5 sexual partners, with no history of cervical disease or external genital, but who may or may not have had an abnormal Pap test at baseline, there was an decrease in the number of subjects who developed VaIN 2/3 during the study (26 in the control group as compared to 15 subjects in the Gardasil group). The cases of VaIN 2/3 related to a vaccine or non-vaccine HPV type which occurred in Gardasil recipients were those with evidence of exposure to HPV 16 and/or 18 or a non-vaccine HPV type prior to vaccination, as well as non-vaccine HPV types to which they had not been exposed. From the few cases related to a non-vaccine HPV type for which a subject was naïve, there is no evidence of cross-protection against non-vaccine HPV types not included in the vaccine. Further analyses in CIN 2/3 cases are presented to review efficacy of Gardasil in the prevention of non-vaccine HPV type related disease.

Table 18 is a summary table of VaIN cases identified in datasets of studies HPV-013 and HPV-015 follows.

TABLE 18

Summary Table of VaIN 2/3 lesions detected at time of close-out studies HPV-013, and HPV-015 (CBER generated)

LESIONS IDENTIFIED IN DATASETS 007, 013, 015 AT CLOSE-OUT – VAIN 2/3						
	Gardasil	Times to development	HPV type(s)	Alum control	Times to development	HPV type(s)
Total number of cases	15			26		
Number of cases (Naïve for relevant HPV type through M7)	**0**			**10**	M12-1 M19-1 M24-3 M30-2 M36-1 M48-2 (one with another lesion @ M24)	6-1 HPV 16 -8 (16,35*-1 16-3 alone 16, 51*-1 16, 56*-3 [one also w/58* @M24]) 18, 31*-1
Number of cases (Naïve for relevant HPV type at baseline)	*0*			*12*	Above+ M12-1 M24 (first lesion Vax 1)-1	HPV 16-2
Number of cases (Infected with relevant HPV type @ baseline)	4	Postvax 3, M12-1 M12-1 M19&24 M24-1	16-1 16, new 31, then 16, 35-1 18, new 33, new 56, new 58-1 59-1	2	Vax 2-1 M12, 18-1	HPV 16-2 (16, 33, new 56-1; 1 -16 alone)
Number of cases (Non-vaccine HPV type related cases, negative @ baseline for relevant non-vaccine HPV type)	10	M12-1 M12&24-1 M19&24-1 M24-1 M30-2 M36-1 M48-4	31-2 31, 59-1 51-1 52-2 52, 58-1 52, 59 56 58-1	4	31-1 35-1 52-1 56-1 (followed by new 51)	Vax 1 & Postvax 3-1 Vax 2 & M12-1 M24-2
Number of cases (Negative HPV DNA in lesion)	1	M30-1		8		Postvax 3-1 M18-1 M36-2 M48-4

Key

Bolded numbers: Subjects naïve through Month 7 (sero- and PCR negative at baseline, and PCR negative at Month 7 for relevant vaccine HPV type at baseline).

Italic numbers: Subjects naïve at baseline (sero- and PCR-negative for relevant vaccine HPV type)

Numbers highlighted in yellow: Lesions in subjects infected with relevant HPV type at baseline.

Numbers highlighted in teal: Lesions in subjects naïve (PCR negative) for relevant non-vaccine HPV type associated with lesion.

Numbers highlighted in green: Subjects with lesions negative for any of the 14 HPV types tested (regardless of baseline sero- and/or PCR status).

Source: From datasets labbx.xpt, labxpcr 1-13.xpt, labxpap 1-5.xpt, sero1-2.xpt, study HPV-007, 013, and 015.

*Subjects naïve for non-vaccine HPV types in lesions as well

Reviewer's Comment: VaIN 2/3 lesions associated with vaccine HPV types for which the subject was naïve (either just at baseline or through M7) occurred in the alum control group but not in the Gardasil group. Most of these lesions were also related to HPV 16. There were a higher number of subjects with new non-vaccine HPV type related VaIN 3 in the Gardasil group as compared to the control group, although there were more cases of VaIN without a documented HPV type in the control group.

As noted by the CDER consultant, primary vaginal cancer is rare, and is also rarer than secondary vaginal cancers extending from the cervix. The CDER consultant notes that VaIN is rarely noted in the absence of CIN, and is usually found concurrently with CIN or in women who have had a history of surgery for CIN. Most VaIN 3 lesions are associated with HPV 16, although non-vaccine HPV types have also been reported. The CDER consultant notes that many, but not all vaginal cancers, are HPV-related.

In summary, in adding the indication of prevention of vulvar and vaginal cancer to the package insert for Gardasil, VIN 2/3 and VaIN 2/3 were considered acceptable surrogates for vulvar and vaginal squamous cell cancers, because progression from these lesions to invasive cancers have been reported in multiple studies in the medical literature, and these intraepithelial lesions have been located adjacent to invasive cancers. As noted by our consultant, vulvar and vaginal cancers are rare, and only those related to vaccine HPV types may be prevented. Not all vulvar and vaginal cancers are HPV related. Therefore, the impact of the vaccine on these conditions will be small due to the low prevalence of these diseases. In cases identified, the benefit is noted in prevention of dysplastic lesions related to HPV 16 and/or 18 if the subject has not yet been exposed to that HPV type. Most of the lesions identified in the datasets are related to HPV 16. There was no apparent benefit in prevention of lesions not related to HPV 16 and/or 18 in those receiving Gardasil, nor in prevention of lesions associated with an HPV type already present at the time of vaccination. (See consultant's review for full discussion).

In the package insert, CBER has inserted language to indicate that not all vulvar and vaginal cancers are HPV related, and to specify that only those related to vaccine HPV types 16 and 18 may be prevented by the vaccine.

Efficacy in prevention of AIS, CIN 2/3 or worse, CIN 1, and Condyloma Acuminata from close-out data

Efficacy Against Adenocarcinoma in situ (AIS), final analysis

The analyses by Merck as presented in the original BLA submission, and at the final close-out are noted in Table 19 below. The PPE population represents the prophylactic efficacy in subjects naïve through Month 7 for the relevant vaccine HPV type with cases counted after Month 7, and MITT-3 population includes subjects included regardless of baseline HPV status (both naïve and non-naïve), with cases counted 1 day after Month 1.

TABLE 19
Studies HPV-005, -007, -013, and -015: Analysis of Efficacy Against HPV 16, 18 Related AIS: Per Protocol Efficacy population [PPE] and Modified Intent to Treat-3 population [MITT-3] (Original and Close-Out Data)

	Gardasil + HPV 16 N=10268				Alum Control N=10273					
HPV 16, 18 related AIS	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE (Original)	8487	0		0.0	8460	6		0.0	**100%**	**14.8, 100%**
MITT-3 (Original)	9831	5		0.0	1896	12		0.1	**58.1%**	**-27.9, 88.4%**
	Gardasil N=10,268				**Control N=10273**					
PPE (Final close-out data)	8493	0	25150.2	0.0	8464	7	25194.6	0.0	**100%**	**30.6, 100%**
MITT-3 (final close-out data)	9836	6	33375.1	0.0	9904	15	33456.9	0.0	**60.0%**	**-9.1, 87.3%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit;
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: Table 5-1. 125126/0.24 efficacy amendment 4/24/06, and STN 125126/-(b)(4)-, p. 21, 23.

To characterize all AIS cases, datasets were searched as follows:

- Labbx.xpt dataset for studies 013 and 015 were searched for histopathological diagnoses (as per MRL Pathology Panel) of Adenocarcinoma in Situ (AIS) by treatment group. Time to event was noted.
- For each lesion identified, serostatus and Pap test at baseline was recorded, as well as PCR status at baseline, HPV PCR in the lesion. (Location of the lesion identified was noted so as to identify HPV PCR in that exact location).

Number of lesions was tabulated for each diagnosis according to the following classifications:

- Subject naïve (seronegative and PCR negative) for the vaccine HPV type at baseline and PCR negative through Month 7 and cases counted after Month 7 (similar to PPE, includes protocol violators).
- Subject naïve (seronegative and PCR negative) for the vaccine HPV type at baseline and cases counted after day 1. (Similar to the Naïve to Relevant HPV type).
- Subject naïve (PCR negative) for non-vaccine HPV type at Day 1 and developed case related to that type. (Cases counted after Day 1).

- Subject non-naïve for vaccine or non-vaccine HPV type at baseline and developed case related to the HPV type with which they were originally infected; cases counted after Day 1.
- Subjects who developed a lesion without associated HPV identified in specific location, but may have been non-naïve for other HPV types at baseline.

Please see Appendix 2, which includes tables of all AIS lesions which were detected in studies HPV-013 and 015 at the time of the final close out.

Prophylactic Efficacy for Vaccine HPV related AIS:

- There were 9 AIS cases related to a vaccine HPV type for which the subject was naïve through Month 7 in the control group as compared to 0 such cases in the Gardasil group (analogous to the per protocol group).
- When considering AIS cases in subjects naïve for a vaccine HPV type at baseline, there were a total of 11 AIS cases related to a vaccine HPV type for which a subject was naïve at baseline in the control group as compared to 0 in the Gardasil group.

Efficacy Not Demonstrated for Prevention of AIS related to HPV in subjects already infected with that HPV type at baseline:

- There were 4 lesions related to a vaccine or non-vaccine HPV type with which the subject was infected at baseline in the group as compared to 6 in the Gardasil group. All of these lesions in each treatment group were associated with a vaccine HPV type (either HPV 16 and/or 18 with or without a non-vaccine HPV type).

AIS Lesions Negative for HPV:

- For subjects in whom no HPV type was detected in the lesion, there were 1 AIS lesion was noted in the control group and 0 in the Gardasil group. However, the lesion was diagnosed at the time of vaccination 2, and the subject was seropositive and PCR positive for HPV 16 and PCR positive for HPV 45 present at baseline, as well as having HSIL at baseline as well. This lesion was certainly present at the time of vaccination.

Overall Impact on AIS in Women 16-26 years of age who participated in study HPV-013 and HPV-015:

- In this population of females 16-26 years of age participating in studies HPV-013 and HPV-015, with a maximum of 4 sexual partners, with no history of cervical disease or external genital, but who may or may not have had an abnormal Pap test at baseline, there was an impact on the number of subjects who developed AIS during the study (16 in the control group as compared to 6 subjects in the Gardasil group). The 6 cases of AIS noted in the datasets occurred in women with evidence of exposure to HPV 16 and/or 18 prior to vaccination. To maximize benefit in prevention of vaccine related lesions, testing for high-risk HPV types HPV 16 and 18 in sexually active females in this age group prior to vaccination would be optimal. However, such HPV type specific testing is not available for public use, so at the present time, would not be feasible except in perhaps special circumstances.

TABLE 20

Summary Table of AIS lesions detected at time of close-out studies HPV-013, and HPV-015 (CBER generated)

LESIONS IDENTIFIED IN DATASET 013, 015 AT CLOSE-OUT – AIS						
	Gardasil	Times to development	HPV type(s)	Alum control	Times to development	HPV type(s)
Total number of cases	6			16		
Number of cases (Naïve for relevant HPV type through M7)	**0**	NA	NA	**9**	Postvax 3-1 M12-2 M19-1 M24-2 M30-2 M48-1	16-5 alone 16, old 58-1 16,39* 16, 18, 45*, 52*-1 16, old 18, 51*, 52*
Number of cases (Naïve for relevant HPV type at baseline)	*0*	NA	NA	*11*	Above + M12-2	16, 52, 6-1 18-1
Number of cases (Infected with relevant HPV type @ baseline)	6	Vax 2-1 Postvax 3-3 M12-1 M36-1	16, 52-1 16-2 alone 18-2	4	M12-1 M24-2 M48-1	18-1 18, 51*-1 16, 18-1 16, 18, 33, 52, 56
Number of cases (Non-vaccine HPV type related cases, negative @ baseline for relevant non-vaccine HPV type)	0	NA	NA	0	NA	NA
Number of cases (Negative HPV DNA in lesion)	0	NA		1	Vax 2	

Key

0Bolded numbers: Subjects naïve through Month 7 (sero- and PCR negative at baseline, and PCR negative at Month 7 for relevant vaccine HPV type at baseline).

Italic numbers: Subjects naïve at baseline (sero- and PCR-negative for relevant vaccine HPV type)

Numbers highlighted in yellow: Lesions in subjects infected with relevant HPV type at baseline.

Numbers highlighted in teal: Lesions in subjects naïve (PCR negative) for relevant non-vaccine HPV type associated with lesion.

Numbers highlighted in green: Subjects with lesions negative for any of the 14 HPV types tested (regardless of baseline sero- and/or PCR status).

Source: From datasets labbx.xpt, labxpcr 1-13.xpt, labxpap 1-5.xpt, sero1-2.xpt, study HPV-007, 013, and 015.; *Subjects naïve for non-vaccine HPV types in lesions as well

Reviewer's Note: From the table above, the efficacy in the prevention of AIS remains impressive especially in those subjects naïve at baseline for the relevant HPV types. AIS is noted in the literature to be increasing in frequency, and cytological lesions may not reliably lead to diagnosis. In the group that may have been non-naïve or naïve at baseline (MITT-3), the point estimate of efficacy was 60% in this group, does not reach statistical significance.

Efficacy Against CIN 2/3 or worse final analysis

The analyses by Merck in the original submission and in close-out data is noted in Tables 21 and 22 below.

TABLE 21

Studies HPV-005, -007, -013, and -015: Analysis of Efficacy Against HPV 16, 18 Related CIN 2/ 3 or worse: Per Protocol Efficacy population [PPE] and Modified Intent to Treat-3 population [MITT-3]: Original Submission

	Gardasil or HPV 16 vaccine N=10268				Control N=10273					
Study Population HPV 16/18 related CIN 2/3, AIS or worse	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE, combined	8847	0	14178.1	0.0	8460	53	14060.6	0.4	**100.0%**	(92.9, 100%)
MITT-3, combined	9831	122	21107.3	0.6	9896	201	21228.4	0.9	**39.0%**	(23.3, 51.7%)

N=number of subjects randomized to the respective vaccination group who received at least one injection
n=number of subjects who have at least one follow-up visit
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: From STN 125126.0/Table 2.7.3-cervixcaxncer: 29, p. 127-8

TABLE 22

Studies HPV- 005, -007, -013, and -015: Analysis of Efficacy Against HPV 16, 18 Related CIN 2/ 3 or worse: Per Protocol Efficacy population [PPE] and Modified Intent to Treat-3 [MITT-3]: Close Out Data

	Gardasil or HPV 16 vaccine N=10268				Control N=10273					
Study Population HPV 16/18 related CIN 2/3, AIS or worse	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE, combined	8493	2	25150.0	0.0	8464	112	24896.0	0.4	**98.2%**	(93.5, 99.8%)
MITT-3, combined	9836	146	33316.0	0.4	9904	303	33375.4	0.9	**51.8%**	(41.1, 60.7%)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population who have at least one follow-up
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, p. 3-4

As noted in Tables 21 and 22 above, the analyses provided included efficacy against CIN 2/3 or AIS related to vaccine HPV types 16 and 18. The point estimates of efficacy for

the PPE remain high. It is noted that 2 cases were detected in the Gardasil group. These cases are discussed in the CBER analysis which follows.

The sponsor also provided an updated efficacy analysis for prevention of HPV 6, 11, 16, or 18 related CIN 2/3 or worse. The original analysis is shown followed by the analysis including the initial close-out data (the sponsor did not provide the combined analyses for the final close-out data in studies 007, 013, and 015). (See Tables 23 and 24).

TABLE 23
Studies HPV-007, -013, -015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related CIN 2/3 or Worse – Per Protocol Efficacy Population [PPE] and Modified Intent to Treat-3 [MITT-3] Population (Original Submission)

	Gardasil N=9075				Control N=9075					
Study Population HPV 6/11/16/18 related CIN	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE, combined	7858	0	11887.6	0.0	7861	43	11888.4	0.4	**100.0%**	(91.0, 100%)
MITT-3, combined	8814	118	17467.0	0.7	8846	186	17527.5	1.1	**36.3%**	(19.4, 49.9%)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population who have at least one follow-up
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/0, Table 5.3.5.3.2:8, Integrated Summary of Efficacy, p. 43

TABLE 24
Studies HPV- 007, -013, -015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related CIN 2/3 or Worse – Per Protocol Efficacy population [PPE] and Modified Intent to Treat-3 population [MITT-3] (3/20/07)

	Gardasil N=9075				Control N=9075					
Study Population HPV 6/11/16/18 related CIN	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE, combined	7863	1	18922.7	0.0	7863	76	18827.9	0.4	**98.7%**	(92.5, 100%)
MITT-3, combined	8817	138	25185.8	0.5	8847	251	25164.4	0.9	**42.1%**	(28.3, 53.4%)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population who have at least one follow-up
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/419.0, Table 2.7.3-cervixcancer:23, p. 106, 3/20/07

In addition, point estimates of efficacy were also provided against ANY HPV related CIN 2/3 or worse. Gardasil includes 4 HPV types, including HPV types 16 and 18, but there are still other oncogenic HPV types to which a woman may be exposed. Merck has provided an analysis of efficacy against CIN due to any HPV type by lesion type for the combined analyses of HPV 013 and 015 (the studies in which additional HPV type testing was conducted.) The analysis shown includes another modified intent-to-treat population, the **Restricted MITT-2 (RMITT-2 population)**, in which subjects were naïve for all 14 HPV types tested and had negative Pap tests at baseline. Cases were counted starting 1 day after Day 30. In this group, the point estimate of efficacy in the prevention of CIN 2/3 or worse was 42.7% (95% CI: 23.7, 57.3%). It is often cited that 70% of cervical cancers and CIN 3 are related to HPV 16 and 18. However, approximately 50% of CIN 2 may be related to HPV 16 and 18. The point estimate of efficacy has increased since the time of the original submission, but is not 50-70%. This may be related to the less than 100% sensitivity of Pap tests, and the impact of other HPV types (there are app. 4 other non-vaccine HPV types that are oncogenic and were not included in the testing paradigm). The results for the original submission and the close – out data for the RMITT-2 population and MITT-3 cohorts are noted in Tables 25 and 26 below.

TABLE 25

Studies HPV-005, -007, -013 and -015: Analysis of Efficacy Against CIN 2/3 or worse related to ANY HPV type: Restricted Modified Intent to Treat-2 population [RMITT-2] and Modified Intent to Treat-3 population [MITT-3] (Original Submission)

	Gardasil N=8799				Alum Control N=8800					
	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
R-MITT 2 (Original)	5638	59	11333.4	**0.5**	5701	96	11454.4	**0.8**	**37.9%**	**13.2, 55.9%**
MITT-3 (Original)	8814	287	17409.5	**1.6**	8846	328	17469.4	**1.9**	**12.2%**	**<0.0, 25.3%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population who have at least one follow-up
Restricted Modified Intent to Treat-2 population [RMITT-2]: subjects who are naïve for all tested HPV types at baseline with negative Pap tests, with cases counted 1 day after Month 1.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: Summary of Integrated Efficacy, 125126.0, Table 5.3.5.3.2:17, p. 78-9.

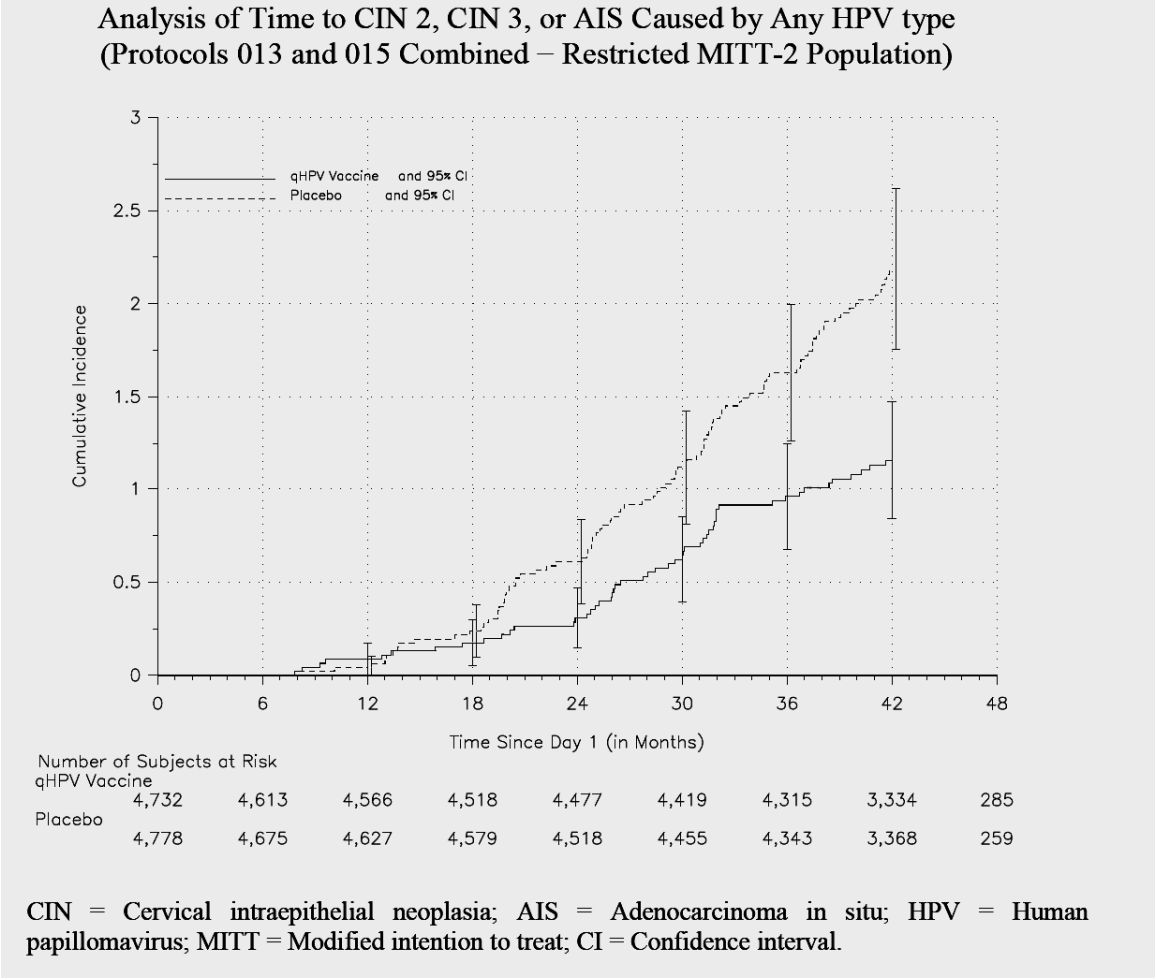
TABLE 26
Studies HPV-005, -007, -013 and -015: Analysis of Efficacy Against CIN 2/3 or worse related to ANY HPV type: Restricted Modified Intent to Treat-2 population [RMITT-2] and Modified Intent to Treat population [MITT-3] (Close-Out Data)

	Gardasil+HPV 16 N= 8799				Alum Control N=8800					
R-MITT 2 (Final close-out data)	4616	77	15995.5	**0.5**	4680	136	16186.2	**0.8**	**42.7%**	**23.7, 57.3%**
MITT-3 (final close-out data)	8559	421	28830.3	**1.5**	8592	516	28847.0	**1.8**	**18.4%**	**7.0, 27.7%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population who have at least one follow-up
Restricted Modified Intent to Treat-2 population [RMITT-2]: subjects who are naïve for all tested HPV types at baseline with negative Pap tests, with cases counted 1 day after Month 1.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
STN 125126/serial 118, submitted 12/21/07. , Table 24, Integrated Summary of Efficacy Update (Report 2155), p. 81-82;

Time to event figures for both populations are provided below. In the additional review which follows, the positive impact in the generally naïve population is likely related to prevention of HPV related disease to which a subject is naïve, rather than to prevention against additional HPV types.

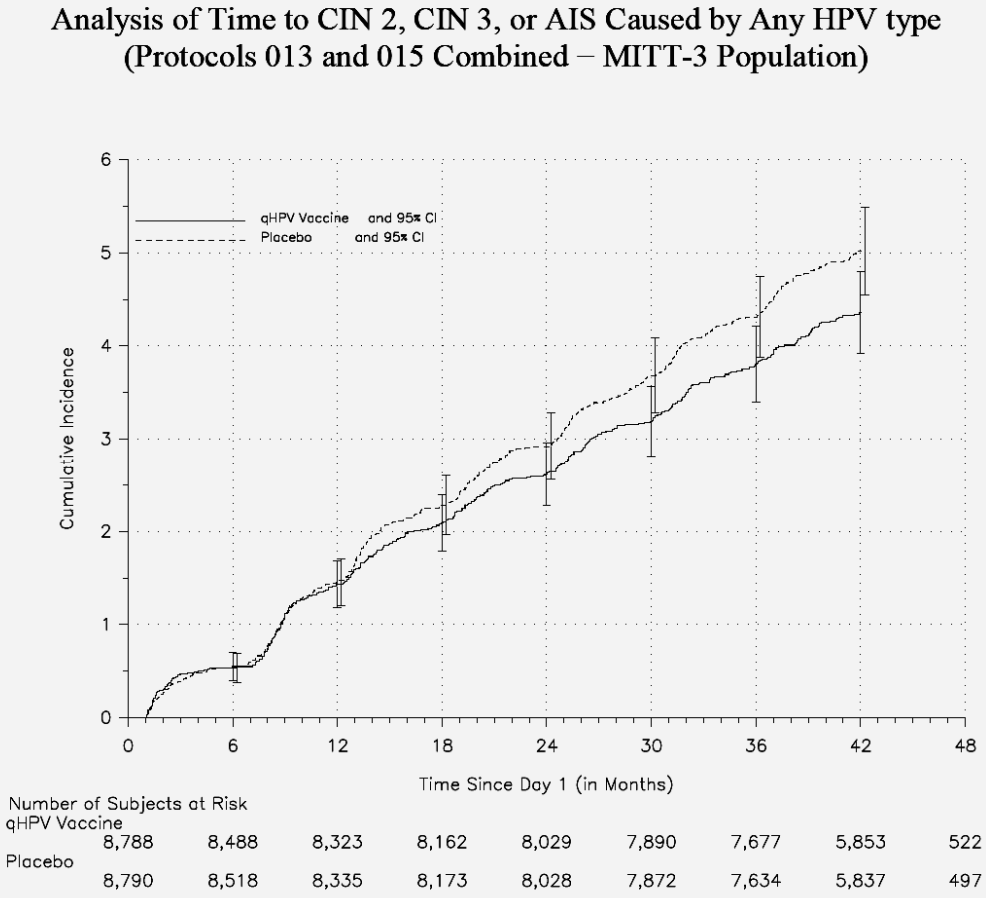
FIGURE 1



CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; HPV = Human papillomavirus; MITT = Modified intention to treat; CI = Confidence interval.

Source: STN 125126/-(b)(4)-, p. 12, submitted 2/22/08

FIGURE 2



CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; HPV = Human papillomavirus; MITT = Modified intention to treat; CI = Confidence interval.

Source: STN 125126/-(b)(4)-, p. 13, efficacy-information-amendment 22Feb2008

Evaluation of Efficacy in Prevention of CIN 2/3 or worse related to Non-Vaccine HPV types

In the close-out data submitted for studies HPV-013 and HPV-015, PCR testing of genital swabs and histopathological lesions for non-vaccine HPV types were also performed. From the data provided, CBER analyzed the number of cases associated with non-vaccine HPV types in subjects who were naïve (not previously exposed to a specific non-vaccine HPV type as determined by PCR at baseline) and in subjects who were non-naïve (previously exposed to a specific non-vaccine HPV type by PCR). It was postulated that because several non-vaccine HPV types were phylogenetically related to HPV 16 ad 18 there would be additional protection afforded by the vaccine against non-vaccine HPV types. There are animal studies which support this hypothesis [HPV 45, which is

phylogenetically related to HPV 18] (Smith et al[7]), although the data from studies HPV-013 and HPV-015 were not obviously concordant with this animal study.

In the CBER review of the CIN 2/3 lesions which were detected in subjects participating in studies HPV-013 and HPV-015, multiple HPV types were noted either within the lesions or were present at baseline or were detected during the trials. Given the presence of multiple non-vaccine HPV types in subjects who developed CIN and CIN 3 in the datasets for studies HPV-013 and HPV-015, and given the ----------(b)(4)----------
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----------, CBER considered these non-vaccine HPV types in characterization of CIN 2 and CIN 3 lesions.

Reviewer's Comment: As can be noted from Table 26, there were app. 100 fewer subjects with CIN 2/3 or worse due to any HPV type in the Gardasil group as compared to the control group. To understand more fully which subjects were being afforded protection, and against which HPV related genital diseases, additional review of the CIN 2 and CIN 3 cases was undertaken.

CBER conducted an analysis of all CIN 2 and CIN 3 cases in the final close out datasets for studies HPV-013 and HPV-015. Studies HPV-013 and HPV-015 were included because data relating to non-vaccine HPV types were included in these datasets. Data from studies HPV-005 (monovalent HPV-16) and HPV-007 (dose ranging study) were not included in CBER analyses because there was absent or incomplete testing for non-vaccine HPV types. All cases of CIN 2 and 3 from studies HPV-013 and HPV-015 were included regardless of HPV type involved in the lesion, and counted from Day 1. The methods were as described for the characterization of VIN 2/3 and VaIN 2/3 lesions and AIS lesions. Because a number of subjects with CIN 3 also had CIN 2 detected simultaneously, those subjects with CIN 2 who also developed CIN 3 lesions were counted once as a CIN 3 lesion and not included in the CIN 2 totals. Using this method, CBER identified 245 CIN 3 lesions + 198 CIN 2 lesions (excluding subjects with both CIN 3 and CIN 2) = 443 subjects with CIN 2/3 in the Gardasil group as compared to the 292 CIN 3 lesions + 241 CIN 2 lesions (excluding subjects with both CIN 3 as well as CIN 2) = 533 subjects with CIN 2/3 in the control group. Since subjects were counted from Day 1 and included protocol violators, the total numbers were higher than those noted in Table 26 above. (CBER conducted a count of the total lesions as well, and findings were similar to those as presented in this review, although impact by subject is more clinically relevant.)

The proportions of subjects in each treatment group who developed a CIN 2/3 lesion during studies HPV-013 and HPV-015, as well as the proportion of subjects who developed a CIN 2/3 lesion associated with a specific HPV type within each treatment group is provided in the CBER generated table below. Please note that one lesion may have contained more than one HPV type. Also provided is the proportion of subjects with lesions in which the specific HPV type is detected in the group that developed CIN

[7] Smith JF et al. Human Vaccines 2007; 3(4):109-15

2/3. The sponsor indicated that the numbers of cases in certain groups were slightly different, but the differences are small, and do not change CBER 's conclusions.

TABLE 27
Studies HPV-013 and HPV-015: Number and percentages of subjects who developed CIN 2/3 by HPV type and Treatment Group (Final close out data) (CBER Generated)

HPV Type	Gardasil subjects with CIN 2/3 N= 8799	Control subjects with CIN 2/3 N =8800
	n (%) [P]	n (%) [P]
Total CIN 2/3 cases	443 (5.0%)	553 (6.3%)
6	2 (0.02%) [0.5%]	21 (0.24%) [3.8%]
11	0 (0%) [0%]	7 (0.08%) [1.3%]
16	138 (1.6%) [31.2%]	284 (3.2%) [51.4%]
18	7 (0.08%) [1.6%]	53 (0.6%) [9.6%]
31	69 (0.8%) [15.6%]	89 (1.0%) [16.1%]
33	53 (0.6%) [12.0%]	55 (0.6%) [9.9%]
35	20 (0.2%) [7.9%]	25 (0.3%) [4.5%]
39	29 (0.3%) [6.5%]	34 (0.4%) [6.1%]
45	18 (0.2%) [4.1%]	20 (0.2%) [3.6%]
51	51 (0.6%) [11.5%]	63 (0.7%) [11.4%]
52	76 (0.9%) [17.2%]	81 (0.9%) [14.6%]
56	41 (0.5%) [9.3%]	44 (0.5%) [8.0%]
58	36 (0.4%) [8.1%]	55 (0.6%) [9.9%]
59	10 (0.1%) [2.3%]	16 (0.2%) [2.9%]
No HPV detected in lesion	52 (0.6%) [11.7%]	46 (0.5%) [8.3%]

N=total number of subjects in studies HPV-013 and HPV-015
n = number of subjects who developed CIN 2/3 for specific HPV type
% = percentage of total treatment group who developed CIN 2/3 lesion
[P] = percentage of subjects with CIN 2/3 lesions with a specific HPV type

Table 28 below presents the total number of cases in subjects who were naïve for the relevant vaccine HPV types through Month 7 (seronegative D1 and PCR negative through M7); those who were only naïve at baseline for the relevant vaccine HPV type (seronegative and PCR negative for the relevant HPV type at D1); the total of these two groups (total naïve from baseline for the relevant HPV type); and the subjects who were non-naïve (seropositive and/or PCR positive for the relevant vaccine HPV types D1) at baseline and developed a lesion associated with the relevant vaccine HPV type for which they were non-naïve. In the original review, CBER had noted there was a higher number of CIN 2/3 associated with the relevant vaccine HPV type for which the subject was non-naïve in study HPV-013, but an imbalance was not noted in study HPV-015. In study HPV-013, the imbalance may have been related to abnormal Pap tests (higher proportion of subjects with High Grade Intraepithelial Lesion [HSIL] in the Gardasil group as compared to the control group). These were post-hoc subgroup exploratory analyses, and there are many shortcomings to such analyses. The point estimates of efficacy for these analyses did not reach statistical significance. In the CBER generated table (counting cases from Day 1) for this non-naïve group, there is a slightly higher number of CIN 2/3 lesions in the Gardasil group (95) as compared to the control group (89), but the difference is small. Again, subjects in the studies were sexually experienced, may or may not have positive Pap tests, and did not have testing for 4 other common non-vaccine

oncogenic types were not conducted, so it possible they were non-naïve for those other 4 non-vaccine HPV types. The numbers of cases of CIN 2/3 without an identified HPV type were similar to the those calculated by CBER; the incidence per 100 person years as calculated by Merck was 5.4 in each treatment group, and the point estimate of efficacy was -0.7% [95% CI: -37.4, 26.2%]. (Source: STN 125126/-(b)(4)-, efficacy supplement 2/22/07, p. 11).

TABLE 28

Cases of CIN 3 and CIN 2 (highest CIN grade in each subject) in final close-out datasets for studies HPV-013 and HPV-015 Associated with Vaccine HPV types by baseline status and treatment group (Close-Out Data study HPV-013 and HPV-015) (CBER generated)

CIN 3 and CIN 2 cases (Totals)	Gardasil N=2717 (013) N=6082 (015) Total = 8799	Control N=2725 (013) N=6075 (015) Total = 8800
(A) Cases associated with Vaccine HPV type (S-,P- M0 and P- M7 for relevant HPV type)	2	126
HPV 16	2	89
HPV 18	0	24
HPV 11	0	5
HPV 6	0	13
(B) Additional Cases associated with Vaccine HPV types (S-P- M0, cases counted after D1)	2	36
HPV 16	2	27
HPV 18	0	10
HPV 11	0	1
HPV 6	0	2
(C) Total Cases associated with Vaccine HPV types (S-P- M0, cases counted after D1) =[A+B]	4	162
HPV 16	4	116
HPV 18	0	35
HPV 11	0	6
HPV 6	0	15
(D) Cases associated with Vaccine HPV types present at baseline (S+ &/or P+)	142	140
HPV 16	134	122
HPV 18	7	18
HPV 11	0	1
HPV 6	2	6
Cases in subjects who were S+ **and** P+ at baseline for relevant vaccine HPV type	84	83
HPV 16	81	73
HPV 18	3	9
HPV 11	0	1
HPV 6	1	3
Cases in subjects who had detectable antibodies and were P+ for the relevant HPV type	11	6
Anti-HPV 16 detectable	9	2
Anti-HPV 18 detectable	1	2
Anti-HPV 6 detectable	1	2
TOTAL S detectable or +/P+	95	89

N=Number of subjects who received at least one dose of Gardasil in study HPV-013, study HPV-015, and in total across two trials

Subjects may have more than 1 HPV type and may be counted in more than once for the HPV type

Tables 29 and 30 below include cases of CIN 2/3 which developed in those naïve for a vaccine HPV type. The subjects included in Table 29 were naïve for the relevant HPV type through Month 7, and the subjects in Table 30 were additional subjects who were only naïve at Day 1.

TABLE 29

CIN 3 and CIN 2 cases (highest CIN grade in each subject) associated with Vaccine HPV type (S-P- M0 and P- M7 for relevant HPV type) (Close-Out Data Studies HPV-013 and HPV-15) (CBER generated)

CIN 3	Gardasil N=2717 (013) N=6082 (015) Total = 8799	Control N=2725 (013) N=6075 (015) Total = 8800	CIN 2	Gardasil N=2717 (013) N=6082 (015) Total = 8799	Control N=2725 (013) N=6075 (015) Total = 8800
HPV *16* Total	2	55	HPV *16* Total	0	34
16 alone	1	25	*16* alone	0	18
16, 6	0	2	*16, 6, 31, 39*	0	1
16, 6, *33*	0	1	*16, 18*	0	2
16, 18	0	5	*16, 18, 31, 56*	0	1
16, 31(1 31 new)	0	2	*16, 31, 33, 45, 58*	0	1
16, 31, 33, 58	0	1	*16, 35*	0	1
16, 31, 39, 51	0	1	*16, 39*	0	1
16, 31, 51, 52	0	1	*16, 45*	0	1
16, 39	0	2	*16, 51*	0	3
16, 45	0	1	*16, 51, 52, 58*	0	1
16, 45, 52	0	1	*16, 52*	0	1
16, 45, 59	0	1	*16, 56*	0	2
16, 52	0	3	*16, 59*	0	1
16, 52, 56	0	3			
16, 52, 58	1	1			
16, 56	0	1			
16, 56, 58, 59	0	1			
16, 58	0	1			
16, 59	0	2			
HPV *18* Total	0	12	HPV *18* Total	0	12
18 alone	0	2	*18* alone	0	2
18, *11*, 16, 51, *56, 58*	0	1	*18, 16*	0	2
18, 16	0	5	*18, 16, 31, 56*	0	1
18, 16, 31, *45*	0	1	*18, 31, 51*	0	1
18, 31,45	0	1	*18, 35, 51*	0	1
18, 33	0	1	*18, 51, 52, 58*	0	1
18, 52	0	1	*18, 52, 56*, 59	0	1
			18, 56	0	2
			18, 59	0	1
HPV *11* Total	0	3	HPV *11* Total	0	1
11, 16	0	1	*11, 51*	0	1
11, 16**,** *18*, 51, 56, 58	0	1			
11, 16, *56*	0	1			
HPV *6* Total	0	7	HPV *6* Total	0	6
6, 16	0	3	*6, 16, 31, 39*	0	1
6, 16, 33	0	1	*6, 39*	0	1
6, 31	0	1	*6, 51*	0	1
6, 33	0	1	*6*, 51	0	1
6, 58	0	1	*6, 52*	0	1
			6, 58	0	1

HPV types in italics represent P- for the relevant vaccine and non-vaccine HPV types

Case may appear in more than one table for both CIN 2 and CIN 3 cases.

TABLE 30

Additional CIN 3 and CIN 2 Cases (highest CIN grade in each subject) associated with Vaccine HPV types (S-P- M0, cases counted after D1) (Close-Out Data Studies HPV-013 and HPV-15) (CBER generated)

CIN 3	Gardasil N=2717 (013) N=6082 (015) Total = 8799	Control N=2725 (013) N=6075 (015) Total = 8800	CIN 2	Gardasil N=2717 (013) N=6082 (015) Total = 8799	Control N=2725 (013) N=6075 (015) Total = 8800
HPV *16* Total	2	18	HPV *16* Total	1	9
16 alone	1	10	*16* alone	1	5
16, 6	0	1	*16, 31*	0	1
16, 11	0	1	*16*, 33	0	1
16, 18, 31	0	1	*16, 35, 59*	0	1
16, 33	0	1	*16*, 51	0	1
16, 39	0	1			
16, 51	1	1			
16, 52	0	2			
HPV *18* Total	0	4	HPV *18* Total	0	6
			18 alone	0	2
18, 6	0	1	*18*, 31, *58*	0	1
18, 6, *35* 45, *51*, 52, *56*	0	1	*18, 33, 56*	0	2
18, 16, 31	0	1	*18, 39*, 52	0	1
18, 31	0	1			
HPV *11* Total	0	1	HPV *11* Total	0	0
11, 16	0	1			
HPV *6* Total	0	2	HPV *6* Total	0	1
6, 16	0	1			
6, 18	0	1			

HPV types in italics represent P- for the relevant non-vaccine HPV type
Case may appear in more than one table for both CIN 2 and CIN 3 cases.

Reviewer's Comment: From Tables 28, 29 and 30, Gardasil is noted to prevent disease related to a vaccine HPV type for which the subject has not been exposed. Counting cases from Day 1, CBER identified five (4) subjects with a diagnosis of CIN 2/3 associated with a vaccine HPV type for which they were naïve. Two subjects with CIN 3 were considered included within the PPE population, and the other 2 (CIN 3) were included in an unmodified Intent to Treat population. Details about these subjects are noted here:

1. AN 40208 (015): CIN 3 related to HPV 16 @ M48: This subject was S-P- for HPV 16 at baseline and through M7; had a negative Pap test @ baseline; was positive for HPV 51 detected at Day 1 and HPV 56 detected at M48 (by PCR).
2. AN 49266 (015): CIN 3 related to HPV 16, 52 @ M24: This subject was S-P- for HPV 16 @baseline and through M7; had a negative Pap test; was positive for HPV 52 @ baseline. The lesion included HPV 52 in addition to HPV 16.
3. AN 56701 (015): CIN 3 related to HPV 16 @ M24: This subject was S-P- for HPV 16 @ baseline but HPV 16 was detected at M7; had anti-HPV 18 antibodies which were detectable but below seropositive cutoff at Day 1; had a negative Pap test @ baseline; was positive for HPV 52 detected at Day 1; HPV 16 and 52 were detected at M7; and HPV 16 and 45 were detected at M24.

4. AN 56651 (015): CIN 3 related to HPV 16, 51 @ M12: This subject was S-P- for HPV 16 @ baseline but had HPV 33, 39, 52, 56, 58, and 59 at Day 1; had LSIL baseline Pap; at M7 had HPV 16, 33, 39, 52 and 58 detected; at M12 had HPV 39, 51, and 16 detected.

All 4 subjects were infected with other non-vaccine HPV types at baseline. One lesion involved a non-vaccine HPV type for which the subject was already exposed (HPV 52), and one lesion involved a non-vaccine HPV type for which the subject was not apparently exposed, 51 (although this subject was infected with multiple other non-vaccine HPV types at baseline, and this latter subject also had an abnormal Pap test at baseline).

TABLE 31

CIN 3 and CIN 2 cases (highest grade CIN) in final close-out datasets for studies HPV-013 and HPV-015 Associated with Non-Vaccine HPV types or no HPV by baseline status and treatment group (CBER generated)

CIN 3 and CIN 2 cases	Gardasil N=2717 (013) N=6082 (015) Total = 8799	Control N=2725 (013) N=6075 (015) Total = 8800
Cases associated with Non-Vaccine HPV types and P+ at baseline for relevant HPV types	153	154
Case Occurred Before M7	26	22
Subjects non-naïve for vax HPV type @D1	57	47
Subjects also naïve for vax HPV type @ D1	1	16
HPV 31	46	36
HPV 33	20	22
HPV 35	7	9
HPV 39	15	8
HPV 45	6	7
HPV 51	22	25
HPV 52	34	30
HPV 56	11	12
HPV 58	16	22
HPV 59	1	3
(1) Cases associated with Non-Vaccine HPV types and P- at baseline for relevant HPV types	159	212
Subjects non-naïve for vax HPV @ D1	(CIN 3)+2	(CIN 3) +0
Subjects also naïve for vax HPV @ D1	1	80
HPV 31	23 (14 alone)	53 (13 also naïve for V HPV) [40] (21 alone)
HPV 33	33 (14 alone)	33 (10 also naïve for V HPV) [23] (11 alone)
HPV 35	13 (6 alone)	16 (4 also naïve for V HPV) [12] (8 alone)
HPV 39	14 (5 alone)	26 (6 also naïve for V HPV) [20] (3 alone)
HPV 45	12 (4 alone)	13 (6 also naïve for V HPV) [7] (1 alone)
HPV 51	29 (1 also naïve for V HPV) [28] (10 alone)	38 (14 also naïve for V HPV) [24] (7 alone)
HPV 52	42 (20 alone)	51 (14 also naïve for V HPV) [37] (12 alone)
HPV 56	30 (9 alone)	32 (13 also naïve for V HPV) [19] (2 alone)
HPV 58	20 (10 alone)	33 (11 also naïve for V HPV) [22] (10 alone)
HPV 59	9 (2 alone)	13 (6 also naïve for V HPV) [7] (1 alone)
Cases not associated with any HPV type	52	46
Naïve subjects (S-/P-) at M0 for any HPV) (Pap test may be positive or negative)	22	11
Non-naïve for any HPV (S+ &/or – at M0)	30	35

N=Number of subjects who received at least one dose of Gardasil in study HPV-013, study HPV-015, and in total across two trials; Subject may be included in more than one HPV type; [number] = number of cases excluding subjects who were also naïve for a vaccine HPV type.

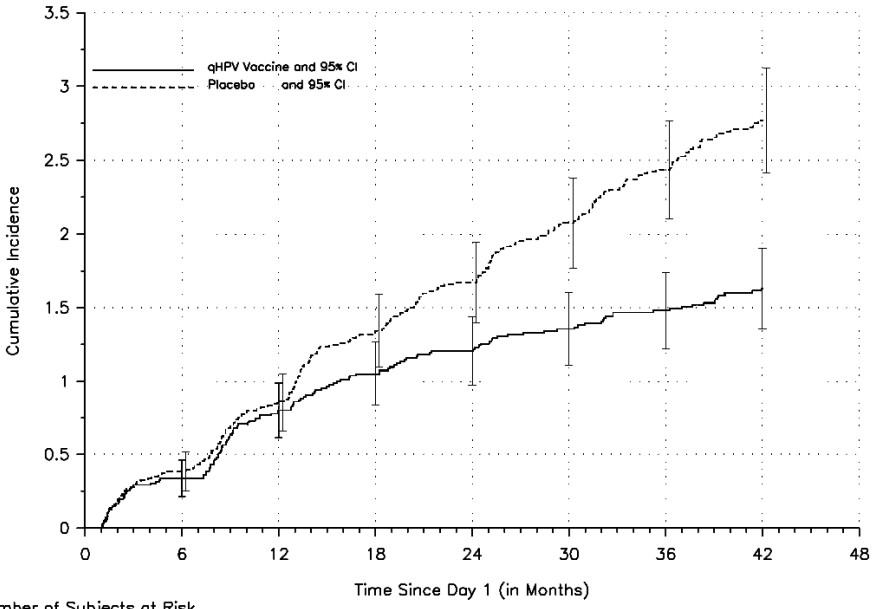
Prophylactic Efficacy for Vaccine HPV related CIN 2/3:

- As noted in Table 28, in subjects who did not have evidence of exposure to the relevant vaccine HPV type, there were 162 subjects with CIN 2 or CIN 3 as highest grade CIN in the placebo group as compared to 4 subjects in the Gardasil group. In the 4 subjects who developed CIN 3, 2 became infected with the relevant vaccine HPV type during the vaccination period. All 4 had evidence of having been exposed to other non-vaccine HPV types at baseline.

FIGURE 3

Figure 4-27

Time to Detection of 6/11/16/18-related CIN (Any Grade) or AIS
(Protocol 013 and 015 Combined – MITT-3 Population)



Number of Subjects at Risk

qHPV Vaccine	8,788	8,493	8,345	8,197	8,064	7,926	7,716	5,881	529
Placebo	8,790	8,523	8,357	8,198	8,059	7,910	7,670	5,865	507

Case counting began at Day 30 for this population. Two hundred twenty nine (229) of the 8,788 subjects who received qHPV vaccine and 198 of the 8,790 subjects who received placebo in this population did not have follow-up after Day 30.
CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; HPV = Human papillomavirus; MITT = Modified intention-to-treat.

Source: Figure 4-27, STN 125126/-(b)(4)-, reference 2154, p. 218

Efficacy Not Demonstrated for Prevention of CIN related to HPV in subjects already infected with HPV type at baseline:

- Also noted in Table 28, in subjects who had been exposed to a vaccine HPV type prior to vaccination, there was no evidence of benefit in prevention of CIN 2/3 related to the relevant vaccine HPV type with which they were infected. There was an approximately equal number of subjects who were previously exposed to the relevant

vaccine HPV type and then received Gardasil (142 subjects) as compared to 140 subjects in the control group. [Please note that the sponsor's total of the cases in each category is close to CBER's calculations, but not exactly the same.]

- In Table 31, in subjects who had been exposed to a non-vaccine HPV type prior to vaccination, there was no apparent benefit in prevention of CIN 2/3 related to the relevant HPV type with which they were infected. There was again an approximately equal number of subjects who were previously exposed to the relevant non-vaccine HPV type and then received Gardasil (153) as compared to 154 subjects in the control group.

Prophylactic Efficacy Not Demonstrated for Prevention of CIN 2/3 associated with Non-Vaccine HPV Types:

- CBER acknowledges that the prevalence of individual non-vaccine HPV types is lower than the prevalence of the vaccine HPV types.
- On first review of the number of lesions in which a subject was naïve for the relevant non-vaccine HPV type, one would note that there are fewer subjects in the Gardasil group who developed CIN 2/3 related to the relevant non-vaccine HPV type and received control (212) as compared to the Gardasil group (159). However, on further analysis, 80 of the subjects in the control group who developed such a lesion were also naïve for a vaccine HPV type prior to vaccination. This is in contrast to 1 subject in the Gardasil group who was also naïve for a vaccine HPV type and went onto develop CIN 2/3 related to a non-vaccine HPV type to which they were also naïve. From analysis of Tables 29 and 30, one can see that nearly all CIN 2/3 lesions were prevented which were associated with the relevant vaccine HPV type if the subject is naïve for that HPV type. From the number of subjects who developed a lesion related to the non-vaccine HPV type alone for which they were naïve, only for HPV 31 related lesions is there a decrease in number of cases in the Gardasil group (14) as compared to the control group (21). The same degree of preventive efficacy is not noted as for the vaccine HPV types. Other case splits are also less than impressive. Even though animal studies have demonstrated that there may be cross-protection for non-vaccine types when considered individually, the clinical benefit is unclear given the multiplicity of HPV types noted to be associated with development of these lesions. CBER acknowledges that the studies were not powered to assess efficacy of individual non-vaccine HPV types, but the results are of interest nonetheless. Smith et al[8] note that in vitro neutralization studies indicate that cross-neutralizing titers are lower than type-specific titers.

CIN 2/3 Lesions Negative for HPV:

- There was no benefit in prevention of CIN 2/3 lesions in which no HPV was identified (52 in the Gardasil group as compared to 46 in the control group). This group was divided into 2 groups: those naïve for any identified HPV type at baseline (naïve for a total of 14 HPV types) and had a negative Pap test at baseline, and those non-naïve for any HPV type. The group which was non-naïve for another HPV type had slightly more subjects with CIN 2/3 negative for an identified HPV type in the control group

[8] Smith JF et al. Human Vaccines 2007; 3(4):109-15

(35) as compared to the Gardasil group (30). In the group naïve for the 14 HPV types with a negative Pap test at baseline, there were 22 lesions in the Gardasil group as compared to 11 subjects in the control group. The concern for this subgroup is that they most closely resemble subjects prior to sexual exposure, and this imbalance raises the question as to whether there is evidence of replacement with non-vaccine HPV type. However, the vast majority of the study population are sexually experienced. It is also known that Pap tests are < 100% sensitive, and 4 oncogenic additional non-vaccine HPV types were not tested for, and subjects might have been positive prior for these additional non-vaccine HPV types prior to vaccination. The reverse trend was seen for the VIN 2/3 lesions, where there was a higher number of subjects with no HPV identified in the control group (8) as compared to the Gardasil group (1), and 3/8 also had negative baseline Pap tests and were naïve for any HPV at baseline, as compared to 0 in the Gardasil group. The numbers are small, and illustrate problems of subgroup analyses. Merck will be following long-term efficacy in subjects in the Nordic countries in which the issue of possible replacement with non-vaccine HPV types will be evaluated.

Overall Impact on CIN 2/3 in Women 16-26 years of age who participated in studies HPV-013 and HPV-015:

- The most important observation is that Gardasil has different effects on reduction of HPV related CIN 2/3, based on the baseline status in regards to previous infection with a vaccine HPV type, and which HPV type is being evaluated. As noted in the overall efficacy analyses for efficacy against CIN 2/3 or worse related to ANY HPV type, there was only an 18.4% [95% CI: 7.0, 27.7%] reduction of any HPV related CIN 2/3 in the entire study population. Practitioners must keep in mind that the overall study population included a select group of sexually active women (4-5 lifetime sexual partners, without a history of known cervical or external genital disease). In addition, cases were counted starting after 1 month (not immediately after dose 1). In general use, subjects may have a history of prior HPV related cervical and/or external genital dysplasias, and lower overall reductions in any HPV related CIN 2/3 may be observed. The vaccine efficacy in prevention of CIN 2/3 related to any HPV type as calculated for any subject in the RMITT-2 population related to vaccine HPV types is much more robust (VE=42.7%: [95% CI: 23.7, 57.3%]) because these subjects more closely approximate the truly "naïve" population, although not perfectly. However, in both populations, it appears that the positive efficacy is related to protection against CIN 2/3 related to vaccine HPV types for which a subject is naïve. Nonetheless, in the sexually experienced population involved in the studies, there were still a fair number of women who did not have evidence of prior HPV disease (RMITT-2 population) and who may benefit from vaccination. At the time of the final close out data, 4616/8799 evaluable Gardasil subjects (approximately 52%) and 4680/8800 (approximately 53%) evaluable control subjects were included in the RMITT-2 analyses. HPV type specific screening for PCR (for at least the 12 oncogenic HPV types tested in this study, perhaps adding 4 other oncogenic types) might be a way to predict if someone will benefit from vaccination, short of vaccinating only those subjects prior to sexual activity, but this type of testing is not available, and even if available, might not be cost-effective.

Appendix 3 includes CBER generated tables which include subjects who were naïve for each non-vaccine HPV type and developed a CIN 2/3 lesion related to that HPV type (+/- other HPV types). These subjects are included in the summary Table 31 which includes cases related to non-vaccine HPV types.

Efficacy Against Condyloma Acuminata, final analysis

The sponsor also provided updated combined analyses of efficacy for condylomata and external genital lesions from studies 007, 013 and 015.

TABLE 32

Studies HPV-007, -013, and -015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related Condyloma–Per Protocol Efficacy Population [PPE] and Modified Intent to Treat-3 population [MITT-3] (Original Submission)

	Gardasil N=9075				Control N=9075					
EGL Type	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE Population										
HPV 6, 11, 16 , 18 condyloma	7897	1	11977.9	0.0	7899	91	11953.4	0.8	98.9%	(93.7, 100.0%)
MITT-3 population										
HPV 6, 11, 16, 18 related condyloma	8954	58	17068.3	**0.3**	8962	184	17593.1	**1.0**	**68.5%**	**(57.5, 77.0%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit; Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: Amendment 34, Tables 1-1 and 1-3, Efficacy Information Amendment, 5/17/06

TABLE 33

Studies HPV-007, -013, and -015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related Condyloma–Per Protocol Efficacy population [PPE] and Modified Intent to Treat population [MITT-3] (Final Close-Out Data)

	Gardasil N=9075				Control N=9075					
EGL Type	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE Population										
HPV 6, 11, 16 , 18 condyloma	7900	2 [2]	23606.5	0.0	7902	193 [189]	23411.1	0.8	99.0%	(96.2, 99.9%)
MITT-3 population										
HPV 6, 11, 16, 18 related condyloma	8955	61 [60]	30351.4	**0.2**	8968	307 [300]	30157.2	**1.0**	**80.3%**	**(73.9, 85.3%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection. n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, efficacy amendment submitted 2/22/08, p. 21, 23)
"[ ]" Number of cases related to HPV 6/11.

Reviewer's Comment: As noted for calculations for CIN 2/3 or worse, the point estimates of efficacy were generally higher for both the PPE population and MITT-3 population in the close-out data. Even in the MITT-3 population, the point estimate of efficacy is quite high. One important factor is that subjects were excluded from the studies if they had a history of genital warts, and it would be expected that a subject would have more readily identified a genital wart (which is external and may cause symptoms such as discomfort or itching) as compared to knowledge of prior cervical lesions which are not as readily identified (either by the subject or by cytology, given the less than 100% sensitivity of the Pap test). The vast majority of the condylomas are related to HPV 6/11.

The sponsor also provided efficacy in the prevention of condyloma acuminata related to ANY HPV type in the Restricted MITT-2 population (although HPV 6 and 11 is reportedly related to app. 90% of condyloma).

TABLE 34

Studies HPV-013 and -015: Analysis of Efficacy Against Condyloma Related to ANY HPV – Restricted Modified Intent to Treat-2 population [RMITT-2] and Modified Intent to Treat-3 population [MITT-3] (Final Close-out data)

	Gardasil N=9075				Control N=9075					
Population/Lesion	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
RMITT-2	4688	29	16044.1	**0.2**	4735	169	16110.5	**1.0**	**82.8%**	**74.3, 88.8%**
MITT-3	8688	132	29485.7	**0.4**	8701	350	29345.9	**1.2**	**62.5%**	**54.0, 69.5%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Restricted Modified Intent to Treat-2 population [RMITT-2]: subjects who are naïve for all tested HPV types at baseline with negative Pap tests, with cases counted 1 day after Month 1.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, efficacy amendment 2/22/08, p. 29**.**

Efficacy Against CIN 1, first close out results

Efficacy against CIN 1 was also included in the close-out data, and is included in this review. The original analysis and close-out data are compared in Table 35 below.

TABLE 35

Studies HPV-007, -013, and -015: Analysis of Efficacy of HPV 6, 11, 16, 18 related CIN 1 (Per Protocol Efficacy Population [PPE], and Modified Intent to Treat-3 population [MITT-3] (Original Analysis)

Gardasil N=9075				Control N=9075					
n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE									
7858	4	11884.0	0.03	7861	58	11878.4	0.5	**93.1%**	(81.4, 98.2%)
MITT-3									
8814	97	17443.9	0.6	8846	213	17457.5	1.2	**54.4%**	(41.8, 64.5%)

N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n= number of subjects evaluable, i.e., the number of subjects in the given population who also have at least one follow-up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126.0, Table 5.3.5.3.2:8, Integrated Summary of Efficacy, p. 43-44

TABLE 36

Studies HPV-007, -013, and -015: Analysis of Efficacy of HPV 6, 11, 16, 18 related CIN 1 (Per Protocol Efficacy population [PPE] and Modified Intent to Treat-3 population [MITT-3] (Initial Close Out Data)

Gardasil N=9075				Control N=9075					
n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE									
7863	5	18917.0	0.0	7863	111	13794.6	0.6	**95.5%**	89.2, 98.6%
MITT-3									
8817	103	25152.5	0.4	8847	289	25018.3	1.2	**64.5%**	55.5, 72.0%

N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n= number of subjects evaluable, i.e., the number of subjects in the given population who also have at least one follow-up visit.
Per-protocol efficacy population [PPE]: seronegative for relevant vaccine HPV type at baseline, PCR negative for relevant vaccine HPV type through Month 7, without protocol violations, with positive or negative Pap tests, with cases counted 1 day after Month 7.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
STN 125126/419/0, Table 2.3.3-cervixcancer:23, p. 106,

Reviewer's Comment: As for the other endpoints discussed, with continued follow-up, the point estimates of efficacy increased, with tightening of the 95% CIs.

The sponsor has also presented efficacy estimates of CIN 1 related to ANY HPV type in the RMITT-2 population and MITT-3 population in studies HPV-013 and HPV-015.

TABLE 37
Studies HPV-013 and -015: Analysis of Efficacy Against CIN 1 related to ANY HPV type: Restricted Modified Intent to Treat-2 population [RMITT-2] and Modified Intent to Treat-3 population [MITT-3] (Final Close-Out Data)

	Gardasil+HPV 16 N= 8799				**Alum Control N=8800**					
	n	Cases	Person Years at Risk	Incidence	n	Cases	Person Years at Risk	**Incidence**	**Observed Efficacy**	**95% CI**
R-MITT 2 (Final close-out data)	4616	241	15817.0	1.5	4680	346	15956.5	**2.2**	**29.7%**	**16.9, 40.6%**
MITT-3 (final close-out data)	8559	778	28212.2	**2.8**	8592	973	28065.0	**3.5**	**20.5%**	**12.5, 27.7%**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Restricted Modified Intent to Treat-2 population [RMITT-2]: subjects who are naïve for all tested HPV types at baseline with negative Pap tests, with cases counted 1 day after Month 1.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/-(b)(4)-, efficacy amendment, 2/22/08, p. 5-6

Reviewer's Comment: In the original license application, the point estimates of efficacy against CIN 1 or worse related to ANY HPV type were somewhat lower (for RMITT-2, 21.9% [95% CI: 6.6, 34.7%]; for MITT-3, 13.7% [95% CI: 4.2, 22.2%]) as compared to the final close out data.

Impact on Definitive Cervical and External Genital Procedures
One additional exploratory analysis was conducted by the sponsor to assess if there was an impact in reducing the proportion of Gardasil recipients who required a definitive cervical or external genital procedure as compared to subjects who received alum control. This analysis was presented in the original submission, and the original analysis and analysis on the close-out data are presented in Table 38 below.

TABLE 38

Impact of Gardasil on Selected Invasive Procedures in the Restricted Modified Intent to Treat-2 population [RMITT-2] and Modified Intent to Treat-3 population [MITT-3] (Original Submission)

Population/ Procedure	N	Number of cases	N	Number of Cases	% reduction	95% CI
RMITT-2/ Definitive Cervical procedure (007, 013, 015)	5638	76	5701	107	28.1%	2.7, 47.2%
MITT-3/ Definitive Cervical Procedure (007, 013, 015)	8817	322	8848	387	16.5%	2.9, 36.0%
RMITT-2/ Genital lesion Definitive Therapy (013)	1726	38	1733	70	45.7%	18.3, 64.4%
MITT-3/ Genital lesion definitive Therapy (013)	2671	96	2668	130	26.5%	3.6, 44.2%

N=number of evaluable subjects

Point Estimates and CIs are adjusted for person time of follow-up

Restricted Modified Intent to Treat-2 population [RMITT-2]: subjects who are naïve for all tested HPV types at baseline with negative Pap tests, with cases counted 1 day after Month 1.

Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.

Source: STN 125126/0, Appendix 2.5:18, p. 74, Clinical Overview

TABLE 39

Impact of Gardasil on Selected Invasive Procedures in Restricted Modified Intent to Treat-2 population [RMITT-2] and Modified Intent to Treat-3 population [MITT-3] (Initial Close-Out Data)

Population/ Procedure (Study)	N	Number of cases	Person Years at Risk	Incidence	N	Number of Cases	Person Years at Risk	Incidence	% Reduction	95% CI
RMITT-2/ Definitive Cervical procedure (007, 013, 015)	4696	82	13752.6	0.6	4574	138	13866.5	1.0	40.0%	20.7, 55.0%
MITT-3/ Definitive Cervical Procedure (007, 013, 015)	8820	466	25249.1	1.8	8849	582	25239.2	2.3	20.0%	9.4, 29.3%
RMITT-2/ Genital lesion Definitive Therapy (013)	1461	37	4156.2	0.9	1471	69	4140.5	1.7	46.6%	19.2, 65.2%
MITT-3/ Genital lesion definitive Therapy (013)	2671	115	7452.7	1.5	2668	171	7392.8	2.3	33.3%	15.0, 47.8%

N=number of subjects randomized who received at least 1 dose of study material
n=Number of subjects with follow-up of at least 30 days after dose 1
Restricted Modified Intent to Treat-2 population [RMITT-2]: subjects who are naïve for all tested HPV types at baseline with negative Pap tests, with cases counted 1 day after Month 1.
Modified Intent to Treat-3 population [MITT-3]: Modified Intent to Treat-3 Population [MITT-3]: Subjects included regardless of baseline HPV status, regardless of baseline Pap test, and cases counted after 1 day after Month 1.
Source: STN 125126/419.0, Table 27.3, cervixcancer: 43, p.171; Table 2.7.3 exgenlesions: 23, p. 82, and Appendix 2.7.3 exgenlesions:11, p.108
Subjects are counted once in each category but may appear in more than one category

Reviewer's Comment: In the final close-out data, the proportion of subjects who required a definitive cervical procedure (e.g., LEEP) was decreased by approximately 40% in the relatively naïve population, as compared to app. 20% for the entire population (includes naïve and non-naïve subjects). This analysis includes cases after Day 30, and excludes cases which were diagnosed in the first 30 days after dose 1. CBER acknowledges that lesions which required treatment within the first month were present at baseline, and represented disease already present at the start of vaccination. The efficacy analyses in prevention of abnormal Pap tests related to vaccine HPV types is not considered supportive of prevention of clinically relevant disease, since Pap tests are screening tests, and these tests are < 100% sensitive.

Efficacy Conclusions:

1. The data support the proposed additional indication for prevention of some vulvar and vaginal cancers related to HPV 16 and 18. CBER requested a consultation from the Center for Drug Evaluation and Research (CDER), and Dr. Gerry Willett provided an expert opinion as to the validity of using prevention of HPV 16 or 18 related VIN 2/3 and VaIN 2/3 as appropriate surrogates of disease, similar to the use of CIN 2/3 or worse as a surrogate for cervical cancer. There is evidence that in subjects who have not been exposed to HPV 16 or 18 before vaccination, there is benefit in prevention of VIN 2/3 and VaIN 2/3 lesions, which would translate into prevention of vulvar and vaginal cancers, respectively, related to HPV 16 and/or 18. As noted by the CDER consultant, these lesions are rare, and not all are related to HPV. There would be no apparent impact on prevention of vulvar and vaginal dysplasias in subjects who were previously exposed to a vaccine or non-vaccine HPV.
2. The efficacy against histopathological lesions including AIS, CIN 2/3, Condylomata, and CIN 1 through extended follow-up of individuals participating in the pivotal Phase III studies (and Phase IIb studies HPV-007 and Phase II study HPV-005, in selected analyses) remain similar and higher than those noted at the time of original analyses. New cases continued to accrue in both treatment groups through this extended time, although to a somewhat greater degree in the control group as compared to the Gardasil group, in the overall population. For those who were naïve for the relevant HPV type at baseline, the vaccine efficacy remains high, and few additional cases related to the relevant HPV type were noted in these originally naïve subjects. The 4 subjects who were naïve and developed a CIN 3 lesion subsequently were all also infected with another non-vaccine HPV type. No immune correlate of protection was as yet identified from these few cases. Immunogenicity will be further discussed in the overview of immunogenicity.
3. Efficacy is related to a subject's prior exposure to a vaccine HPV type. Efficacy is not demonstrated for the prevention of lesions associated with an HPV type (both vaccine and non-vaccine types) to which a subject has been exposed, in that an almost equal number of subjects in each treatment group developed such lesions.
4. Prophylactic efficacy has not been demonstrated against lesions associated with non-vaccine HPV types to which a subject is naive. The apparent positive effect that was noted in CBER analyses conducted appear to have been related to the prevention of disease related to a <u>vaccine</u> HPV type for which the subject was also naïve. When considering cases of non-vaccine HPV related CIN 2/3, there was a modest reduction in the number of CIN 2/3 related to HPV 31 (only that HPV type found in the lesion), with a case split of 21 in the control group and 14 in the Gardasil group. This does not approach the near 100% efficacy noted for prevention of vaccine HPV related CIN 2/3 in those naïve for the relevant vaccine HPV type.
5. CBER has continued to focus on histopathological endpoints in assessment of efficacy. Although persistent infection has been reported in the literature to be an adequate predictor of prevention of CIN 2/3 and cervical cancer associated with that particular HPV type, the multiplicity of HPV types with which a subject is infected complicates assessment of actual benefit that the subject may realize after vaccination. Persistent infection of at least 12 months duration may prove most useful, but there is still much to be learned as to the ultimate usefulness of this surrogate, given the

complexity of HPV related genital disease. Multiplicity of HPV types and analysis of cases related to the relevant HPV type make analyses difficult to sort out. If a subject did not develop CIN 2/3 related to a vaccine HPV type, they still might have developed a lesion related to a vaccine or non-vaccine HPV type for which they had been exposed, or to a non-HPV vaccine type for which they may have been naïve.

10. Overall Safety-Follow-up Data in 16-26 year old women (Close out Studies HPV-007, 013, and 015), safety follow-up through Month 24 in 9-15 year old girls and boys in Study HPV-018 (and safety data from Month 12 of Study HPV-016); and Adverse Events of significant importance (Deaths, SAEs, Pregnancy Outcomes, Congenital Anomalies) in women 27-45 years of age (interim safety data)

Follow-up safety data is included in supplements 125126/419, as well as supplements -(b)(4)- and -(b)(4)-. Supplement 419 includes the Summary of Clinical Safety through the initial close-out data presentation for studies 007, 013, and 015. In addition, Safety data through Month 24 was provided for study HPV-018 (study in girls and boys 9-15 years of age of Gardasil as compared to placebo). Supplement -(b)(4)- contains the final close-out safety summary tables for studies HPV-013 and HPV-015. Supplement -(b)(4)- includes an updated overall clinical summary of safety for final close out data from 007, 013, 015, 016, 018) and compilation of congenital anomalies in all subjects who received Gardasil in completed studies as well as safety data for subjects who participated in study HPV-019 (mid-adult women, 27-45 years of age).

In this section, the review contains updates to deaths, serious adverse events, discontinuations due to adverse events that occurred during the clinical studies, an overview of severe adverse events in studies 013 and 015 safety datasets, review of new medical conditions which developed during the course of the study, including potentially autoimmune events, as well as selected conditions which appeared on a summary table and were of interest given adverse events that have been reported to VAERS in the post-marketing period. In addition, an update to pregnancy outcomes will be reviewed, as well as congenital anomalies that were reported to the BLA since the time of original licensure. Reference is made to the original clinical review already cited which contains the methods used for reporting adverse events. (See Overall Safety, p. 371-435, at http://www.fda.gov/cber/review/hpvmer060806r.pdf.)

Overall Extent of Exposure

21,480 subjects were vaccinated in studies HPV-007, 013, 015, 016, and 018. A total of 11,912 subjects received at least 1 dose of Gardasil. This includes a total of 120 subjects in the extension study of Protocol 007 who had received a 3-dose regimen of alum control in the primary study, and then received 3 doses of Gardasil in the extension study. Excluding the subjects who received Gardasil in the extension study of 007, there were 11792 subjects who received at least 1 dose of vaccine. A total of 9688 subjects received at least 1 dose of alum control or saline placebo. Including study HPV-019, 13,822 subjects received at least one dose of Gardasil in studies 007, 013, 015, 016, 018, and 019. A total of 11,595 subjects received placebo in these studies. (In study HPV-019, 1910 women received Gardasil and 1907 received alum control).

Reviewer's Comment: Both totals are provided so that denominators for deaths and serious adverse events are known.

The cut-off date for original application was 11/11/05. The date for cut-off for studies HPV-013 and HPV-015 at the time of the initial close out data was 6/15/06; for HPV-007, the date was 10/3/06, and for HPV-018, the date was 10/24/06.
The cut-off dates for data presented in this review are noted in Table 40 below.

TABLE 40
Safety Data Close-out Dates for Studies HPV-007, -013, -015, -016, -018, and -019 (CBER generated table)

Protocol	Initial Close out data cut-off date	Final Close out data safety cut-off date
007	10/3/06	9/17/07
013	6/15/06	4/6/07
015	6/15/06	3/31/07
016	9/20/04	9/20/04
018	10/24/06	6/1/07
019	7/13/07*	Not available

*Ongoing study

The safety populations included in this review include:
Safety Population: All subjects enrolled in studies 007, 013, 015, 016, and 018 (and 019 for selected adverse events) who received Gardasil or control.
Detailed Safety Population: Subjects enrolled in studies 007, 013, 015. 016, and 018 (and 019 for selected adverse events) who received Gardasil or control using the Vaccine Report Card.

Summary of Clinical Adverse Events (Cumulative Data)
Table 41 below shows the overall summary of clinical adverse events from Day 1 through the entire trial.

TABLE 41
Studies HPV-007, -013, -015, -016, -018, and -019: Clinical Adverse Experience Summary (Days 1 Through Entire study Period after any Vaccination Visit) - Detailed Safety Population (Ages 9-17 and 18-26 years) (12/2/07)

	Gardasil Age 9-17 years N=2463	Alum Control or saline Placebo Age 9-17 years N=795	Gardasil Age 18-26 years N=3983	Alum Control Age 18-26 years N=3544
Subjects with Follow-up	2430	781	3921	3485
Subjects with ≥ 1 AE	2087 (85.9%)	564 (72.2%)	3627 (92.5%)	3079 (88.4%)
Injection Site AEs	1869 (76.9%)	433 (55.4%)	3397 (86.6%)	2684 (77.0%)
Systemic AEs	1247 (51.3%)	385 (49.3%)	2534 (64.6%)	2199 (63.1%)

Source: Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Appendix 2.7.4:5 and 2.7.4:6, p. 146-9 (12/07); Percentages are based on number of subjects with follow-up.

TABLE 42

Studies HPV-007, -013, -015, -016, -018, and -019: Clinical Adverse Experience Summary (Days 1 Through Entire study Period after any Vaccination Visit) - Safety Population (Ages 9-17 and 18-26 years) (12/2/07)

	Gardasil Age 9-17 years N=3420	Alum Control or saline Placebo Age 9-17 years N=1753	Gardasil Age 18-26 years N=8644	Alum Control Age 18-26 years N=8208
Subjects with Follow-up	3384	1738	8538	8208
Subjects with ≥ 1 AE	2096 (61.9%)	583 (33.5%)	3911 (45.8%)	3330 (41.1%)
Injection Site AEs	1869 (55.2%)	434 (25.0%)	3550 (41.6%)	2791 (34.4%)
Systemic AEs	1256 (37.1%)	403 (23.2%)	3698 (31.6%)	2366 (29.2%)
Subjects with SAEs	19 (0.6%)	18 (1.0%)	90 (1.1%)	87 (1.1%)
Deaths	1 (0.03%)	3 (0.2%)	10 (0.1%)	4 (0.05%)
Discontinued due to AE	7 (0.2%)	4 (0.2%)	19 (0.1%)	16 (0.2%)
Discontinued due to SAE	2 (0.1%)	3 (0.2%)	9 (0.1%)	1 (0.0%)

Source: Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Appendix 2.7.4:3 and 2.7.4:4, p. 142-145 (12/07); Percentages are based on number of subjects with follow-up.

Reviewer's Comment:

In the Detailed Safety Population (includes only subjects who completed a Vaccine Report Card)**,** the following pattern was noted:

- In subjects 9-17 years of age, throughout the entire study period, there was a higher proportion of subjects with any adverse event (85.9% Gardasil, 72.2% placebo or alum control), which appears to be related to a higher proportion of subjects with an injection site adverse event in the Gardasil group (76.9%) as compared to alum control or saline placebo (55.4%).
- This pattern was also seen in subjects 18-26 years of age.

In the Safety Population (includes subjects who did not complete a Vaccine Report Card as well as those who completed a Vaccine Report Card), after Day 1 and followed throughout the study:

- The overall proportions of subjects with any adverse event, any injection site adverse event, and any systemic adverse events were lower than in those who did complete a Vaccine Report Card.
- Comparing the two treatment groups, there was a higher proportion of subjects with systemic adverse events in the 9-17 year old age group who received Gardasil (37.1%) as compared to the control group (23.2%), although the proportions of subjects with systemic adverse events were comparable in the 18-26 year old age group (31.6% Gardasil, 29.6% control).
- Most of the reports of systemic adverse events appeared to come from the subjects in the Detailed Safety group, and the overall lower proportions when considering the entire population may indicate the larger denominator used in the overall safety calculations.

Significant/Potentially Significant Events
Deaths
There were 17 deaths reported at the time of original licensure (10 in the Gardasil group and 7 in the control group).

In the updated safety reports (STN 125126/419.0, 125126/-(b)(4)-, and 125126/-(b)(4)-[mid-adult women]), there were a total of 24 deaths (15 in the Gardasil group and 9 in the placebo or saline control group). Deaths which occurred in study HPV-019 (women 27-45 years of age) are included in the updated PI, and are included in Table 43 below.

TABLE 43
Studies HPV-007, -013, -015, -016, -018, -019: Deaths
(Original Unbolded and New Deaths Bolded)

	Gardasil N=13697	Days postdose	Placebo N=11593	Days postdose
Trauma	4 19 y/o f 23 y/o f 20 y/o f 22 y/o f	 373 days postdose 3 8 days postdose 2 90 days postdose 3 800 days postdose 3	3 18 y/o f 17 y/o/f 16 y/o f	 2 day postdose 2 342 days postdose 3 798 days postdose 3
DVT/PE	1 (22 y/o f)	19 days postdose 1	1 (23 y/o f)	202 days postdose 2
Sepsis, DIC	1 (21 y/o f)	359 days postdose 3		
Pneumonia, sepsis	1 (21 y/o f)	625 days postdose 3		
Pancreatic cancer	1 (25 y/o f)	578 days postdose 3		
Arrythmia	1 (15 y/o m)	27 days postdose 1		
Convulsion, drug use	1 (21 y/o f)	4 days postdose 3		
Suicide	**1** **20 y/o f**	**1177 days postdose 3**	2 17 y/o f 21 y/o f	 200 days postdose 3 517 days postdose 3
Asphyxiation post C-section (took meds, was in tub)			1 (18 y/o f)	256 days postdose 2
Medulloblastoma			**1 (11 y/o m)**	**Dx'd 165 days postdose 2; died 650 days postdose 2**
Post-op complications	**1 (43 y/o f)**	**595 days postdose 3**		
Pulmonary TB	**1 (34 y/o f)**	**Dx'd. 139 days postdose 2, died app. 240 days postdose 2**		
SLE (dx'd 671 days postdose 3)	**1 (39.y/o f)**	**Dx'd 671 days postdose 3, died app. 756 days postdose 3**		
Thyrotoxicosis (Hepatitis B)	**1 (32 y/o f)**	**203 postdose 3**		
Acute Lymphoblastic leukemia			**1 (34 y/o f)**	**Dx'd 595 days postdose 3; died app. 625 days postdose 3**
Total Percentage of subjects	15 (0.11%)		9 (0.08%)	

Source: Summary of Clinical Efficacy, Table 2.7.4:20, p. 56-61 (3/8/06)
STN 419.0, Summary of Safety, Table 2.7.4:6, p. 72; STN 125126/-(b)(4)-; STN 125126/773.0

Narratives are provided for the additional deaths below.

- **AN 30322 [COMPLETED SUICIDE]**, a 20 year old white female participating in study HPV-012 (substudy of study HPV-013), died from a completed suicide at Day 1177 after dose 3 Gardasil. This death was not considered to be related to vaccine administration.

Reviewer's Comment: Given the long interval between vaccination and event, it is highly unlikely that this event was related to Gardasil.

In the 24 Month safety follow-up report for study **HPV-018 (safety and immunogenicity study of boys and girls 9-15 years of age)**, submitted in 125126/ -(b)(4)-, there was the following death in the saline control group**:**

- **AN 71910 [MEDULLUBLASTOMA]:** an 11-year-old Hispanic male, died from Medulloblastoma 650 days after his second and final dose of saline placebo. The subject's mother refused the third dose due subject's obesity. The subject did, however, continue for follow-up. He had a history of sulfonamide allergy, headache, obesity, hypercholesterolemia, hypercorticoidism, hyperinsulinism, gastroesophageal reflux, and ventricular drainage (extra cranial ventricular shunt replacement). Approximately 165 days post Dose 2 the subject suffered from what was believed to be a "cerebral tumor with cervical spine metastasis," however this diagnosis was changed 290 days post Dose 2 to medulloblastoma. The investigator determined that the death was not related to the vaccine or any procedure performed within the study.

Additional deaths were reported for study HPV-019 in a separate supplement (125126/ -(b)(4)-). There were 5 subjects who died: 4 subjects in the Gardasil group and 1 subject in the alum control group. None of these deaths were considered to be vaccine related. (1910 subjects received Gardasil and 1907 subjects received alum control in study HPV-019). Narratives for these subjects are noted below.

Study HPV-019, additional deaths:
Gardasil Subjects:

- **AN 81322 [PULMONARY TB]**, a 34-year-old Asian female with history of anemia, was vaccinated with her first and second doses of Gardasil on 1/26/05 and 3/11/05, respectively. On approximately Day 139 (5/18/05) Postdose 2, the subject experienced pulmonary tuberculosis. The subject was prescribed anti-TB therapy. On --(b)(6)-, the subject was hospitalized with difficulty in breathing. She was discharged against medical advice after 2 weeks of hospitalization. The subject was allegedly not taking tuberculosis medication daily. On -(b)(6)-, the subject died of cardio-pulmonary arrest due to acute respiratory failure, secondary to active pulmonary tuberculosis. The investigator determined that the worsening pulmonary tuberculosis resulting in death was definitely not related to study therapy.

- **AN 81654 [THYROTOXICOSIS, HEPATITIS B],** a 32-year-old Asian female with a medical history of hepatitis B (diagnosed 2/06), ascites, bipedal edema, toxic nodular goiter, and hyperthyroidism (diagnosed in 5/05), was vaccinated with her first, second, and third doses of Gardasil on 2/18/05, 4/26/05, and 8/13/05, respectively. On approximately Day 203 3/3/06 Postdose 3, the subject experienced vomiting, dizziness, jaundice, ascites and grade 1 bipedal edema. The subject was prescribed to take methimazone (5mg 1 tab TID), propranolol (20mg 1 tab TID), spironolactone

(25mg 1 tab TID), and metoclopromide (10mg 1 tab TID before meals and prn). The subject was hospitalized on -(b)(6)-, following dyspnea with fainting episode after intake of propanolol. The symptoms were determined to be due to thyrotoxicosis/hyperthyroidism, the subject was discharged against medical advice, and died on -(b)(6)-, -(b)(6)- after discharge, with cardiorespiratory arrest due to cardiac failure secondary to thyrotoxicosis. The investigator determined that the vomiting, dizziness, cardio-respiratory arrest, cardiac failure, and thyrotoxicosis/hyperthyroidism were definitely not related to study therapy.

Reviewer's Comment: It is noted that the subject was diagnosed with hyperthyroidism in May 2005, which was < 1 month after dose 2 of vaccine, and had a toxic nodular goiter diagnosed the same time. She went onto receive her third dose of vaccine. She was also diagnosed with Hepatitis B app. 6 months after dose 3, which possibly was associated with ascites.

- **AN 84097 [SLE],** a 39-year-old Hispanic female, was vaccinated with her first, second, and third doses of Gardasil on 1/4/05, 3/7/05, and 6/14/05, respectively. On approximately Day 751 (7/4/07) Postdose 3, the subject experienced thoracic (precordia) pain and syncope. She was previously diagnosed with chronic hypertension, systemic lupus erythematosus (approximately Day 671 Postdose 3), vasculitis, nephrotic syndrome and acute myocardial infarction. The subject was hospitalized to rule out a coronary event and a possible pulmonary thromboembolism. Tests showed indirect signs of pulmonary hypertension, pericarditis, and ejection fraction of 50%. After 4 days of treatment, the subject suddenly developed a cardiac arrest, with no response to cardiopulmonary resuscitation after 40 minutes. She died on -(b)(6)-. The investigator determined that the pericarditis, systemic lupus erythematosus, and cardiac arrest were definitely not related to study therapy.

Reviewer's Comment: The patient was diagnosed with SLE app. 1.8 years after dose 3 of the vaccine. In the original licensure, there was no imbalance in the number of subjects with SLE, and the longer time interval between vaccination and the adverse event make it less likely that the event was related to study material. It is noted that in the younger age population, in a short term safety follow-up in a large managed care organization, autoimmune illnesses are being collected as part of a post-marketing commitment.

- **AN 84366 [POST-OP COMPLICATIONS, LEIOMYOMA]**, a 43-year-old Asian female, was vaccinated with her first, second, and third doses of Gardasil on 3/9/05, 5/17/05, and 9/10/05, respectively. The subject was hospitalized on -(b)(6)- with an admitting diagnosis of myoma uteri for a total abdominal hysterectomy with bilateral salpingo-oophorectomy. On approximately Day -(b)(6)- (-(b)(6)-) Postdose 3, 12 days after the operation the subject died due to acute respiratory failure probably secondary to massive pulmonary embolism. Other contributing factors to death were adenomyosis, endometriosis, myoma uteri, upper GI bleeding, and acute renal failure secondary to severe dehydration. The investigator determined that the acute respiratory failure, acute renal failure, myoma uteri, pelvic endometriosis, severe dehydration, upper gastrointestinal hemorrhage, pulmonary embolism, and adenomyosis were definitely not related to study therapy.

Reviewer Comment: This event appears to be related to a post-operative complication, and it appears unlikely that this was related to administration of the study material.

Alum control Recipients:

- **AN 81009, [Acute Lymphoblastic Leukemia]:** a 34-year-old Asian female, was vaccinated with her first, second, and third doses of alum control on 12/16/04, 3/8/05, and 6/11/05, respectively. On approximately Day -(b)(6)- (-(b)(6)-) Postdose 3, the subject was hospitalized with a diagnosis of acute lymphoblastic leukemia. Three months prior to admission, the subject presented to the hospital with pallor, easy fatigability, and a diagnosis of megaloblastic anemia, but against medical advice, went home after blood transfusion. One month prior to admission cervical lymphadenopathy was also noted. During the admission, the subject received blood transfusion, prednisone, and chemotherapy. On 4/14/07, peripheral blood smear and bone marrow aspirate were consistent with acute lymphoblastic leukemia. A treatment protocol was established but the subject died on -(b)(6)- with the immediate cause of death of acute respiratory failure due to pulmonary thromboembolism and hypercoagulable state secondary to acute lymphoblastic leukemia. Other significant conditions contributing to death were pneumonia, acute pharyngitis. The investigator determined that the acute lymphoblastic leukemia, pneumonia, acute respiratory failure, pulmonary thromboembolism, and acute pharyngitis were definitely not related to study therapy.

With these additional 5 deaths in the Gardasil group (which includes older women) and the 1 additional death in the control group, the total deaths increases to 15 in the Gardasil group and 9 in the control/placebo group in studies 005, 007, 013, 015, 018, and 019. None of the deaths were considered related to study medication or control. Adding the subjects who participated in study 019 in each treatment group (1910-Gardasil and 1907 –alum control), there were 15/13702=0.11% in the Gardasil group and 9/11595=0.08% in the control or placebo group.

Deaths in Ongoing studies (reported after cut-off dates)

- **Protocol 019:** AN 83962 died 858 days after last dose of Gardasil of cardiopulmonary arrest, cerebrovascular accident, and cerebrovascular disorder.
- **Protocol 020 (male efficacy study, blinded):** AN 74351 and AN 74843 died of gun shot wounds; AN 75296 died due to poisoning; AN 74084 died due to traumatic brain injury; AN 73615 died due to multiple drug intoxication; and AN 73330 died due to completed suicide. None of these deaths were considered to be related to study material. There were no deaths reported in other ongoing studies (Protocols 021, 024, 025, 027, 028, 029, and 032 as of 10/31/07).

Other Serious Adverse Experiences (Studies HPV-007, 013, 015, 016, 018, 019 and Extension Study HPV-007)

In the original application, in the General Safety population, 102 subjects who received Gardasil and 99 subjects who received Placebo developed an SAE during the course of the study. The original SAEs were presented in Table 298 of the original clinical review. Overall, the proportions of subjects who reported serious systemic clinical adverse experiences were comparable between the 2 vaccination groups. The most

frequent System Organ Classifications for the serious systemic clinical adverse experiences were Pregnancy, Puerperium, and Perinatal Conditions; Injury, Poisoning, and Procedural Complications; and Infections and Infestations, all of which had reported frequencies of <0.5%. A table with the overall proportions of subjects with SAEs by System Organ Class is provided. (See Table 44 below).

SAEs from study HPV-019 are also included at this time, since the information is included in the package insert. In study HPV-019, an additional 12 SAEs were reported in subjects who received Gardasil in study HPV-019, and an additional 15 subjects experienced an SAE in control recipients.

In studies 007 extension, 013, 015, 016, and 018, there were 107/11641 (0.9%) serious adverse events in the Gardasil group and 103/9578 (1.1%) serious adverse events in the control group.

In the age group from 9-26 years of age, including subjects who participated in extensions studies 007, 013, 015, 016, 018 and 019, there were 108/11922 (0.9%) Gardasil recipients with a reported serious adverse event, as compared to 105/9850 (1.1%) control recipients with a serious adverse event.
Reviewer's Comment: Adding the approximately 288 Gardasil recipients and 280 control subjects who were between the ages of 24-26 and participated in study HPV-019, there was little difference in total number of SAEs as compared to calculations which exclude these subjects. The proportion of subjects with a serious adverse event which occurred during the studies overall were comparable in proportions. See Table 45.

In subjects 27-45 years of age, there were 10/1608 (0.6%) Gardasil recipients with a serious adverse event, and 13/1614 control recipients (0.8%) control subjects with a serious adverse event. See Table 46.

TABLE 44
Summary of Serious Adverse Events by System Organ System Class
(Studies HPV-007, -013, -015, -016, and -018) (2/22/08)

SOC	Gardasil N=11778	Control N=9686
Subjects with follow-up	11641	9578
Subjects with one or more systemic SAE	107 (0.9%)	103 (1.1%)
Blood and Lymphatic System disorders	3 (0.03%)	0 (0.0%)
Cardiac Disorders	3 (0.03%)	1 (0.01%)
Gastrointestinal disorders	4 (0.03%)	2 (0.02%)
General disorders and administration site disorders	0 (0.0%)	2 (0.02%)
Hepatobiliary disorders	2 (0.02%)	0 (0.0%)
Immune system disorders	0 (0.0%)	2 (0.02%)
Infections and infestations	22 (0.2%)	14 (0.1%)
Injury, poisoning and procedural complications	26 (0.2%)	32 (0.3%)
Metabolism and Nutrition disorders	2 (0.02%)	0 (0.0%)
Musculoskeletal and Connective Tissue disorders	1 (0.01%)	2 (0.0%)
Neoplasms benign, malignant including cysts	1 (0.0%)	1 (0.01%)
Nervous system disorders	5 (0.04%)	5 (0.05%)
Pregnancy, puerperium, and perinatal conditions	34 (0.3%)	38 (0.4%)
Psychiatric disorders	3 (0.03%)	2 90.02%)
Renal and urinary disorders	2 (0.02%)	2 (0.02%)
Reproductive system and breast disorders	4 (0.03%)	4 (0.04%)
Respiratory, thoracic, and mediastinal disorders	5 (0.04%)	4 (0.04%)
Skin and subcutaneous disorders	1 (0.01%)	1 (0.01%)
Vascular disorders	4 (0.04%)	2 (0.02%)

Source: STN 125126/-(b)(4)-, Safety Update, p. 90-101;
Percentages are calculated based on the number of subjects with follow-up.
Although a subject may have had two or more systemic adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

TABLE 45
Summary of Serious Adverse Events by System Organ System Class Ages 9-26
(Studies HPV-007, -013, -015, -016, -018, -019) (12/2/07)

SOC	Gardasil N=12064	Control N=9961
Subjects with follow-up	11922	9850
Subjects with one or more systemic SAE	108 (0.9%)	105 (1.1%)
Blood and Lymphatic System disorders	3 (0.03%)	0 (0%)
Cardiac Disorders	3 (0.03%)	1 (0.01%)
Gastrointestinal disorders	4 (0.03%)	2 (0.02%)
General disorders and administration site disorders	0 (0.0%)	2 (0.02%)
Hepatobiliary disorders	2 (0.02%)	0 (0.0%)
Immune system disorders	0 (0.0%)	2 (0.02%)
Infections and infestations	22 (0.2%)	15 (0.16%)
Injury, poisoning and procedural complications	26 (0.3%)	32 (0.33%)
Metabolism and Nutrition disorders	2 (0.02%)	0 (0.0%)
Musculoskeletal and Connective Tissue disorders	1 (0.01%)	2 (0.02%)
Neoplasms benign, malignant including cysts	1 (0.01%)	1 (0.01%)
Nervous system disorders	6 (0.04%)	5 (0.05%)
Pregnancy, puerperium, and perinatal conditions	34 (0.3%)	39 (0.40%)
Psychiatric disorders	3 (0.03%)	2 (0.02%
Renal and urinary disorders	2 (0.02%)	2 (0.02%)
Reproductive system and breast disorders	4 (0.03%)	5 (0.05%)
Respiratory, thoracic, and mediastinal disorders	5 (0.04%)	3 (0.03%)
Skin and subcutaneous disorders	1 (0.01%)	1 (0.01%)
Vascular disorders	5 (0.04%)	2 (0.02%)

Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Appendix 2.7.4:84 and 85, p. 446-455; 456-465

Percentages are calculated based on the number of subjects with follow-up.

Although a subject may have had two or more systemic adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

TABLE 46
Summary of Serious Adverse Events by System Organ System Class Ages 27-45 Years (Study HPV-019) (12/2/07)

SOC	Gardasil N=1622	Control N=1627
Subjects with follow-up	1608	1614
Subjects with one or more systemic SAE	10 (0.6%)	13 (0.8%)
Blood and Lymphatic System disorders	0 (0.0%)	1 (0.1%)
Cardiac Disorders	2 (0.1%)	0 (0.0%)
Ear and labyrinth disorders	1 (0.06%)	0 (0.0%)
Endocrine disorders	1 (0.06%)	0 (0.0%)
Gastrointestinal disorders	2 (0.1%)	0 (0.0%)
General disorders and administration site disorders	0 (0.0%)	0 (0.0%)
Hepatobiliary disorders	0 (0.0%)	0 (0.0%)
Immune system disorders	0 (0.0%)	0 (0.0%)
Infections and infestations	3 (0.2%)	7 (0.4%)
Injury, poisoning and procedural complications	0 (0.0%)	0 (0.0%)
Metabolism and Nutrition disorders	1 (0.01%)	0 (0.0%)
Musculoskeletal and Connective Tissue disorders	1 (0.01%)	0 (0.0%)
Neoplasms benign, malignant including cysts	1 (0.01%)	2 (0.1%)
Nervous system disorders	1 (0.01%)	0 (0.0%)
Pregnancy, puerperium, and perinatal conditions	3 (0.19%)	3 (0.2%)
Psychiatric disorders	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	1 (0.01%)	0 (0.0%)
Reproductive system and breast disorders	1 (0.01%)	2 (0.1%)
Respiratory, thoracic, and mediastinal disorders	1 (0.01%)	1 (0.1%)
Skin and subcutaneous disorders	0 (0.0%)	0 (0.0%)
Vascular disorders	0 (0.0%)	1 (0.1%)

Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Appendix 2.7.4:84 and 85, p. 446-455; 456-465

Percentages are calculated based on the number of subjects with follow-up.
Although a subject may have had two or more systemic adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Subjects in studies HPV-007, -013, -015, -016, and -018 who reported a serious adverse event since the time of the original licensure are noted in Tables 47 (Gardasil recipients) and 48 (control recipients). Please refer to original clinical review for SAEs reported at the time of original licensure. As noted, the majority of the additional SAEs occurred at a longer time after vaccination with two exceptions (AN 33757 and AN 8415 in the Gardasil group).

TABLE 47
Additional Serious Adverse Events Occurring in Gardasil recipients
Safety Population, Studies HPV-007, -013, -015, -016, and -018
(Final Close-Out Data) + HPV-007 Extension study

AN/Study (age)	Event/intensity	Time/Duration	Investigator attribution	Recovered	Action
31784/012 19 yo f	Postprocedural hemorrhage, severe	988 days postdose 3 x 5 days	Definitely related to study procedure	Y	None
32267/012 21 yo f	Postoperative infection/moderate	785 days postdose 3 x 4 days	Definitely not related	Y	None
30322/012 20 yo f	Completed suicide /severe (included in deaths)	1177 days postdose 3x1 day	Definitely not related	N-Fatal	D/C follow-up
31812/012 19 yo f	Premature labor/severe	1345 days postdose 3 x 1 day	Definitely not related	Y	None
33757/012 17 yo f	Gastroenteritis and dehydration/moderate	8 days postdose 1x5 days	Probably not, definitely not	Y	None
55895/015 17yo f	Sepsis/moderate	1226 days postdose 3 x 12 day	Definitely not related	Y	None
70834/018 12 yo f	Ulcerative Colitis/severe	389 days postdose 3	Possibly related	N-CONT.	None
8415/007 18 yo f	Drug toxicity [acetaminophen]/severe	6 days postdose 4 x 20 hrs.	Definitely not related	Y	None

Source: STN 125126/419.0, Tables 2.7.4:7 and 8, Summary of Clinical Safety, p. 38-79 and STN 125126/-(b)(4)-, 2/22/08, Safety Update Information, p. 102-142

Additional SAEs in Gardasil Recipients (Reported in close-out data)

- **AN 31784 (012) [BLEEDING POST-PROCEDURE]:** 19-year-old white female received 3 doses of Gardasil on 11/26/02, 1/30/03, and 7/3/03. On 3/8/06, the subject underwent a cone-biopsy (definitive therapy) to remove a CIN-2 lesion as part of the study protocol. On --(b)(6)-, the subject was hospitalized for operative revision due the bleeding that occurred subsequent to the cone-biopsy. The post-procedural hemorrhaging episode was severe in intensity and the subject recovered. The investigator determined that the post-procedural hemorrhaging was related to the cone-biopsy procedure performed as part of the study protocol and was definitely not related to Gardasil.

Reviewer's Comment: The biopsy taken on 3/8/06 was located in the study dataset (labbx.xpt). The material was read as reactive by the Pathology Panel, and the highest grade CIN was CIN 1, although the ----(b)(4)---- (not considered the pathology panel diagnosis) was read as CIN 2. The diagnosis by the -----(b)(4)----- was the diagnosis which directed management, but the diagnosis by the expert Pathology Panel was considered the diagnosis of the study.

- **AN 32267 (012) [BLEEDING POST-PROCEDURE]:** 21-year-old white female received 3 doses of Gardasil on 1/9/02, 3/13/03, and 7/24/03. On -(b)(6)-, the subject underwent a Loop Electrosurgical Excision Procedure (LEEP) to remove a CIN-2

lesion as part of the study protocol. Subsequently, the subject developed a fever and vaginal infection and was hospitalized. After treatment with oral antibiotics, the subject recovered from the postoperative infection and was discharged from the hospital on -(b)(6)-. The postoperative infection was moderate in intensity and the subject recovered. The investigator determined that the postoperative infection was related to the LEEP procedure performed as part of the study protocol and was definitely not related to study material.

Reviewer's Comment: The biopsy was read as CIN 2 by the MRL Pathology Panel. This subject was noted to be seronegative and PCR negative for HPV PCR at Day 1, but HPV 52 was detected at vaccination 2 (2 months after dose 1). HPV 31 and 52 were detected at postvaccination 3 visit and Month 12. At Month 18, HPV 52 and 58 were detected; at month 24, HPV 52, 58, and 59 were detected; at Month 30, HPV 45, 52, and 58 were detected; at Month 36, HPV 45 and 58 were detected; and at Month 48, HPV 31, 45, and 58 were detected. There were 3 samples read as CIN 2 in the samples taken at month 30: in two of the samples, no HPV was detected, and in one sample, HPV 52 and 58 were detected. This subject developed a CIN 2 lesion related, in part, to a non-vaccine HPV type (HPV 52) acquired at Month 3 (during the vaccination period), but also due to a non-vaccine HPV type (HPV 58) which was first detected at Month 18. As noted in the efficacy overview, there was no apparent prevention of non-vaccine HPV type related CIN 2/3 demonstrated during the clinical trials.

- **AN 31812 (012) [PREMATURITY AND DEATH OF INFANT]:** 19 year old female who received Gardasil on 11/27/02, 1/29/03, and 5/19/03. Subsequently, she became pregnant and delivered a premature female infant on -(b)(6)- (24 gestational weeks). On Day -(b)(6)- (-(b)(6)-) Post Dose 3, the infant died. The autopsy report determined the cause of death as prematurity. There was no congenital abnormality. The investigator determined that the premature delivery and premature baby was definitely not related to the study material. (Information from CSR 013-10, final report, submitted 2/6/08, 125126/-(b)(4)-).

Reviewer's Comment: The interval between vaccination and event was several years, which makes relation to vaccine less likely. The overall rates of premature delivery were comparable in the two treatment groups.

- **AN 33757 (012) [GASTROENTERITIS AND DEHYDRATION]:** 17-year-old female who was vaccinated with her first dose of Gardasil on 3/14/03. On -(b)(6)-, Day 8 Post Dose 1, the subject was admitted to the hospital for gastroenteritis and dehydration of moderate intensity. The subject received ciimetidine for gastritis, acetaminophen with codeine for pain, and promethazine for nausea. The subject subsequently recovered from the gastroenteritis and was discharged from the hospital on -(b)(6)-. The subject continued in the study and received Dose 2 and Dose 3 on 6/2/03 and 8/18/03 without reported adverse events. The investigator determined that the gastroenteritis was probably not related to study vaccine/placebo. It was not previously reported but the investigator determined that the dehydration was definitely not related to study vaccine

Reviewer's Comment: The event occurred in a relatively short time period after vaccination, although the subject recovered and went onto receive 2 additional doses of Gardasil without reported adverse events.

- **AN 55895 (015) [PREMATURE RUPTURE OF MEMBRAMES]:** 17-year-old White female, was vaccinated with Gardasil on 2/25/03, 4/25/03, and 8/21/03. On approximately Day -(b)(6)- (-(b)(6)-) Postdose 3, the subject delivered a premature baby (34 weeks gestational age) due to early rupture of SAC and was treated for sepsis with ampicillin 13 hours before delivery and then for 10 days. The investigator determined that the sepsis was definitely not related to the study material.

Reviewer's Comment: This event occurred several years after receipt of study material, and premature rupture of membranes is reported to occur in the general population.

- **AN 70834 (018) [ULCERATIVE COLITIS]:** 13-year-old White female received Gardasil on 2/24/04, 4/20/04, and 8/26/04. On -(b)(6)-, the subject was hospitalized for severe ulcerative colitis at -(b)(6)- days after receiving Dose 3. She had a history of asthma (1998) and eczema (1997). She was hospitalized for 12 days and was treated with prednisolone. The subject was discharged from the hospital although her ulcerative colitis persisted. The reporting investigator determined that the ulcerative colitis was possibly related to the study therapy. The subject continued in the study. (Information from WAES report and CSR 018 Month 24, reference 2050 in STN 125126/419.0).

Reviewer's Comment: Adverse events of potentially autoimmune nature are discussed as a group later in this review. There was no imbalance in proportion of subjects diagnosed with new inflammatory bowel disease in the treatment groups.

- **AN 8415 (Extension 007) [DRUG INTOXICATION]:** 23 year old white female received dose 4 of Gardasil on 12/8/05. On -(b)(6)-, the subject experienced leg pain and took 10 tables acetaminophen (7.5g) for the pain. On -(b)(6)-, the subject was hospitalized for nausea, tachycardia, and dizziness due to drug intoxication. She was treated with IV meds, and discharged the same day. She recovered, and the event was assessed by the investigator as not related to study material.

Reviewer's Comment: It is not clear as to the etiology of the leg pain which occurred after vaccination, although there were no reports of other serious adverse events for this subject.

TABLE 48
Additional Serious Adverse Events Occurring in Control recipients
Safety Population, Studies HPV-007, -013, -015, -016, and -018
(Final Close-Out Data) + HPV-007 Extension study

AN/Study (age)	Event/intensity	Time/Duration	Investigator attribution	Recovered	Action
24211/011 16 yo f	Overdose/mild	542 days postdose 3 (both placebos) x 1 day	Definitely not related	Y	None
20343/011	Overdose/mild	543 days postdose 3 (both placebos) x 1 day	Definitely not related	Y	None
30361/012 22 yo f	Postprocedural hemorrhage/severe	1059 days postdose 3 x 18 days	Definitely not related	Y	None
48447/015 23 yo f	Abortion threatened	84 days postdose 3 x 3 days	Probably not related	Y	None
56743/015 20 yo f	Postprocedural hemorrhage/severe	1180 days postdose 3 x 2 days	Definitely not related	Y	None
49394/015 18yo f	Cervical incompetence, premature labor/moderate	1053 days postdose 3 (CONT; x 1 day)	Probably not related	N, Y	None
9043/007 27 yo f	Cervix hemorrhage/moderate [THIS OCCURRED @ M 58]	1589 days postdose 3 x 7 days and 1599 days postdose 3 x 12 days	Definitely not to study material; related to study procedure	Y	None

Source: STN 125126/419.0, Tables 2.7.4:7 and 8, Summary of Clinical Safety, p. 38-79; and STN 125126/-(b)(4)-, 2/22/08, Safety Update Information, p. 102-142

SAEs in Alum Control or Saline Placebo Recipients

- **AN 24211 (011) [OVERDOSE]:** 16-year-old white female received 3 doses of both Gardasil and Hepatitis B placebos on 11/27/02, 1/20/03, and 5/13/03. As part of the rolling unblinding protocol-defined process, the subject elected to receive active hepatitis B vaccine on 5/5/04, 6/2/04, and 11/8/04. Per the clinical protocol, subjects <20 years of age were to receive a 0.5-mL dose of hepatitis B placebo Subjects ≥20 years of age were to receive 1.0 mL of hepatitis B placebo. The subject was age 18 years of age for all 3 doses. For Dose 3, 11/8/04 the subject received 1.0 mL of active hepatitis B vaccine. The event was considered an overdose of mild intensity and was reported as a serious clinical adverse experience. The investigator determined that the overdose was definitely not related to study material.

- **AN 20343 (011) [OVERDOSE]:** 18-year-old white female received 3 doses of both Gardasil and Hepatitis B placebos on 9/19/02, 11/23/02, and 3/7/03. As part of the rolling unblinding protocol-defined process, the subject elected to receive her first, second, and third doses of active hepatitis B vaccine on 3/1/04, 4/1/04, and 8/30/04. Per the clinical protocol, subjects <20 years of age were to receive a 0.5-mL dose of hepatitis B placebo. Subjects ≥ 20 years of age were to receive 1.0 mL of hepatitis B placebo. The dose was to remain consistent for all 3 vaccinations, based on the age of the subject at first vaccination. The subject was age 19 years of age for Doses 1 and 2. The subject was 20 years of age for Dose 3 and received 1.0 mL of active hepatitis B vaccine. The event was considered an overdose of mild intensity and was reported as a

serious clinical adverse experience. The investigator determined that the overdose was definitely not related to study material.

- **AN 24058 (011) [POST-PROCEDURAL BLEEDING]:** 18-year-old White female received 3 doses of Gardasil Placebo and 3 doses of Hepatitis B vaccine on 10/16/02, 1/6/03, and 4/29/03. On --(b)(6)--, following cervical definitive therapy with a Loop Electrosurgical Excision Procedure (LEEP) for a CIN 2 cervical biopsy result as part of the study protocol. During the procedure, the subject experienced cervical bleeding of moderate intensity and was hospitalized the same day for haemostatic suturing and follow-up blood tests. The subject was observed for 24 hours and released. On -(b)(6)-, she was seen in the emergency room due to cervical bleeding and relieved with vaginal tamponade. The subject underwent follow-up care for a cervical hemorrhage of moderate intensity that was resolved. The investigator felt that the post-procedural hemorrhaging and subsequent cervical hemorrhaging were related to the study procedure but were definitely not related to study material.

Reviewer's Comment: In review of the labbx.xpt dataset, the pathology diagnosis was reactive as per the pathology panel, although the highest grade lesion detected by -----(b)(4)----- was CIN 2.

- **AN 30361 (012) [POST-PROCEDURAL BLEEDING]:** 22-year-old Asian female received 3 doses of placebo on 8/20/02, 10/28/02, and 2/20/03. On 1/5/06, the subject underwent a second Loop Electrosurgical Excision Procedure (LEEP) to remove a CIN-2 lesion as part of the study protocol. On -(b)(6)-, the subject was seen for menorrhagia and was hospitalized overnight for observation and discharged the next day on Metronidazole and Cephalexin. On 1/19/06, the subject underwent electrocauterization with Monsel solution application to the cervix for persistent bleeding. The subject recovered, with the vaginal bleeding ceasing on 1/22/06. The investigator determined that the post-procedural hemorrhaging was related to the LEEP procedure performed as part of the study protocol and was definitely not related to study material.

Reviewer's Comment: This subject was seropositive for HPV 11 at baseline, and Pap test negative. HPV 52 was detected at baseline, and persisted throughout the study. In addition, HPV 51 was first detected at Month 30, and HPV 18, 51, 52, and 59 were detected at Month 36. At the Month 30, CIN 3 in which HPV 52 was detected was noted on biopsy (3.25/05). At the Month 36 visits, CIN 2/3 was detected in which HPV 18, 51 and 52 were detected (9/12/05) and at time of 1/5/06, no HPV DNA by PCR was detected on 1/5/06.

- **AN 56743 (015) [POST-PROCEDURAL BLEEDING]:** 20-year-old white female received alum control on 3/10/03, 5/13/03, and 9/30/03. On approximately Day -(b)(6)- (-(b)(6)-) Postdose 3, the subject experienced postoperative bleeding and was hospitalized. This was following a cervical conization that was performed on 12/8/06 for CIN 2. The subject experienced moderate bleeding that continued for approximately 12 hours. Following admission to the hospital, the subject underwent an operation and received three stitches, cauterization and blood transfusions. The

subject was discharged on --(b)(6)--. The investigator determined the postoperative bleeding was definitely not related to the study material.

Reviewer's Comment: The CIN 2 lesion was read as such by ----(b)(4)----, and read by the MRL Pathology Panel as CIN 1 or negative. HPV 31 and 51 were identified in the lesions biopsied (Month 48 follow-up).

- **AN 49394 (015) [PREMATURE LABOR]:** 18-year-old white female received alum control on 2/12/03, 4/3/03, and 9/10/03. On approximately Day -(b)(6)- (-(b)(6)-) Postdose 3, the subject experienced premature labor due to cervical incompetence. The cervical conization performed on 2/24/04 due to CIN 3 and was considered is a probable cause of the premature delivery. The premature infant SAE was listed separately under the infant SAEs. The investigator determined that the premature labor and cervical incompetence was probably not related to the study material.

Reviewer's Comment: This subject was infected with HPV 16 at Day 1, and the CIN 3 (associated with HPV 16) lesion was diagnosed (by MRL Pathology Panel) by the time of Postvaccination 3 visit.

- **AN 9043 (007) [POST-PROCEDURAL BLEEDING]:** 27 year old female received 3 doses of alum control (450 mcg), last dose 5/31/01. She continued in the extension study, and app. at Month 58, she experienced moderate cervix bleeding post LEEP procedure, and required two hospitalizations to control the bleeding. She recovered and continued in the study. This subject was seronegative for vaccine HPV types at baseline, and her Pap at baseline was negative. All PCR samples were negative for vaccine HPV at baseline and in samples. It is still plausible that this lesion involved a non-vaccine HPV type (which was not tested in study HPV-007).

Because all SAEs were included in the updated PI, SAEs from study HPV-019 are noted. There were 12 subjects with one or more SAEs who received Gardasil (total 24 events), and there were 24 SAEs in 14 subjects who received alum control. . One of the Gardasil subjects experienced an SAE (angioedema) after a dose of alum control which she received in error*.

TABLE 49
Serious Adverse Events Occurring in Gardasil Recipients in Mid-Adult Women (Study HPV-019, CBER generated)

AN (age)	Event	Time	Investigator attribution	Recovered	Action
80058 (28)	Fetal distress syndrome	346 days after dose 2 x 20 hours	Definitely not	Y	None
81228(31)	Rhinitis	7 days after dose 1 x 22 days	Definitely not	Y	None
83827 (37)	Antepartum hemorrhage	59 days after dose 1 x 8 days	Definitely not	Y	None
83917 (45)	Vertigo	9 days after dose 3 x 5.95months	Probably not	Y	None
80619 (27)	Ruptured ectopic pregnancy	87 days after dose 2x 6 days	Definitely not	Y	None
80776 (25)	Tension headache	4 days after dose 2 x 6 days	Definitely not	Y	None
80560 (27)*	Angioedema	Day 1 of dose 1 x 4 days	Probably not	Y	None
81322(34)	Pulmonary TB	139 days after dose 2 x 1.35 months	Definitely not	N [FATAL]	Vax D/C'd
81654 (32)	Dizziness Hyperthyroid Vomiting Cardiac failure Cardiopulmonary arrest	203 days after dose 3 203 days after dose 3 203 days after dose 3 205 days after dose 3 205 days after dose 3	Definitely not	N [FATAL]	-
84366 (43)	Adenomyosis Dehydration Endometriosis Renal failure UGI hemorrghage Uterine leiomyonma Acute respiratory failure PE	583 days after dose 3 583 days after dose 3 583 days after dose 3 599 days after dose 3 583 days after dose 3 583 days after dose 3 599 days after dose 3 599 days after dose 3	Definitely not	N[FATAL]	-
81411(28)	PID	335 days after dose 3 x 1.05 months	Definitely not	Y	None
84097(39)	SLE Pericarditis	671 days after dose 3 x 2.83 months 751 days after dose 3 x 6 days	Definitely not Definitely not	N [FATAL]	-

*Subject AN 80560 received alum control/alum control/Gardasil and experienced the angioedema after the first dose of alum control.
Source: STN 125126/-(b)(4)-, AE dataset and Table 12-19, p. 469-475

TABLE 50
Serious Adverse Events Occurring in Alum Control Recipients in Mid-Adult Women (Study HPV-019, CBER generated)

AN (age)	Event	Time	Investigator attribution	Recovered	Action
80212(25)	Fallopian tube cyst Premature labor Premature labor Premature labor	61 days after dose 2 201 days after dose 2 238 days after dose 2 239 days after dose 2	Definitely not	Y	None
80670(27)	Gastroenteritis	6 days after dose 3 x 2 days	Definitely not	Y	None
81154(32)	Peritoneal TB' GI TB	12 days after dose 2, CONT.	Definitely not	N	None
81687 (33)	False labor	237 days after dose 2	Definitely not	Y	None
84336(37)	PID	291 days after dose 3 x 4 days	Probably not	Y	None
80765(25)	PID	281 days after dose 3 x 5 days	Definitely not	Y	None
84818(36)	Dysfunctional uterine bleeding Anemia	44 days after dose 2 x 3.02Months 1 days after dose 3 x 9 days	Definitely not Definitely not	Y	None
80797(34)	Pyelonephritis	4 days after dose 2 x 17 days	Probably not	Y	None
82043(27)	Blighted ovum Gestational trophoblastic tumor	101 days after dose 1 101 days after dose 1	Definitely not	Y	None
80537(32)	Hypertensive crisis	259 days after dose 1	Definitely not	Y	None
80741(34)	Uterine hemorrhage	54 days after dose 2 x 7.39 months	Definitely not	Y	None
84929(43)	Hepatitis A	6 days after dose 1 x 2 days	Definitely not	Y	None
80693(31)	Pyelonephritis acute	10 days after dose 1 x 14 days	Definitely not	Y	None
81009(34)	ALL Pneumonia Acute respiratory failure Pharyngitis PE	599 days after dose 3 674 days after dose 3 678 days after dose 3 678 days after dose 3 678 days after dose 3	Definitely not	N [FATAL]	-

Source: STN 125126/-(b)(4)- , AE dataset and Table 12-19, p. 469-475

There were no new serious injection-site adverse experiences have been reported since the time of the original licensure.

Other Serious Adverse Experiences in Ongoing Studies

- **AN 60283 (016) [CIN 2]:** One SAE of interest was a 17 year old subject who participated in study HPV-016, and who received 3 doses of the 20% Gardasil formulation at age 12 during the study. She was seronegative for all 4 vaccine HPV types, and was noted to have immune responses to all 4 HPV types which were below the levels noted in the PPI population. At Month 7, anti-HPV 6 =186; anti-HPV 11=139; anti-HPV-16=192; and anti-HPV 18 = 186. In that study, the 20% formulation was found to be non-inferior as to immune response elicited by the 100% formulation in the PPI. This subject's response is noted to be above serostatus cut-off, but lower than the anti-HPV 6 (553.1 mMU/mL), anti-HPV 11 (596.6 mMU/mL); anti-HPV 16 (2258.9 mMU/mL); and anti-HPV 18 (518.7 mMU/mL) in other subjects who received the 20% formulation and were included in the PPI. The estimated fold difference to assess NI was < 2-fold, and all LBs of the 95% CI were ≥ 0.5). At age 17, she required a colposcopy and was noted to have developed CIN II. This procedure was not part of the study (since the study had ended in 2004). We do not know if this lesion was related to a vaccine HPV type or to a non-vaccine HPV type.

Reviewer's Comment: Gardasil has not been demonstrated to prevent CIN 2/3 related to non-vaccine types. Information was not available as to the HPV type involved in this

subject's CIN II lesion, and the procedure occurred after completion of the study. From the close-out data, the efficacy in prevention of any HPV related CIN 2/3 was app. 42% in a subgroup who was naïve for all vaccine and non-vaccine HPV types at baseline, with a negative Pap test at baseline. Further, this subject's immune responses to the vaccine HPV types were lower than those seen in the Per Protocol for Immunogenicity population who received the 20% formulation, and is not known as to the HPV type associated with the lesion, . HPV typing is not ordinarily available in tissue in subjects outside clinical studies. Additional information was requested to see if HPV typing was able to be obtained on tissue. At the time of this clinical review, this information was pending.

- **AN 70721 (018) [PERIPHERAL NEUROPATHY]**: Subject received saline placebo and developed peripheral neuropathy. The investigator assessed the event as possibly related to study material.

----------(b)(4)----------

- **----------(b)(4), (b)(6)----------**
- **----------(b)(4), (b)(6)----------**
- **----------(b)(4), (b)(6)----------**
- **----------(b)(4), (b)(6)--- ----------**

----------(b)(4)----------

----------(b)(4)----------

- **----------(b)(4), (b)(6)----------**

----------(b)(4)----------

Subjects who discontinued from study due to AE (Studies 007, 013, 015, 016, 018, and 019)

In comparison to the Safety Update Report Data available at the time of original licensure, there was 1 additional subject who discontinued due to an AE at any time during the studies in subjects in the Safety Population. This was subjects AN 30322 (study 012) who died due to a completed suicide at Day 1177 after dose 3. This SAE was discussed within the deaths.

There was additional information on subject AN 42548 (015) who developed carpal tunnel syndrome at day 21 postdose 1 and who had been reported to have discontinued due to an AE. The duration of the carpal tunnel syndrome was 11.79 months, and the subject recovered.

In studies 007, 013, 015, 016, and 018, 42 subjects discontinued due to an adverse event. Of those who discontinued, 24 (0.2%) received Gardasil and 18 (0.2%) received control or saline placebo; and no subjects discontinued due to an AE in the HPV-007 extension study.

When subjects from study HPV-019 are included, a total of 51 subjects discontinued due to an adverse event (9 additional subjects, with 7 in the Gardasil group and 2 in the alum control group). These subjects are included in Table 51 below. (Four of these subjects, 2 in each treatment group) were 26 years of age.

TABLE 51

Study HPV-019: Gardasil Recipients who Discontinued from Study Due to Adverse Event

AN (age)	Event/grade	Time	Investigator attribution	Recovered
80004 (26 yo f)	Hypersensitivity/moderate (NS)	Day 1 of dose 1 x 4 hours	Probably related	Y
80293 (30 yo f)	Pharyngeal edema, Urticaria/Mild (NS)	Day 4 after dose 1 x 1, 2 days	Possible related	Y
80490 (31 yo f)	Mouth ulceration/severe (NS)	Day 14 after dose 1 x 13 days	Possibly related	Y
80446 (26 yo f)	Injection site pain and swelling/moderate (NS)	Day 1 of Dose 1 x 5 days, 10 hrs	Definitely related	Y
83364 (44 yo f)	Lip edema/mild (NS)	Day 7 after dose 2 x 2 days	Probably related	Y
81322 (34 yo f)	Pulmonary TB/severe (S)	Day 139 after dose 2 x 1.35 mos	Definitely not	FATAL
81654 (32 yo f)	Hyperthyroidism/severe (S)	Day 203 after dose 3 x 3 days	Definitely not	FATAL

Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Table 2.7.4:14, p. 76-88

TABLE 52

Study HPV-019: Control Recipients who Discontinued from Study Due to Adverse Event

AN (age)	Event/grade	Time	Investigator attribution	Recovered
80029 (26 yo f)	Dizziness/moderate (NS) Fatigue/severe (NS)	Day 1 of Dose 1 x 2 days Day 1 of Dose 1 x 4 days	Both Possibly related	Y
80305 (26 yo f)	Overdose/mild (NS)	Day 716 after dose 3 x 1 min.	Possibly related	Y

Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Table 2.7.4:14, p. 76-88

Pregnancy Outcomes in Clinical Studies of Gardasil

A cumulative pregnancy outcome summary for Protocols 013, 015, 016, 018, and 019 was presented in STN 125126/-(b)(4)-. This information is reported in this review because it represents the most inclusive review of pregnancy outcomes available for all study results available to date. Although Gardasil is not recommended for use in women who are pregnant, it is important to provide an extensive report of the pregnancy and pregnancy outcome data because the vaccine is indicated for women up to age 26 years of age who may become pregnant during the course of the vaccine series. Thus, the following 20 pages (99-119) provide a detailed summary of all data on pregnancy and pregnancy outcomes that were available for review. There are no new safety concerns regarding pregnancy or pregnancy outcomes upon review of the updated data. The recommendation against the use of Gardasil in women who are pregnant will be maintained in product labeling because the clinical development program excluded pregnant women at baseline and did not offer vaccine to women who became pregnant during study participation.

A total of 3620 subjects (15.5 % of the study population) reported at least 1 pregnancy, with a total of 4206 pregnancies reported. Pregnancy outcomes were compared between vaccination groups. Overall, the number of subjects with pregnancies (1796 subjects in the group that received Gardasil and 1824 in the alum control group), the number of pregnancies (2085 in the group that received Gardasil and 2121 in the alum control group), and the number of pregnancies with a known outcome (2008 in the group that received Gardasil and 2029 in the alum control group) were comparable between the vaccination groups.

In both vaccination groups, the proportion of infants with a normal outcome was lower among proximate pregnancies (82.3% in the group that received Gardasil group and 88.1% in the alum control group) than among non-proximate pregnancies (94.3% in the group that received Gardasil and 95.5% in the alum control group).

The overall proportions of pregnancies that resulted in a negative outcome (includes numbers of spontaneous abortion, late fetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known, and excluding elective terminations), were 23.3% (423/1812) in the Gardasil group and 24.1% (438/1820) in the alum control group. The proportion of pregnancies resulting in fetal loss was also comparable among subjects who received Gardasil compared with subjects who received alum control (27.8% vs 29.7% respectively). See Table 53 for summary of all pregnancies.

TABLE 53
Pregnancy Outcome Summary (Entire Study Period) Female Subjects in the Safety Population (Studies HPV-013, -015, -016, -018 and -019)

	Gardasil N=12326	Control N=11022
Subjects with pregnancies	1796 (14.6%)	1824 (16.5%)
Number of pregnancies	2085	2121
Number of pregnancies with known outcome	2008	2029
Live Births*	1447 (72.1%)	1424 (70.2%)
Infant Outcomes (Based on Live Births)**		
Normal	1355 (93.6%)	1354 (95.1%)
Abnormal	88 (6.1%)	66 (4.6%)
Congenital anomaly	31 (2.1%)	20 (1.4%)
Other abnormality	4 (0.3%)	4 (0.3%)
Fetal Loss*	559 (27.8%)	602 (29.7%)
Type of Loss***		
Spontaneous abortion	366 (65.5%) [18.2%]****	395 (65.6%) [19.5%]****
Late Fetal Death	17 (3.0%) [0.85%]****	15 (2.5%) [0.74%]****
Elective abortion	175 (31.3%) [8.7%]****	191 (31.7%) [9.4%]****
Ectopic pregnancy	2 (0.1%)	3 (0.1%)

*Percentages calculated based on number of pregnancies with known outcomes.
**Percentages of infant outcomes based on number of live births.
***Percentages of types of loss based on total number of fetal losses.
[]****Percentage based on number of pregnancies with known outcome
Source: STN 125126/-(b)(4)-, Ref 2158, Table 4, p. 25-27, Update on congenital anomalies

Proximate pregnancies (Estimated Date of Conception within 30 days of vaccination):

- The proportion of pregnancies that resulted in a live birth was slightly higher among subjects in the Gardasil group (62.7%) compared with the alum control group (60.9%).
- Among the live births, the majority of infant outcomes were normal; the proportion of infants with a normal outcome was somewhat lower among subjects who received Gardasil (82.3%) compared with subjects who received alum control (88.1%). 5 cases of congenital anomaly were detected in the Gardasil group and 1 was detected in the alum control group.
- The proportions of **proximate pregnancies** that resulted in a negative outcome (the combined numbers of spontaneous abortion, late fetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known and excluding elective terminations), were 29.1% (30/103) in the Gardasil group and 26.8% (30/112) in the alum control group.
- **Fetal Losses**:
  - A slightly smaller proportion of fetal losses were due to spontaneous abortions among pregnancies with known outcomes in the Gardasil group (18.3% - 25/126) compared with the alum control group (21%-29/138).
  - There were 2 cases of late fetal death in pregnant subjects who received Gardasil and 0 cases in the alum control group.
  - The overall proportions of fetal losses resulting from spontaneous causes (spontaneous abortions and late fetal deaths) were 19.8% (25/126) among subjects who received Gardasil and 21.0% (29/138) among subjects who received alum control**.**

- The proportion of pregnancies with a known outcome that ended in elective termination was 17.5% among subjects who received Gardasil compared with 16.7% among subjects who received alum control**.**

- Of the total documented fetal anomalies, there were 2 ectopic pregnancies among alum control recipients compared to none among subjects who received Gardasil.

The proximate pregnancies are summarized in Table 54.

TABLE 54
Pregnancy Outcome Summary - Pregnancies With Estimated Conception Dates Within 30 Days of Any Vaccination (Entire Study Period) Female Subjects in the Safety Population (Studies HPV-013, -015, -016, -018 and -019)

	Gardasil N=126	Control N=138
Subjects with pregnancies	126	138
Number of pregnancies	128	138
Number of pregnancies with known outcome	126	138
Live Births*	79 (62.7%)	84 (60..9%)
Infant Outcomes (Based on Live Births)**		
Normal	65 (82.3%)	74 (88.1%)
Abnormal	14 (17.7%)	9 (10.7%)
Congenital anomaly	5 (6.3%)	1 (1.2%)
Other abnormality	9 (11.4%)	8 (9.5%)
Fetal Loss*	47 (37.3%)	52 (37.7%)
Type of Loss***		
Spontaneous abortion	23 (48.9%) [18.3%]****	29 (55.8%) [21.0%]****
Late Fetal Death	2 (4.3%) [1.6%]****	0 (0.0%)
Elective abortion	22 (46.8%) [17.5%]****	23 (44.7%) [16.7%]****
Ectopic pregnancy	0	2 (1.4%)

*Percentages calculated based on number of pregnancies with known outcomes.
**Percentages of infant outcomes based on number of live births.
***Percentages of types of loss based on total number of fetal losses.
[]****Percentage based on number of pregnancies with known outcome
Source: STN 125126/-(b)(4)-, Reference 2158, Table 5, p. 28-30, Updated summary of congenital anomalies

Non-proximate pregnancies:

- The proportions of pregnancies that resulted in live births were 72.8% in the group that received Gardasil and 70.9% in the alum control group.
- The proportion of non-proximate pregnancies that resulted in a negative outcome, i.e. the combined numbers of spontaneous abortion, late fetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 22.9% (390/1704) in the Gardasil group and 23.8% (406/1704) in the alum control group.
- With respect to **live births**:
  - Among the live births, the proportions of infants in whom an abnormality was detected were 5.4% in the group that received Gardasil and 4.3% in the alum control group**.**
  - Twenty five (25) infants born to subjects who received Gardasil and 21 infants born to subjects in the alum control group were found to have a congenital anomaly in the neonatal period. Eight (8) infants were diagnosed with congenital anomalies in-utero (5 in the Gardasil group and 3 in the alum control group). There were 5 cases (3 in the Gardasil group and 2 in the alum control group) diagnosed beyond the neonatal period. One infant born to subject AN 80754 with the umbilical hernia

and patent ductus arteriosus was not considered by the investigator to have a congenital anomaly.

- Among all non-proximate pregnancies, there were 33 infants with a congenital anomaly born to subjects who received Gardasil and 26 cases in subjects who received alum control.
- With respect to **fetal losses**:
  - Five (5) congenital anomaly cases resulted in fetal losses (2 in the Gardasil group and 3 in the alum control group).
  - The proportions of pregnancies that resulted in fetal loss were 27.1% in the group that received Gardasil and 29.0% in the alum control group.
  - The proportions of fetal loss due to late fetal death for all pregnancies with known outcome were comparable between the vaccination groups (0.8% in the group that received Gardasil and 0.8% in the alum control group).
  - Two (2) cases of congenital anomaly were detected in the Gardasil group and 3 were detected in the alum control group.
  - The proportions of **fetal loss due to spontaneous abortion** were comparable between the vaccination groups (18.1% in the Gardasil group and 19.3% in the alum control group based on number of known pregnancies.
  - The proportions of **fetal loss due to elective termination** in pregnancies with known outcome were comparable between the vaccination groups, 8.7% in the Gardasil group and 9.4% in the control group based on number of pregnancies with known outcome.

The non-proximate pregnancies are summarized in Table 55.

TABLE 55
Pregnancy Outcome Summary - Pregnancies With Estimated Conception Dates Not Within 30 Days of Any Vaccination (Entire Study Period) Female Subjects in the Safety Population (Studies HPV-013, -015, -016, -018 and -019)

	Gardasil N=1701	Control N=1717
Subjects with pregnancies	1701	1717
Number of pregnancies	1951	1979
Number of pregnancies with known outcome	1877	1886
Live Births*	1366 (72.8%)	1338 (70.9%)
Infant Outcomes (Based on Live Births)**		
Normal	1288 (94.3%)	1278 (95.5%)
Abnormal	74 (5.4%)	57 (4.3%)
Congenital anomaly	26 (1.9%)	19 (1.4%)
Other abnormality	53 (3.9%)	38 (2.8%)
Fetal Loss*	509 (27.1%)	547 (29.9%)
Type of Loss***		
Spontaneous abortion	340 (66.8%) [18.1%]****	364 (66.5%) [19.3%]****
Late Fetal Death	15 (2.9%) [0.8%]****	15 (2.7%) [0.8*]****
Elective abortion	153 (30.1%) [8.2%]****	167 (30.5%) [8.9%]****
Ectopic pregnancy	2 (0.1%)	1 (0.1%)

*Percentages calculated based on number of pregnancies with known outcomes.
**Percentages of infant outcomes based on number of live births.
***Percentages of types of loss based on total number of fetal losses.
[]****Percentage based on number of pregnancies with known outcome
Source: STN 125126/-(b)(4)-, Reference 2158, Table 5, p. 28-30, Updated summary of congenital anomalies

As of the time of preparation of the updated congenital anomaly report submitted to the BLA in January, 2008. a total of 70 infants/fetuses have been diagnosed with congenital

anomalies in the Phase III studies: 40 cases occurred in the Gardasil group and 30 cases occurred in the alum control group. Table 56 summarizes the reporting of these cases.

TABLE 56
Summary of Reporting of Congenital Anomaly Outcomes Clinical Trials of Gardasil

Reporting Period	Cases of Congenital Anomalies	
	Gardasil N=40	Alum control N=30
Original BLA	13	12
Supplemental BLA (3/07)	12	10
Supplemental BLA (1/08)	15	8

Source: STN 125126/-(b)(4)-, Table 1, Updated report congenital anomalies, p. 12.

TABLE 57
Distribution of Congenital Anomaly Cases in the Phase III Database by Timing of Diagnosis Relative to Birth and by Vaccination Group
(Studies HPV-013, -015, -016, -018, and -019)

	qHPV vaccine	Placebo
Infant/fetus with Congenital anomalies	**40**	**30**
Live birth with diagnosis made in the neonatal period	30	22
Live birth with diagnosis made beyond the neonatal period	3	2
Live birth with diagnosis made in utero	5	3
Fetal loss	2	3

Source: STN 125126/-(b)(4)-, Table 2.7.4:23, Summary of Clinical Safety, p. 125

Of the 1447 pregnancies that resulted in a live birth among subjects who received Gardasil in the combined Phase III database, 38 live born infants (2.6% of total) were found to have a congenital anomaly. Of the 1424 pregnancies that resulted in a live birth among subjects who received alum control in the combined Phase III database, 27 live born infants (1.9% of total) were found to have a congenital anomaly.

Among proximate pregnancies (vaccination within 30 days of estimated date of conception), 5 of 79 (6.3%) of live births among subjects who received Gardasil and 1 of 84 (1.2%) of live births among subjects who received alum control resulted in a congenital anomaly. As noted in the original review, the observed anomalies were pathogenetically unrelated suggesting varying etiologies and made a common association less likely. The majority of the observed anomalies were assessed as relatively common, and their prevalence rates within the study population were consistent with the prevalence rates described in surveillance registries and the literature.

Among non-proximate pregnancies (estimated date of conception > 30 days within vaccination), 33 of 1366 (2.4%) of live births among subjects who received Gardasil and 26 of 1338 (1.9%) of live births among subjects who received alum control resulted in a congenital anomaly. Two (2) additional cases in the Gardasil group and 3 additional cases in the alum control group were congenital anomalies that occurred in pregnancies resulting in fetal loss (including fetal loss due to therapeutic abortion). Thus, among non-proximate pregnancies, there were 35 infants/fetuses with congenital anomalies in the

Gardasil group and 29 infants/fetuses with congenital anomalies in the alum control group. In the review provided in supplement -(b)(4)-, the sponsor reports the findings of four independent experts who reviewed each of the 70 congenital anomaly cases; a fifth expert was only available to review the first 25 cases. Both prior to and following unblinding of data regarding individual vaccination assignments, the independent experts determined that it was unlikely that any of the congenital anomaly cases was causally related to study vaccination. These experts included the following: ----------(b)(4)----------. A fifth independent expert, ----------(b)(4)----------, reviewed the first 25 congenital anomaly cases in 2006, but was not available for the 2007 review of the additional 45 cases. The data were initially assessed by the independent experts while they were blinded to treatment assignments. These reviews were then followed by a supplementary assessment of unblinded data by each independent expert.

The adverse experience profile of subjects who received Gardasil and whose pregnancy resulted in a congenital anomaly was comparable to the profile in the general population of women who received Gardasil. Anti-HPV responses to Gardasil observed in each subject who received Gardasil and whose pregnancy resulted in a congenital anomaly were comparable to those observed in the overall Phase III study population.

As noted in the original application, developmental and reproductive studies did not reveal treatment-related effects in the study animals (rats) or in the offspring of study animals, both during the study as well as at necropsy.

In Protocol 007, a Phase IIb, dose-ranging safety, immunogenicity, and efficacy study of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in 1155 16- to 23-year-old women, 863 subjects received one of 3 dose formulations of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, including the dose formulation used in Phase III studies, and 292 subjects received alum control. Few subjects became pregnant. There was one congenital anomaly case in this group: the anomaly occurred in an infant born to subject AN 8284, who was an alum control recipient who became pregnant approximately 754 days Post dose 3 of alum control. A fetal ultrasound revealed a cyst in the right kidney. The investigator determined that the right kidney cyst was probably not related to study therapy. The only other abnormal infant outcomes in Protocol 007 included twin infants born prematurely with respiratory distress syndrome in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group.

Anomalies associated with chromosomal or a single gene etiology, or inherited from an affected parent.

- In the Gardasil group, there are 4 such cases (Trisomy 21; unbalanced 9; 16 translocation, Crouzon syndrome inherited from a parent, alpha Thalassemia).

- In the alum control group, there were 3 such cases: (chondrodystrophy; congenital musculoskeletal anomaly; glucose-6-phosphate-dehydrogenase deficiency).

TABLE 58
Listing of Genetic/Familial Congenital Anomalies by Vaccination Group

Genetic/Familial Congenital Anomaly	qHPV Vaccine (N=5 infants)	Placebo (N=4 infants)	Comment
Trisomy 21	X		Chromosomal abnormality
Partial Trisomy 16; partial Monosomy 9	X		Father affected with chromosome 9;16 balanced translocation
Alpha thalassemia	X		Affected father; associated with gene mutations
Glucose-6-phosphate-dehydrogenase deficiency		X	Affected mother; associated with gene mutations
Craniosynostosis ("Crouzon syndrome")	X		Affected mother; associated with gene defect
Chondrodystrophy		X	Associated with gene mutations
Congenital musculoskeletal anomaly		X	Associated with gene mutations

Source: Source: STN 125126/-(b)(4)-, Reference 2158,Table 8, p. 38, Updated Summary of Congenital Anomalies

Excluding these cases related to chromosomal or gene mutation, the total number of congenital anomalies is 36 in the Gardasil group and 27 in the alum control group.

TABLE 59
Summary of Congenital Abnormalities by Etiology
(Studies HPV-007, 013, 015, 016, 018, and 019)

	qHPV vaccine	Placebo
Infant/fetus with Congenital anomalies	**40**	**30**
Inherited/Single Gene Defect/chromosomal	4	3
Diverse etiology	35	26
Etiology Unknown (Congenital Anomaly Not further Specified)	1	1

Gardasil vaccine = Gardasil
Source: STN 125126/-(b)(4)-, Reference 2158,Table 9, p. 38, Updated Summary of Congenital Anomalies

TABLE 60

Listing of Congenital Anomalies Observed in the Phase III Clinical Database (Studies HPV-011, -012, -013, -015, -016, -018 and 019) by Vaccination Group

CONGENITAL ANOMALY	qHPV vaccine (N =40 Infants)	PLACEBO (N = 30 Infants)
Abdominal Wall Defect	**2**	**0**
Exomphalus/umbilical hernia	0	4[1, 11]
Gastroschisis	2	0
Hernia, congenital	0	2
Cardiac	**10**	**12**
Anomalous pulmonary venous connection	1	0
Atrial Septal Defect	0	3[1,2,11]
Atrioventricular Septal Defect	1	0
Cardiac Murmur	1	0
Cardiac Septal Defect	1	0
Congenital Pulmonary Valve Atresia	1	0
Fallot's Tetralogy	0	1
Heart Disease, Congenital	1	0
Persistent Foetal Circulation/Patent Ductus Arteriosis	2	2[11]
Tricuspid Valve Incompetence	1	1[11]
Ventricular Septal Defect	1	5[1,11,12]
Congenital Malformation NOS	**2**	**1**
Birth defects (meningocele and bilateral renal agenesis)	1	0
Congenital Anomaly	0	1
Foetal Disorder	1	0
Chromosomal Abnormality	**2**	**0**
Trisomy 21	1[9]	0
Partial Trisomy 16 and Partial Monosomy 9[12]	1[9]	0
Craniofacial/ENT	**11**	**6**
Accessory Auricle	1	0
Ankyloglossia, Congenital	1[1]	0
Anotia	0	2
Branchial Cyst	1	0
Choanal Atresia	1	0
Cleft Lip	1	0
Cleft Lip and Palate	1	2
Craniosynostosis ("Crouzon syndrome")	1	0
Ear Malformation	1	0
Eyelid Ptosis, Congenital	1	0
Hypoacusis, Unilateral	1	0
Laryngomalacia	0	1
Low Set Ears	1[3]	0
Mandibulofascial Dysostosis	0	1
Gastrointestinal	**3**	**1**
Congenital Megacolon	1	0
Pyloric Stenosis (NOS, congenital, hypertrophic)	2[1]	1

CONGENITAL ANOMALY	qHPV vaccine (N = 40 Infants)	PLACEBO (N = 30 Infants)
Hematological	**1**	**1**
Glucose-6-phosphate-dehydrogenase Deficiency	0	1
Thalassemia Alpha	1	0
Hepatic	**0**	**1**
Liver Disorder ("Congenital Left Liver")	0	1
Orthopedic/Musculoskeletal	**7**	**7**
Amniotic Band Syndrome	0	1
Adactyly	0	1
Chondrodystrophy	0	1
Congenital Hip deformity	0	1[1]
Congenital Musculoskeletal Anomaly	0	1
Hip Dysplasia	3	1
Limb Malformation	1[§]	0
Polydactyly	2	1
Talipes	1	0
Renal	**2**	**2**
Congenital Hydronephrosis	1	2
Renal Aplasia	1	0
Reproductive tract	**1**	**0**
Cryptorchism	1	0
Neoplasms benign, malignant and unspecified	**1**	**0**
Adrenal neoplasm	1	0

[1] Exomphalos, atrial septal defect, and congenital hip deformity occurred in the same infant.
[2] Atrial septal defect and ventricular septal defect occurred in the same infant.
[#] Low set ears and limb malformation occurred in the same infant.
[|] Ankyloglossia and pyloric stenosis occurred in the same infant.
[¶] The infant with Trisomy 21 also had duodenal atresia and congenital heart disease
[#] The infant with partial Trisomy 16 and partial Monosomy 9 also had atrial septal defect, ventricular septal defect, kidney malformation and kidney duplex
[††] Atrial septal defect, ventricular septal defect and tricuspid valve incompetence occurred in the same infant.
[‡‡] Originally reported as translocation of chromosomes 9 and 15.
[##] Ventricular septal defect and patent ductus arteriosus occurred in the same infant
[||] Umbilical hernia and patent ductus arteriosus occurred in the same infant.
NOS = Not otherwise specified

Source: STN 125126/-(b)(4)-, Reference 2158,Table 7, p. 36-37, Updated Summary of Congenital Anomalies

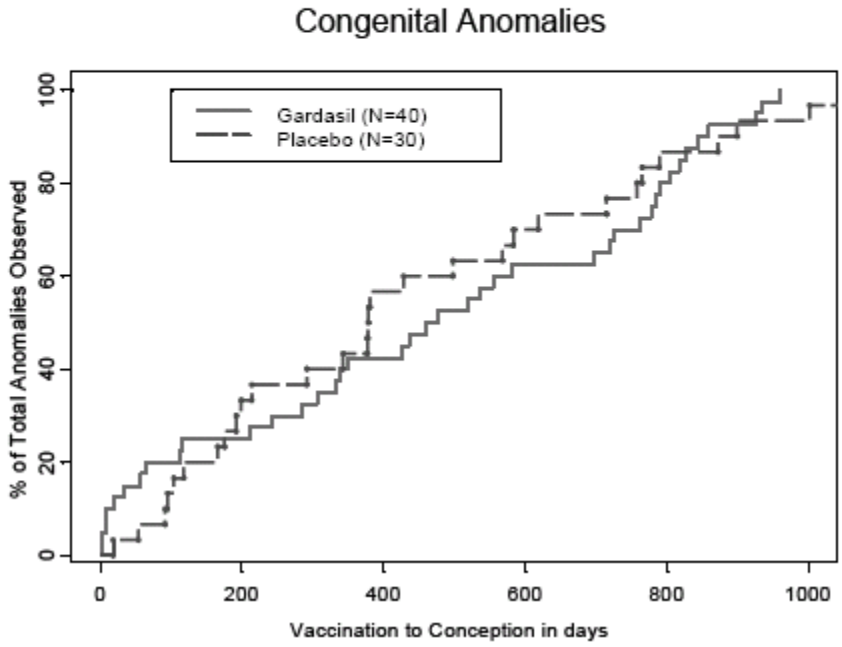
Combining all congenital anomaly cases (including fetal losses), 40 cases out of 1447 live birth outcomes, or 2.8% in the Gardasil group, and 30 cases out of 1424 live birth outcomes, or 2.1% in the alum control group, resulted in a congenital anomaly.

To date, a total of 6 infants, 5 in the Gardasil group and 1 in the alum control group, had other abnormalities reported in addition to the congenital anomaly. Two (2) of these were among the congenital anomaly cases reported since the initial license application (1 in the Gardasil group and 1 in the alum control group).

FIGURE 4

Figure 3

Kaplan Meier Curve of Congenital Anomalies Observed in the Phase III Clinical Database (Protocols 013, 015, 016, 018, and 019) by Vaccination Group



Source: STN 125126/-(b)(4)-, Reference 2158,Figure 3, p. 46, Summary of Congenital Anomalies

Maternal Factors Considered Among Congenital Anomaly Cases in Phase III Studies of Gardasil (Studies HPV-013, -015, -016, -018, -019)

Pregnancy History: The proportions of subjects with a family history of congenital anomalies were comparable between the vaccination groups, although a higher proportion of subjects in the Gardasil group whose pregnancy resulted in a fetus with a congenital anomaly had histories of significant prior pregnancy difficulties compared with the alum control group.

Baseline Demographics: Among subjects whose pregnancy resulted in a congenital anomaly, baseline demographic characteristics were generally comparable between vaccination groups, although baseline serostatus positive was somewhat higher in the Gardasil group (12/40 or 30%) compared with the alum control group (5/30 or 17%). Baseline demographic characteristics were also comparable to those of the general population of 16- to 45-year-old women enrolled in the Phase III studies, although the sponsor reported that the majority of congenital anomalies occurred in Latin America, but most of the pregnancies occurred in this region. There was no apparent association between smoking and incidence of congenital anomalies in these studies.

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Reviewer's Comment: There is difficulty in assessing true differences in rates of events since study of outcomes in pregnancy was not controlled or randomized. The proportions of subjects whose child had a congenital anomaly were comparable in the treatment groups, and there was no identified consistent anomaly reported for either group.

Adverse Events in mothers of babies with congenital anomalies

- Although the subject numbers are small, the proportion of subjects with one or more adverse experiences, and the proportion of subjects with systemic adverse experiences were somewhat higher in the alum control group (53.3% in the alum control group versus 50.0% in the Gardasil group, and 36.7% in the alum control group versus 17.5% in the Gardasil group, respectively).
  - 1 recipient of Gardasil had a serious adverse experience that was judged by the investigator to be unrelated to vaccine (AN 24658 in study 011, premature labor and preeclampsia).
  - Since the time of the original report, 1 additional Gardasil recipient who had a baby with a congenital anomaly experienced a pregnancy related SAE (premature labor) but this was in a pregnancy prior to the pregnancy which resulted in the congenital anomaly.
  - In addition, the sponsor noted that although the number of subjects in either vaccination group is small, the proportions of subjects whose pregnancy resulted in a congenital anomaly who reported an adverse experience, and the categories of reported adverse experiences, were generally comparable with the proportions of subjects in the overall Phase III program safety population who reported such adverse experiences.

Congenital anomalies for each treatment group are listed in Tables 61 and 62, with brief narratives below each table.

TABLE 61

Congenital Anomalies in subjects who received Gardasil and became pregnant (Combined Studies HPV-013, -015, -016, -018, and -019)

AN	EDCn Relative to Vaccination	Congenital Anomaly
24658	1/postdose 1	Hip dysplasia
49389	**818/postdose 3**	**Congenital hip dysplasia**
46580	**784/postdose 3**	**Congenital hip dysplasia**
33319	2/predose 2	Congenital hydronephrosis
41894	7/postdose 3	Congenital megacolon
45992	9/postdose 1	Talipes
30580	19/postdose 1	Congenital Ankyloglossia, pyloric stenosis
31764	**960/postdose 3**	**Pyloric stenosis**
41941	**934/postdose 3**	**Gastroschisis**
48154	**696/postdose 3**	**Gastroschisis**
43428	**555/postdose 3**	**Choanal atresia**
47851	33/postdose 1	Heart disease congenital, duodenal atresia, trisomy 21 **(F)**
43445	477/postdose 3	Partial trisomy 16 and partial monosomy 9, kidney malformation, kidney duplex, ASD, VSD
45861	**827/postdose 3**	**Craniosynostosis (Crouzon)syndrome)**
57040	**112/postdose 3**	**Thalassemia, alpha**
31701	**536/postdose 3***	**Ear malformation**
56026	**719/postdose 3**	**Accessory auricles**
24836	285/postdose 3	Low set ears, limb malformation **(F)**
Protocol 004**	App. 1 month postdose 1 Monovalent 16	Tracheomalacia
40450	212/postdose 3	Branchial cyst
56355	57/postdose 2	Anomalous pulmonary venous connection **(F)**
47862	116/postdose 2	Persistent fetal circulation
33724	**763/postdose 3**	**Patent ductus arteriosus**
25428	332/postdose 3	Tricuspid valve incompetence
55443	351/postdose 3	Cardiac murmur
40086	**859/postdose 3**	**Congenital pulmonary valve atresia**
43702	**427/postdose 3***	**Atrioventricular septal defect**
55837	**437/postdose 3**	**Cardiac septal defect**
80464	**64/postdose 3**	**Ventricular septal defect**
56884	**306/postdose 3**	**Congenital heart disease (inter-auricular communication, inter-ventricular communication, persistent fetal circulation and pulmonary hypertension.)**
33370	**844/postdose 3**	**Cleft lip**
55090	**778/postdose 3**	**Cleft palate and lip**
24019	**789/postdose 3**	**Polydactyly**
54825	**460/postdose 3**	**Polydactyly**
49779	**726/postdose 3**	**Cryptorchism**
32615	**528/postdose 3**	**Renal aplasia**
81486	**339/postdose 3**	**Birth defects (absent kidneys and meningocele)**
33808	**925/postdose 3**	**Hypoacusis unilateral**
54816	**519/postdose 3congenital**	**Congenital Eyelid ptosis**
80244	**243/postdose 3**	**Adrenal neoplasm**
54517	**804/postdose 3**	**Foetal disorder**

NOTE: *Cases were noted in the safety update of the original submission and days after vaccination corrected with this update.

Cases bolded reported in updated congenital anomaly report. Not considered to be related (probably not and definitely not). ; Cases highlighted represent inherited abnormalities.

New cases reported since original licensure (includes assessment of relationship to vaccine as per investigator attribution):

- **AN 24019** (Brazil, study 013): **additional small finger** removed at 20 days of age. [Relationship not stated]
- **31701** (Colombia, study 013): associated with **moderately decreased hearing in right malformed ear.** Mother gave birth subsequently to a normal baby. [Probably Not Related]

- **31654** (Colombia, study 013): **pyloric stenosis** (corrective surgery). [Probably not related]
- **32615** (Colombia, study 013): **renal aplasia**; mother had a subsequent pregnancy with a spontaneous abortion. [Probably not related]
- **33370** (Canada, study 013): **cleft lip;** child had corrective surgery. [Probably not related]
- **33724** (Colombia, study 013): **PDA** closed spontaneously. [Definitely not related]
- **33808** (Mexico, study 013): **Left ear deafness**, right eat normal. [Probably Not related
- **40086** (US, study 015**): Congenital pulmonary valve atresia**; child had 3 corrective surgeries. [Definitely not related]
- **41941** (Norway, study 015): **Gastroschisis;** child had corrective surgery. [Probably not related]
- **43428** (US, study 015): **Choanal atresia;** child had corrective surgery. [Probably not related]
- **43702** (Iceland, study 015): **AV septal defect**; child underwent surgical repair. [Probably not related]
- **45861** (Peru, study 015): **Craniosynostosis;** positive family history, including mother. [Definitely not related]
- **46580** (Colombia, study 015): **Congenital hip dysplasia** [Probably not related]
- **48154** (US, study 015): **Gastroschisis;** child had corrective surgery, and will need additional surgeries. [PN]
- **49389** (Norway, study 015): **Congenital hip dysplasia**; positive family history, including mother. [Definitely not related]
- **49779** (Brazil, study 015): **Crytptorchism** [Definitely not related]
- **54517** (Sweden, study 015): Mother had elective abortion at 16 weeks gestation (history of 1 normal pregnancy, 1 prior elective abortion). The abnormality was not specified. [Probably not related]
- **54816** (Colombia, study 015): **Congenital eyelid ptosis** [Probably not related]
- **54825** (Colombia, study 015): **Polydactyly** involved left hand and both feet, child underwent corrective surgery. [Probably not related]
- **55090** (Norway, study 015): **Cleft palate and lip;** [Probably not related]
- **55837** (Denmark, study 015): **VSD** spontaneously recovered. [Probably not related]
- **56026** (Colombia, study 015): **Bilateral pre-auricular appendices**. [Probably not related]
- **55684** (Colombia, study 015): **Cardiac defects** included **inter-auricular communication, inter-ventricular communication, persistent fetal circulation and pulmonary hypertension**. Corrective surgery was planned but patient lost to follow-up. [Definitely not related]
- **57040** (Singapore, study 015): Father with **alpha 2 thalaassemia minor**. [Definitely not related]
- **80244** (US, study 019): **Adrenal neoplasm**; infant also with necrotizing colitis. Previous pregnancy – child with DiGeorge's syndrome (prior to any vaccinations). Mother with methylene tetra hydrofolate reductase (MTHFR) deficiency. [Not related]
- **80464** (Germany, study 019): **VSD** spontaneously resolved. [Probably not related]

- **81486** (Thailand, study 019): **Absent kidneys and meningocoele**; mother had elective abortion at 25 weeks gestation. [Definitely not related]

There was one additional case of a congenital renal cyst (1403 days postdose 3, with baby 364 days of age, in an infant whose mother was participating in study 007 extension (discussed below). No treatment was required at the time of reporting.

Cases Reported in Original BLA and amendments pre-licensure:

- **24658** (Brazil, study 013): **Hip dysplasia** in one infant (twin pregnancy); child treated with Pavlivk harness. [Not related]
- **30580** (UK, study 013): Corrective surgery for **pyloric stenosis; ankyloglossia** being allowed to resolve spontaneously.

TABLE 62

Congenital Anomalies in subjects who received Alum Control and became pregnant (Combined Studies HPV-013, -015, -016, -018, and -019)

Congenital Anomalies in subjects who received Alum control and became pregnant (Combined studies)		
AN	EDCn Relative to Vaccination	Congenital Anomaly
31309	54/postdose 3	Congenital hip deformity, exomphalos, ASD
49420	104/postdose 3	Hip dysplasia
44067	**899/postdose 3**	**Fallot's tetralogy**
46118	166/postdose 3	Ventricular septal defect
44525	**1025/postdose 3**	**Ventricular septal defect**
43363	**428/postdose 3**	**Ventricular septal defect**
33947	95/postdose 3	VSD, ASD
55892	**619/postdose 3**	**VSD, ASD, tricuspid valve incompetence**
80754	**92/postdose 3**	**Patent ductus arteriosus, umbilical hernia**
40133	**872/Postdose 3**	**Pyloric stenosis**
24458	118/postdose 3	Exomphalos
47866	192/Postdose 2*	Exomphalos
24772	214/postdose 3	Bilateral inguinal hernia
25201	176 postdose 3*	Congenital hernia
32072	292/postdose 3	Congenital hydronephrosis
81440	**18/postdose 3**	**Congenital hydronephrosis**
40330	343/postdose 3	Amniotic band syndrome **(F)**
31132	377/postdose 3	Adactyly
47257	379/postdose 3	Polydactyly
30287	378/postdose 3	Cleft lip and palate
44123	**715/postdose 3**	**Cleft lip and palate**
55177	**765/Postdose 3**	**Laryngomalacia**
32464	199 postdose 3*	Mandibulofacial dysostosis (Diagnosed subsequently as Treacher Collin syndrome)
46120	583/postdose 3*	G6PD deficiency
45904	**789/postdose 3**	**Chondrodystrophy (achondroplasia)**
81238	**381/postdose 3**	**Congenital musculoskeletal anomaly (hypochondroplasia)**
31605	**1001/postdose 3**	**Anotia**
57503	**568/Post dose 3**	**Anotia**
30479	**758/postdose 3**	**Liver disorder (congenital left liver)**
46561	498/postdose 3	Congenital anomaly **(F)**

Source: Table 13, p. 50-57, Updated Summary of Congenital anomalies
*Cases were noted in the original BLA (safety update) and present supplement, and days in relation to EDCn were revised.
Cases bolded were reported in the updated congenital anomaly report.
Cases highlighted involve inherited defects.

Cases included in supplemental congenital anomaly report for alum control recipients.

- **81440** (Colombia, study 019): **Congenital hydronephrosis**; baby had corrective surgery. [Probably not related] This case occurred within 30 days of conception.
- **25201** (Brazil, study 013): **Left sided hernia**, surgically corrected. Father with 2 other children with hernia repair in first two years of life (and father had hernia repaired as adult). [Definitely not related]
- **30479** (Colombia, study 013): **Congenital left liver**; mother received MMR at app.4 months after LMP. [relationship not stated]
- **31605** (Mexico, study 013): **Right sided anotia**, under care of ear specialists. [Probably not related]
- **32464** (Puerto Rico, study 013): **Mandibulofacial dysostosis**; needed surgery, difficulty breathing. [Definitely not related]
- **40113** (US, study 015): **Pyloric stenosis**; Corrective surgery. [Probably not related]

- **43363** (Finland, study 015): **VSD;** considered hemodynamically insignificant. [Probably not related]
- **44067** (Singapore, study 015): **Fallot's tetrology**; mother had elective abortion. [Probably not related]
- **44123** (Colombia, study 015): **Cleft lip and palate;** Corrective surgeries. [Definitely not related]
- **44525** (Norway, study 015): **VSD**; no surgery required. [Definitely not related]
- **45904** (Singapore, study 015): **Achondroplasia** [Probably not related]
- **46120** (Singapore, study 015): **G6PD deficiency** [Definitely not related]
- **47866** (Colombia, study 015): **Exomphalos;** corrective surgery. [Definitely not related]
- **55177** (UK, study 015): **Laryngomalacia;** resolved. [Definitely not related]
- **55892** (Brazil, study 015): **ASD, VSD, tricuspid valve incompetence** [Definitely not related]
- **57503** (Mexico, study 015): **Anotia** [Probably not related]
- **80754** (Colombia, study 019): Baby born at 32 weeks gestation, mother with HELLP syndrome. **PDA** closed spontaneously and hernia repaired. [Probably not related]
- **81328** (Thailand, study 019): **Abnormal short fetal extremities (hypochondropalsia**) [Definitely not related]

Adverse Events in mothers of babies with congenital anomalies

- Although the subject numbers are small, the proportion of subjects with one or more adverse experiences, and the proportion of subjects with systemic adverse experiences were somewhat higher in the alum control group (53.3% in the alum control group versus 50.0% in the Gardasil group, and 36.7% in the alum control group versus 17.5% in the Gardasil group, respectively).
  - 1 recipient of Gardasil had a serious adverse experience that was judged by the investigator to be unrelated to vaccine (AN 24658 in study 011, premature labor and preeclampsia).
  - Since the time of the original report, 1 additional Gardasil recipient who had a baby with a congenital anomaly experienced a pregnancy related SAE (premature labor) but this was in a pregnancy prior to the pregnancy which resulted in the congenital anomaly.
  - In addition, the sponsor noted that although the number of subjects in either vaccination group is small, the proportions of subjects whose pregnancy resulted in a congenital anomaly who reported an adverse experience, and the categories of reported adverse experiences, were generally comparable with the proportions of subjects in the overall Phase III program safety population who reported such adverse experiences.

Tables of prevalence of specific congenital anomalies from the literature are provided by the sponsor. The sponsor indicates that these tables demonstrate a wide variability in the prevalence estimates for specific congenital anomalies that is seen across international birth registries, and that is noted in the CBER review. The sponsor has provided additional information regarding several congenital anomalies which occurred in infants born to mothers participating in these studies.

Gastroschisis (AN 41941 and AN 48154)
The incidence of gastroschisis is approximately 1 per 10,000 live births, and has increased worldwide over the past two decades. The etiology of gastroschisis is unclear, and although associations with various vasoactive substances such as cocaine, nicotine, and pseudoephedrine have been suggested, none have been consistently demonstrated. The recurrence risk for mothers with an affected infant is 3 to 5 percent, perhaps suggesting a multifactorial etiology

Cryptorchism (AN 49779)
Cryptorchism, is the most common male genital defect, occurs in 2-5% of term male infants, with approximately 10 percent of cases being bilateral. Surgical correction is recommended if testes have not descended by 6 months of age. Increased alcohol use during pregnancy, exposure to pesticides, low birth weight (including premature birth), gestational diabetes and twinning have been associated with the defect. With regard to birth weight, there is a strong association of cryptorchism with low birth weight due to either prematurity or intrauterine growth restriction; between 2 and 5 percent of full-term and 30 percent of premature male infants are born with an undescended testicle. Cryptorchism is also associated with multiple congenital malformation syndromes including Prader-Willi syndrome and Noonan syndrome.

Congenital Pulmonary Valve Atresia (AN 40086)
This condition is seen in approximately 1 per 10,000 live births, and represents approximately 1 to 3% of all congenital cardiac defects. The majority of these infants require surgical repair, usually within the first week of life, as the condition is lethal if not corrected. The majority of pulmonary valve atresia cases occur sporadically, with no clear identifiable risk factor. In utero infection, with resultant disruption of pulmonary valve embryogenesis, has been proposed as a possible cause of pulmonary valve atresia. No causative agent has been identified.

Accessory Auricle (AN 56026)
The prevalence of accessory auricle anomalies is variably reported as somewhere between 0.47% and 0.22%, and may or may not be associated with other anomalies of the first mandibular arch. The underlying cause of this abnormal development is unknown.

Eyelid Ptosis, Congenital (AN54816)
Congenital ptosis is most often hereditary, although familial associations can be unrecognized when family members are only mildly affected. Surgical correction may be required if the condition is severe, or if cosmetically indicated; the method chosen depends on the amount of levator function present.

Hypoacusis (AN 33308)
Significant hearing loss occurs in approximately one to two per 1000 newborns. Hearing loss is classified as conductive (any cause that in some way limits the amount of external sound that gains access to the inner ear), sensorineural (involving the inner ear, cochlea, or the auditory nerve, generally related to congenital infection, e.g., CMV, rubella,

toxoplasmosis, or syphilis), mixed (conductive and sensorineural), and central (auditory neuropathy-absent or severely distorted brainstem responses).

Congenital Heart Disease, NOS (AN 56884)
Congenital heart defects have a reported prevalence of 7-12 per 1000 live births. The most frequent congenital heart defects (CHD) were ventricular septal defect (41.59%), atrial septal defect (8.67%), aortic (7.77%) and pulmonary (5.81%) stenoses, transposition of the great arteries (5.39%), coarctation of the aorta (5.29%) and persistent ductus arteriosus (5.07%).

Ear Malformation, NOS (AN 31701)
The incidence of ear malformations is relatively rare, at approximately 1.3 per 10,000 births.

Crouzon Syndrome (AN 45861)
Crouzon syndrome is an autosomal dominant inherited form of craniosynostosis, in which there is premature fusion of cranial sutures. The mother of the child in the study had a mild form of the anomaly. Crouzon syndrome is due to mutations in the FGFR2 (fibroblast growth factor receptor 2) gene on chromosome 10q25-26. The FGFR gene family is involved in the stop-signaling of certain fibroblast growth factors. Mutations in FGFR2 result in abnormal stopsignaling of these fibroblast growth factors, ultimately leading to premature fusion of the cranial sutures. Crouzon syndrome can be variable, even within a family. Because it is inherited in an autosomal dominant manner, males and females can be affected, and an affected individual has a 50% chance of passing his or her FGFR2 gene mutation to each pregnancy, regardless of gender. Crouzon syndrome accounts for 4.8% of all craniostoses, with an estimated population incidence of 16.5/1,000,000.

Adrenal Neoplasm (AN 80244)
Adrenocortical neoplasms, which encompass adrenocortical adenomas and carcinomas, are a second type of pediatric adrenal tumor, which is very rare (0.3- 0.38/million in children <15 y.o. They can be associated with Neurofibromatosis, von Hippel Lindau and Sturge Weber syndromes.

Alpha Thalassemia (AN 57040)
Alpha-2 Thalassemia minor was reported in the child. The father of this infant also has alpha-2 Thalassemia minor. The alpha thalassemias are hematologic inherited disorders affecting the synthesis of the alpha-globin subunits of hemoglobin. Alpha globin is a necessary component of hemoglobin, beginning from the 6th week in gestation through adult life. HBA1 and HBA2 are highly homologous genes that are clustered together on chromosome 16p13.3. Deletions and/or mutations in the HBA genes results in decreased or absent alpha globin synthesis. Individuals who have alpha thalassemia trait or are silent carriers have variable associated clinical findings, most of which are typically mild.

Renal Agenesis and Spinal Meningocele (Subject AN 81486)
Renal agenesis is more common in male vs. female infants, and it is estimated that unilateral renal agenesis is 4-8 times more common than bilateral renal agenesis. This subject's child had bilateral renal agenesis. Spinal meningocele is an early embryonic defect in which a cerebrospinal fluid sac comprised of dura and arachnoid herniates through a bony spina bifida. Spinal meningoceles are estimated to account for less than 2.4% of all closed spinal dysraphisms.

Pregnancy Outcomes in Protocol 007 Extension
The sponsor presented updated protocol 007 information separately from the other studies. In STN 125126/419.0, 19 subjects had 20 pregnancies. At the time of the initial follow-up data, outcomes were known for 15/20 of these pregnancies. With the report of 12/2/07, the outcomes were reported for the remainder of the babies.

- Nine (9) pregnancies were reported in 114 subjects who received a primary series of Gardasil in the main study and a fourth dose of Gardasil in the extension phase. Outcomes are known for 9 of the 9 pregnancies. Of the 9 pregnancies with known outcomes, 7 resulted in the live birth a normal infant and 2 resulted in fetal loss (1 spontaneous abortion and 1 elective abortion).
- Ten (10) pregnancies were reported in 127 subjects who received a primary series of Alum control in the main study and Gardasil in the extension phase. Outcomes are known for 9 of the 10 pregnancies. Of the 9 pregnancies with known outcomes, 5 resulted in live birth (4 normal infants and 1 infant with a congenital anomaly) and 4 resulted in fetal loss (3 spontaneous abortions and 1 elective abortion). The 2 pregnancies with unknown outcome are ongoing.

As noted in the discussion of congenital anomalies, one anomaly occurred in an infant born to AN 8284 who received alum control. The subject became pregnant on 5/5/03 (last vaccination visit was on 4/11/01). On 2/11/04, a fetal ultrasound revealed a cyst in the right kidney. The infant was born on --(b)(6)-. Follow-up information indicates the infant is being followed by a pediatrician. The kidney cyst persisted, but no symptoms are reported and no treatment was indicated. The investigator determined that the right kidney cyst was probably not related to study therapy. The subject was enrolled into the study extension on 4/28/05, following pregnancy outcome. No other serious clinical adverse experiences were reported in infants born to study subjects who were vaccinated in the extension phase.

Pregnancy Outcomes in Studies HPV-021, -024, and -025: No pregnancies were reported in these ongoing studies.

Adverse Events in Subjects who became Pregnant During study

TABLE 63
Clinical Adverse Experience Summary (Days 1 Through Entire Study Period Following Any Vaccination Visit) in the Safety Population - Subjects Who Were Pregnant at Any Time During the Study
(Studies HPV-013, -015, -016, -018, and -019)

	Gardasil N=1796	Alum Control or saline Placebo N=1824
Subjects with Follow-up	1789	1816
Subjects with ≥ 1 AE	815 (54.4%)	775 (42.7%)
Injection Site AEs	699 (39.1%)	610 (33.6%)
Systemic AEs	567 (31.7%)	568 (31.3%)
Subjects with SAEs	54 (3.0%)	63 (3.5%)
Deaths	1 (0.1%)	1 (0.1%)
Discontinued due to AE	1 (0.1%)	2 (0.1%)
Discontinued due to SAE	1 (0.1%)	1 (0.1%)

Source: Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Table 2.7.4:24, p. 129-130 (12/07); Percentages are based on number of subjects with follow-up.

Reviewer's Comment: As noted, there was a higher proportion of Gardasil recipients who became pregnant after vaccination who experienced any adverse eventas compared to the control group. This appears to be related to a higher proportion of Gardasil recipients with an injection site adverse event as compared subjects who received control. The most common injection site adverse events reported were injection-site pain, swelling, and erythema. The proportions of subjects with systemic adverse events were similar in the two treatment groups. The most common systemic clinical adverse experiences reported were headache, pyrexia, and nausea. (Source: STN 125126/-(b)(4)-, Appendix 2.7.4:106, 107, p. 1170-3, not shown here). The proportions of subjects who reported an elevated temperature were higher among subjects who received Gardasil (16.4%) compared with control recipients (11.6%). The majority of subjects with an elevated temperature had temperatures < 102 deg F. There was a slightly higher proportion of subjects with a temperature ≥ 102 deg F in the control group (2.6%) as compared to the Gardasil group (1.7%). (Source: STN 125126/-(b)(4)-, Appendix 2.7.4:108, p. 1193, not shown here).

Serious Adverse Events in Subjects who Became Pregnant During the Studies
A listing of serious clinical adverse experiences reported in subjects in the Safety Population who were pregnant at any time during the clinical studies is provided. Overall, 117 subjects (54 subjects who received Gardasil and 63 subjects who received control) who became pregnant at any time during the study reported serious clinical adverse experiences.
Two (2) subjects who were pregnant reported serious adverse experiences that were determined by the investigator to be related to study therapy. Narratives are provided below.

- **Subject AN 56349**, who received Gardasil, reported headache and hypertension on Day 1 Postdose 3. The headache and hypertension were determined to be related to vaccination. The subject became pregnant following Dose 3. During pregnancy,

serious clinical adverse experiences of preeclampsia and oligohydramnios (definitely not vaccine-related) were reported.

- **Subject AN 56346**, who received placebo, reported chills, headache, and pyrexia on Day 1 Postdose 2. The chills, headache, and pyrexia were determined to be related to vaccination. The subject became pregnant following Dose 3. No serious clinical adverse experiences were reported during pregnancy.

The 3 most common serious clinical adverse experiences reported among subjects who became pregnant during the study were: premature labor, abortion threatened, and cephalo-pelvic disproportion. These SAEs are presented in Tables 64 (Gardasil group) and 68 (control group).

TABLE 64
Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period) Subjects Who Were Pregnant at Any Time During the Study (Gardasil Recipients) (Studies HPV-013, -015, -016, -018, and -019)

AN (age)	Event/grade	Time	Investigator attribution	Recovered
20512/011 (19 yo f)	Hypotension/moderate	295d postdose 1x2 hrs G+HB	Probably not related	Y
20388/011 (16yo f)	Cervix dystocia/severe	426d postdose 2x1d G+HB	Definitely not related	Y
25205/011 (19 yo f)	Cervix dystocia/severe	254d postdose 1 x 1d G+HBP	Definitely not related	Y
24739/011 (19 yo f)	Overdose/mild	162d postdose 3 x 1 d G+HB	Definitely not related	Y
24934/011 (19 yo f)	Transverse presentation/severe	403d postdose 2 x 1d G+HB	Definitely not related	Y
24658/011 (21 yo f)	Premature labor/moderate, Anemia/moderate, pre-eclampsia/mild	215, 251d postdose 1x 2d G+HBP	Definitely not related	Y
24090/011 (20 yo f)	Pyelonephritis/severe	7 days postdose 3 x 3d G+HB	Probably not related	Y
24511/011 (22 yo f)	Cervix dystocia	255d postdose 2 x 4d G+HBP	Defintiely not related	Y
24597/011 (21 yo f)	Cervix dystocia/severe	251d postdose 3 x 4d G+HBP	Definitely not related	Y
24815/011 (20 yo f)	Pyelonephritis/severe Prolonged labor/severe	43d postdose 3 x 4 d & 272d postdose 3 x 1d G+HPB	Definitely not related	Y
20126/011 (22yo f)	Cephalo-pelivic disproportion	264d postdose 1x1d G+HB	Definitely not related	Y
24033/011 (20 yo f)	Appendicitis/severe	117d postdose 2x2d G+HB	Definitely not related	Y
24412/011 (21 yo f)	Premature rupture of membrane/sever	550d postdose 3x4d G+HB	Definitely not related	Y
33757/012 (17 yo f)	Dehydration/severe Gastroenteritis/moderate	8d postdose 1 x 1.02yrs 8d posydose 1X 5 days	Definitley not related Probably not related	Y Y
30749/012 (23 yo f)	Asthma/moderate	1 days postdose 1x28d	Probably not related	Y
30938/012 (18 yo f)	Overdose/mild	1 daypostdose 1 & 2x1d	Definitely not related	Y
31812/012 (19yo f)	Premature labor/severe	1345d postdose 3 x 1d	Definitiely not related	Y
32536/012 (20 yo f)	UTI/moderate	229d postdose 2 x 4d	Probably not related	Y
30629/012 (20 yo f)	Breech presentation/severe	261d postdose 2x3d	Defintiely not related	Y
32751/012 (22 yo f)	Hyperventialtion/severe	15d postdose 1 x 2d	Definitely not related	Y
30580/012 (19 yo f)	Fetal malposition/moderate/moderate Operative hemorrhage/severe	272 d postdose 1 x 1d	Definitely not related	Y
30728/012 (19 yo f)	Premature rupture of membranes	255d postdose 1 x 7hrs	Definitely not related	Y
31359/012 (19 yo f)	Oligohydramnios/moderate	617d postdose 1 x 4 days	Definitely not related	Y
33168/012 (21 yo f)	Cephalopelvic disproportion/mild Prolonged labor/moderate	348 d postdose 2x13 hrs	Definitely not related	Y

TABLE 64 (CONT.)
Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period) Subjects Who Were Pregnant at Any Time During the Study (Gardasil Recipients) (Studies HPV-013, -015, -016, -018, and -019)

AN (age)	Event/grade	Time	Investigator attribution	Recovered
54010/015 (26yo f)	Reflux esophagitis/severe	Day 2 postdose 2x4d	Definitely not related	Y
41651/015 (16 yo f)	Pregnancy induced hypertension/moderate	316d postdose x 3d	Definitely not related	Y
40149/015 (22 yo f)	Falied trial of labor/severe	268d postdose 3x1d	Definitely not related	Y
48154/015 (19 yo f)	Premature labor/severe	231d postdose 3x1d	Definitely not related	Y
42471/015 (18yo f)	Failed forceps delivery/severe	413d postdose 2x13hrs	Probably not related	Y
43659/015 (19 yo f)	Abdominal pain/moderate Uterine contractions during pregnancy/moderate	94d postdose 2x1d 217d postdose 2x3d	Definitely not related	Y
41060/015 (21yo f)	Hyperemesis gravidarum/moderate Fetal distress syndrome/severe	42d postdose 3x3d 284d pstdose 2x1hr	Definitely not related	Y
43982/015 (20 yo f)	Postpartum hemorrhage/moderate	315d postdose 2x3d	Definitely not related	Y
44276/015 (19 yo f)	Cervicitis/moderate	230d postdose 2x3d	Definitely not related	Y
42685/015 (23 yo f)	Abortion threatened/moderate	25d postdose 2x2d	Definitely not related	Y
44256/015 (21 yo f)	Infective thrombosis, myocarditism pericarditis, septic shock, DIC	359 days postdose 3x6d	Definitely not related	FATAL (reported in original application)
57856/015 (23 yo f)	Pregnancy induced hypertension/moderate	243d postdose 2x8d	Definitely not related	Y
49548/015 (18 yo f)	Premature labor/moderate	161 d postdose 2x8hrs	Definitely not related	Y
55561/015 (23 yo f)	Fetal distress syndrome/moderate	247d postdose 1x3d	Definitely not related	Y
56349/015 (22yo f)	Headache/severe,hypertension/severe, pre-eclampsia/moderate Oligohydramnios/mild	D1 of dose 3x5d&1d, 260d postdose 3x 2d 261d postdose 3x3d	Definitely related Definitely not related	Y Y
57020/015 (18 yo f)	Fetal distress syndrome/moderate	257d postdose 1x3d	Defintiely not related	Y
42260/015 (21 yo f)	Cervix dystocia/moderate Premature rupture of membranes/moderate	356d postdose 2x2d	Definitely not related	Y
54573/015 (23 yo f)	Abortion threatened/moderate	63 d postdose 1/moderate (Cont)	Definitely not related	N
45992/015 23 yo f	Cholelithiasis/severe	3d postdose 2	Probably not related	Y
44134/015 (22yo f)	Ectopic pregnancy/severe	61d postdose 3x1d	Defintiely not related	Y
40391/015 (19 yo f)	Failed trial of labor/moderate	286d postdose 1 x5d	Definitely not related	Y
48741/015 (20 yo f)	Premature labor/severe	277d postdose 3x1.08mo	Definitely not related	Y

TABLE 64 (CONT.)

Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period)
Subjects Who Were Pregnant at Any Time During the Study (Gardasil Recipients)
(Studies HPV-013, -015, -016, -018, and -019)

AN (age)	Event/grade	Time	Investigator attribution	Recovered
45915/015 (23 yo f)	Endometritis/moderate	116 d postdose 1x6d	Definitely not related	Y
47581/015 (20 yo f)	Hyperemesis gravidarum/severe	37&53d postdose 1x4 and 2 days	Definitely not related	Y
55895/015 (17 yo f)	Sepsis/moderate	1226d postdose 3x 12d	Defintiely not related	Y
42410/015 (22 yo f)	Appendicitis/severe Failed trial of labor/severe	183d postdose 3x4d 261d postdose 3x15 hrs	Defintiely not related	Y
57846/015 (23 yo f)	Bipolar disorder/moderate	105 d postdose x 7d	Defintiely not related	Y
80058/019 28 yo f	Fetal distress syndrome/severe	346 d postdose 2x20hrs	Defintiely not related	Y
83827/019 37 yo f	Antepartum hemorrhage/mild	59d postdose 1x8d	Definitely not related	Y
80619/019 27 yo f	Ruptured ectopic pregnancy	87d postdose 2x6d	Definitely not related	Y

Source: STN125126/-(b)(4)-, Summary of clinical safety, Appendix 2.7.4:109, p. 1194-1219

TABLE 65

Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period) Subjects Who Were Pregnant at Any Time During the Study (Alum Control Recipients) (Studies HPV-013, -015, -016, -018, and -019)

AN (age)	Event/grade	Time	Investigator attribution	Recovered
20034/011 (17 yo f)	Pre-eclampsia/mild	283d postdose 1 x 1d GP+HB	Definitely not related	Y
24399/-11 (22 yo f)	Premature labor/mild	248d postdose 3x4d GP+HBP	Probably not related	Y
25191/011 (23 yo f)	Pre-eclampsia/severe	279d postdose 2x11d GP+HB	Probably not related	Y
20386/011 (17 yo f)	Accidental poisoning/severe	427d postdose 3 x 23 hrs GP+HBP	Definitely not related	Y
24211/011 (16 yo f)	Overdose/mild	542d postdose 3 x 1d GP+HB	Definitely not related	Y
24919/011 (21 yo f)	Fetal distress syndrome/mild	254d postdose 2x 50 min GP+HBP	Definitely not related	Y
20260/011 (19 yo f)	Breech presentation	325 d postdose 2x 1 d GP+HB	Definitely not related	Y
20325/011 (22yo f)	Convulsion/severe Headache/severe	2d postdose 2 x 11 d GP+HBP	Probably not related	Y
20409/011 (17 yo f)	Overdose/mild	D1 of Dose 1x1d GP+HBP	Definitely not related	Y
24034/011 (22yo f)	Cephalo-pelvic disproportion	277d postdose 1x1d GP+HBP	Definitely not related	Y
24058/011 (18 yo f)	Post-procedural hemorrhage/moderate Cervix hemorrhage.moderate	911d postdose 3 x 2hrs HP+HB	Definitely not related	Y
24673/011 (21 yo f)	Failed induction of labor	341 d postdose 2x1d GP+HB	Definitely not related	Y
34207/012 (20 yo f)	Pre-eclampsia	242d postdose 2 x 14 d	Definitely not related	Y
32610/012 (22yo f)	Failed trial of labor/severe	302 d postdose 3 x 1d	Definitely not related	Y
30942/012 (19yo f)	Overdose/mild	Day 1 of dose 1x1d &D1 of dose 2x1d	Definitely not related	Y
31094/012 (22yo f)	Endometritis decidual/moderate	271d postdose 3x4d	Definitely not related	Y
30830/012 920 yo f)	Post-procedural hemorrhage/severe	575d postdose 3x9d	Definitely not related	Y
33565/012 (21 yo f)	Dizziness/moderate	44d postdose 2x2d	Definitely not related	Y
32282/012 (20 yo f)	Abortion threatened/mild Varicella/moderate	105d postdose 1x4d 121d postdose 1x7d 175d postdose 1x29d	Definitely not related	Y
34037/012 (19yo f)	Oligohydramnios/moderate	265d postdose 1x18d	Definitely not related	Y
40119/015 (17 yo f)	Cephalo-pelvic disproportion/severe Failed trial of labor/severe	347d postdose 2x5d	Definitely not related	Y
40161/015 (19 yo f)	Failed trial of labor/severe	262d postdose 1x4d	Definitely not related	Y
57596/015 (21 yo f)	Premature rupture of membranes/severe	214d postdose 2x26d	Definitely not related	Y
40778/015 (23 yo f)	UTI/moderate	7d postdose 3x4d	Definitely not related	Y
55176/015 (20 yo f)	Abdominal pain	111d postdose 2 (cont)	Definitely not related	Y
44485/015 (23 yo f)	Ectopic pregnancy/severe	39d postdose 3x2d	Definitely not related	Y
54091/015 (23 yo f)	Aortic valve disease/moderate Hypertension/moderate	2d postdose 3x1.08mo	Definitely not related	Y
42023/015 (20 yo f)	Uterine infection/severe	94d postdose 1x2d	Probably not related	Y

TABLE 65 (CONT.)
Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period) Subjects Who Were Pregnant at Any Time During the Study (Alum Control Recipients) (Studies HPV-013, -015, -016, -018, and -019)

AN (age)	Event/grade	Time	Investigator attribution	Recovered
46010/015 (19 yo f)	Anaphylactic reaction/moderate	12 d postdose 1x10 min	Definitely related	Y
56463/015 20 yo f	Abortion threatened/moderate	53d postdose 2x2d	Definitely not related	Y
46543/015 (19 yo f)	Abortion threatened/mild	158d postdose 2x3d	Definitely not related	Y
54534/015 (19 yo f)	Pneumonia/moderate	14d postdose 1x4d	Definitely not related	Y
47991/015 (23 yo f)	Imminent abortion/mild Premature labor/mild	217d postdose 2x4d 282d postdose 2x4d	Definitely not related	Y
47999/015 (19yo f)	Cervical incompetence/moderate	191d postdose 3x3.15mo	Definitely not related	Y
48447/015 (23 yo f)	Abortion threatened	84d postdose 3x3d	Probably not related	Y
55943/015 (20 yo f)	Prolonged pregnancy/mild	325d postdose 2x3d	Definitely not related	Y
56248/015 (18 yo f)	Fetal malpresentation/mild Asphyxia/severe	252de postdose 2x3 d 256d postdose 2x1s	Definitely not related	 Fatal
56346/015 (21 yo f)	Chills, headache, pyrexia /moderate	D1 of dose 2x1d	Possibly related	Y
56352/015 (23 yo f)	Cephalo-pelvic disproportion/mild	283d postdose 3x3d	Definitely not related	Y
56634/015 (22 yo f)	Breech presentation/moderate Premature labor/moderate	298d postdose 2x17d 312d postdose 2x3d	Definitely not related	Y
57502/015 (20 yo f)	Cephalopelvic disproportion/mild	378d postdose 2x3d	Definitely not related	Y
41638/015 (18 yo f)	Pneumomediastinum/moderate	275d postdose d1x6d	Definitely not related	Y
47246/015 (17 yo f)	Vaginal laceration/severe	7d postdose 3x26d	Definitely not related	Y
47880/015 (22 yo f)	Cephalopelvic disproportion/severe	266d postdose 3x1d	Definitely not related	Y
48560/015 (20 yo f)	Abortion threatened/moderate	70d postdose 1x6d	Definitely not related	Y
45433/015 16 yo f	Brow presentation/mild Neonatal asphyxia/mild	297d postdose 3x1d	Definitely not related	Y
42196/015 16 yo f	Pre-eclampsia/mild	301d postdose 3x5d	Definitely not related	Y
56019/015 21 yo f	Pregnancy induced hypertension/severe UTI/severe	303 d postdose 3x14d 323d postdose 3x6d	Probably not related	Y
47854/015 23 yo f	Chemical poisoning/severe	15d postdose 3x3d	Definitely not related	Y
46132/015 17 yo f	Fetal distress syndrome/severe	247 d postdose 3x1d	Definitely not related	Y
47825/015 19 yo f	Fetal distress syndrome/severe	255d postdose 1x1d	Definitely not related	Y
48745/015 20 yo f	Gastroitestinal infection/moderate	3 d postdose 1x2d	Definitely not related	Y
54339/015 18 yo f	Prolonged pregnancy/moderate	292d postdose 1x1d	Definitely not related	Y
49473/015 22 yo f	Cephalopelvic disproportion Failed trial of labor	304d postdose 1x6d	Definitely not related	Y
56535/015 23 yo f	Cervix dystocia/mild	345d postdose 2x12 hrs	Definitely not related	Y
47415/015 19 yo f	Premature labor/mild	225 d postdose 1x2d 243d postdose 1x1d	Probably not related	Y
47745/015 19 yo f	Premature labor/moderate	240d postdose 1x1d 262d postdose 1x1d	Probably not related	Y

TABLE 65 (CONT.)
Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period) Subjects Who Were Pregnant at Any Time During the Study (Alum Control Recipients) (Studies HPV-013, -015, -016, -018, and -019) [cont]

AN (age)	Event/grade	Time	Investigator attribution	Recovered
49394/015 18 yo f	Cervical incompetence/moderate Premature labor/moderate	1053d postdose 3 (cont.) 1053d postdose 3x1d	Probably not related	Y
80212/019 25 yo	Fallopian tube cyst/severe Premature labor/severe Premature labor/severe Premature labor/severe	61d postdose 2x2d 201d postdose 2x5d 238 d postdose 2x2d 239 d postdose 2x5d	Definitely not related	Y
81687/019 33 yo f	False labor/severe	237 d postdose 2x2d	Definitely not related	Y
82043/019 27 yo f	Ectopic pregnancy/moderate	11d postdose 1x1d	Probably not related	Y
84815/019 38 yo f	Blighted ovum, gestational trophoblastic tumor/severe	101 d postdose 1x1d	Definitely not related	Y
80537/019 (32 yo f)	Hypertensive crisis/severe	259d postdose 1x2d	Definitely not related	Y

Source: STN125126/-(b)(4)-, Summary of clinical safety, Appendix 2.7.4:109, p. 1194-1219

Medical Conditions in Infants born to subjects who received Gardasil in Studies HPV-007 extension, -013, -015, -016, -018, and -019:

The sponsor has prepared an updated summary of infant adverse outcomes by System Organ Class (Systemic-Neonatal). The sponsor has broken down adverse events in subjects by the following classification: Systemic Neonatal (any SAE from birth through 6 weeks of age); Systemic-Lactation (any SAE during lactation not within the first 6 weeks of life); Systemic-Other (any SAE that are not included in the other two categories). Table 66 presents the proportions of neonates with an SAE by System Organ Class for the first 6 weeks of life. The summary table includes subjects who participated in study 007 extension, but these are not included in the detailed tables.

Systemic-Neonatal serious adverse experiences included (1) congenital anomalies; (2) events recorded as 'other medical events'; and (3) medical events that occurred after the immediate neonatal period and through 6 weeks following birth:

- A total of 117 infants born to study subjects who received Gardasil (representing 8.1% of live births among subjects who received Gardasil) experienced a systemic-neonatal serious adverse event. The 3 most common systemic-neonatal serious adverse events occurred among infants of subjects who received Gardasil were: premature baby (36), neonatal jaundice (24), neonatal respiratory distress syndrome (9).
- A total of 94 infants born to study subjects who received control (representing 6.6% of live births among subjects who received control) experienced a systemic-neonatal serious adverse experiences. The 3 most common systemic-neonatal serious adverse events that occurred among infants of subjects who received control were: premature baby (20), neonatal jaundice (18) and neonatal respiratory distress syndrome (12).

TABLE 66
Summary of Infant Serious Adverse Events by System Organ System Class (neonatal) (Studies HPV-007 extension, -013, -015, -016, -018, and -019)

SOC	Gardasil N=1447	Control N=1424
Cardiac Disorders	3 (0.2%)	2 (0.1%)
Congenital, familial, and genetic disorders	35 (2.4%)	28 (2.0%)
Endocrine disorders	0 (0.0%)	1 (0.1%)
Eye disorders	1 (0.01%)	0 (0.0%)
Gastrointestinal disorders	6 (0.4%)	3 (0.2%)
General disorders and administration site disorders	0 (0.0%)	3 (0.2%)
Hepatobiliary disorders	0 (0.0%)	2 (0.1%)
Immune system disorders	2 (0.1%)	1 (0.1%)
Milk allergy	1 (0.1%)	0 (0.0%)
Rh incompatability	1 (0.1%)	1 (0.1%)
Infections and infestations	26 (1.8%)	15 (1.0%)
Neonatal pneumonia	2 (0.1%)	2 (0.1%)
Pneumonia	2 (0.1%)	1 (0.1%)
Respiratory tract infection	1 (0.1%)	1 (0.1%)
Sepsis neonatal	4 (0.3%)	4 (0.3%)
Injury, poisoning and procedural complications	1 (0.1%)	0 (0.0%)
Investigations	2 (0.1%)	0 (0.0%)
Metabolism and Nutrition disorders	14 (1.0%)	5 (0.4%)
Neoplasms benign, malignantm including cysts	1 (0.1%)	1 (0.1%)
Nervous system disorders	2 (0.1%)	2 (0.1%)
Pregnancy, puerperium, and perinatal conditions	71 (4.9%)	42 (2.9%)
Fetal distress syndrome	0 (0.0%)	1(0.1%)
Fetal growth retardation	2 (0.1%)	0 (0.0%)
Jaundice	3 (0.2%)	0 (0.0%)
Jaundice neonatal	24 (1.6%)	18 (1.3%)
Low weight	1 (0.1%)	0 (0.0%)
Premature baby	36 (2.5%)	20 (1.4%)
Small for dates baby	4 (0.3%)	1 (0.1%)
Renal and urinary disorders	2 (0.1%)	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders	28 (1.9%)	21 (1.5%)
Apnea	1 (0.1%)	1 (0.1%)
Infantile apneic attack	0 (0.0%)	1 (0.1%)
Neonatal respiratory distress syndrome	9 (0.6%)	12 (0.8%)
Neonatal respiratory failure	2 (0.1%)	0 (0.0%)
Sleep apnea syndrome	1 (0.1%)	0 (0.0%)
Transient tachypnea of newborn	4 (0.3%)	1 (0.1%)

Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Appendix 2.7.4:100, p. 1134 - 1137

Reviewer's Comment: The congenital anomalies are presented within the section on updated congenital anomalies.

The additional infants with SAEs in the neonatal period as reported in the summary of clinical safety (12/2/07) are shown in Table 67 below (see table 309 in the original review for infants with SAEs in the neonatal period who were reported at the time of original licensure). The infants with congenital anomalies are already discussed in the section above, so are not included in Table 67 below. As already discussed, pregnancies

were not studied in a controlled fashion, but most of the events added in the follow-up period occurred well after potential exposure to the study material.

TABLE 67
Studies HPV-013, -015, -016, -018, and -019: Listing of Additional SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to test product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (New Data) [Excludes Congenital Anomalies] (12/2/07)**

Gardasil			Control		
Event	AN (study)	Time after dose/age (Outcome)	Event	AN	Time after dose/age (Outcome)
Neonatal jaundice					
Apnea, dyspnea with neonatal jaundice	[24604] (011)	947 d postdose 3 [G+HB]/1d (R)		25345 (011)	916 d postodse 3/HB+GP/1d(R)
Neonatal jaundice	30804 (012)	911 d postdose 3/4d (R)	With aspiration	[31534] (012)	1010 &1015d p0ostdose 3/1&6d/(R)
With NRDS	[32765] (012)	891 d postdose 3/1d (R)		45889 (015)	540 d postdose 3/6d/(R)
	49439 (015)	917 d postdose 3/5d (R)		45895 (015)	834 d postdose 3/3d (R)
	56556 (015)	889 d postdose 3/5d (R)		46109 (015)	924 d postdose 3/2d/(R)
	57040 (015)	386 d postdose 3/10d (R)	Neonatal hyperbilrubinemia with apnea	[54192] (015)	945 d postdose 3/11d (R)
With GERD	43173 (015)	687 & 728 d postdose 3/2&43d/(R)		48745 (015)	918 d postdose 3/6d (R)
Bacterial sepsis w/cerebral hemorrhage, respiratory failure, neonatal jaundice, premature baby, small for dates baby	**[54673] (015)**	**920 days postdose 3/1d (F)**		30258 (012)	1293d postdose 3/3d (R)
	46113 (015)	1172 d postdose 3/1d (R)	With liver disorder	30479 (012)	1047d postdose 3(R) Liver disorder dx'd 62 d of life, NR
With respiratory distress, prematurity	[54001] (015)	1327 & 1329 d postdose 3/5&7d (R)		31310 (012)	1522d postdose 3/1d (R)
With prematurity, hypocalcemia	[57518] (015)	1084 & 1086 d postdose 3/2&4d (R)		40129 (015)	1429d postdose 3/1d (R)
	56509 (015)	1275d postdose 3/1d (R)		49532 (015)	1248d postdose 3/5d (R)
With fetal growth retardation, low weight, polycythemia	[82031] (019)	417d postdose 3/1d (R)			
	81271 (019)	585d postdose 3/9d (R)			
Neonatal sepsis					
Bacterial sepsis w/cerebral hemorrhage, respiratory failure, neonatal jaundice, premature baby, small for dates baby	**[54673] (015)**	**920 days postdose 3/1d (F)**	Staphylococcal scalded skin syndrome	56212 (015)	728 d postdose 3/8d (R)
With prematurity	[31200] (012)	1165 d postdose 3/1d (R)	**Sepsis with Asphyxia, Hypoxic encephalopathy**	**[41303] (015)**	**1227d postdose 3/1d (F)**
	46564 (015)	1060d postdose 3/3d (R)	Neonatal infection	81869 (019)	255d postdose 3/1d (R)
Bacterial sepsis (with cryptorchism)	49779 (015)	972d postdose 3/2d (R)			

TABLE 67 (CONT.)
Studies HPV-013, -015, -016, -018, and -019: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to test product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (New Data) [Excludes Congenital Anomalies] (12/2/07)**

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	Event	AN	Time after dose/age (Outcome)
Prematurity					
Bacterial sepsis w/cerebral hemorrhage, respiratory failure, neonatal jaundice, premature baby, small for dates baby	**[54673] (015)**	**920 days postdose 3/1d (F)**		46236 (015)	797 d postdose 3/1d (R)
With respiratory failure	**[49885] (015)**	**937 d postdose 3/1d [F]**		44961 (015)	1008 d postdose 3/1d (R)
	55148 (015)	952 d postdose 3/1d (R)	**With NSRD**	**[42392] (015)**	**1087 d postdose 3/1d (F)**
	25403 (011)	1164 d postdose 3 G+HBP/1d (R)		31104 (012)	1177d postdose 3/1d (R)
	31812 (012)	**1345 d postdose 3/1d (F)**		43189 (015)	1235d postdose 3/1d (R)
With neonatal sepsis	**[**31200] (012)	1165 d postdose 3/1d (R)		49394 (015)	1053d postdose 3/1d (R)
	33516 (012)	1189 d postdose 3/1d (R)	With bronchiolitis	[80754] (019)	446d postdise 3/149d (R)
With respiratory distress, neonatal jaundice	[54001] (015)	1323 d postdose 3/1d (NR)			
With jaundice neonatal, hypocalcemia	[57518] (015)	1083 d postdose 3/1d (R)			
	45260 (015)	1139d postdose 3/1d (R)			
	45266 (015)	1162d postdose 3/1d (R)			
	56060 (015)	1166d postdose 3 /1d (R)			
	46297 (015)	1071d postdose 3/1d x399d(R)			
	54230 (015)	**1147d postdose 3/1d (F)**			
	45492 (015)	1306d postdose 3 (R)			
With NRDS	[44024] (015)	953d postdose 3/1d (R)			
	55895 (015)	1227d postdose 3/1d (R)			
	46363 (015)	1198d postdose 3/1d (R)			
Jaundice with transient tachypnea of newborn,hypoglycemia	[84025] (019)	256d postdose3/1 & 11d (R)			
Small for dates					
Bacterial sepsis w/cerebral hemorrhage, respiratory failure, neonatal jaundice, premature baby, small for dates baby	**[54673] (015)**	**920 days postdose 3/1d (F)**			
Fetal growth retardation					
With jaundice, low weight, polycythemia	[82031] (019)	417d postdose 3/1d (R)			

TABLE 67 (CONT.)
Studies HPV-013, -015, -018, and -019: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to test product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (New Data) [Excludes Congenital Anomalies] (12/2/07)**

Gardasil			Placebo		
		NRDS			
Event	AN (study)	Time after dose/age (Outcome)	AN (study)	Event	Time after dose/age (Outcome)
With neonatal jaundice	[32765] (012)	891 d postdose 3/1d (R)		24567 (011)	1024 d postdose 3 HBP+GP/1d (R)
	33015 (012)	967 d postdose 3/19d (R)	**With NSRD**	**[42392] (015)**	**1087 d postdose 3/1d (F)**
	30501 (012)	1266 d postdose 3/1d (R)	With Hypoglycemia, hypothermia	[30359] (012)	1288d postdose 3/1d (R)
With neonatal juandice, prematurity	[54001] (015)	1323 postdose 3/1d (R)		84231 (019)	257d postdose 3/1d (R)
With prematurity	[44024] (015)	953d postdose 3/1d (R)		82049 (019)	364d postdose 3/1d (R)
	84824 (019)	393d postdose 3/1d (R)			
Respiratory events/infection					
Pneumonia, omphalitis	[25134] (011)	887 d postdose 3 [G+HBP]/15 d (R)	With neonatal jaundice	[31534] (012)	1010 &1015d p0ostdose 3/1&6d/(R)
Neonatal aspiration, bronchiolitis	32138 (012)	901 & 928 d postdose 3/1&38d/(R)	Apnea, neonatal hyperbilrubinemia	[54192] (015)	945 d postdose 3/11d (R)
Pneumonia	41005 (015)	1068 d postdose 3/98d (R)	Pneumonia	24308 (011)	1158d postdose 3/2d (R)
Respiratory failure with prematurity	**[49885] (015)**	**937 d postdose 3/1d [F]**	Hypoxia	33468 (012)	1010d postdose 3/1 (R)
Bacterial sepsis w/cerebral hemorrhage, respiratory failure, neonatal jaundice, premature baby, small for dates baby	**[54673] (015)**	**920 days postdose 3/1d (F)**	**Asphyxia, Hypoxic encephalopathy, Sepsis**	**[41303] (015)**	**1227d postdose 3/1d (F)**
	47829 (015)	1020d postdose 3/1d (R)	Bronchiolitis with prematurity	[80754] (019)	446d postdise 3/149d (R)
Bronchiolitis	54322 (015)	1020 d postdose 3/11d (R)	Bronchiolitis	80566 (019)	459d postdose 3/177d (R)
Bronchiolitis	49530 (015)	1012d postdose 340d (R)	Neonatal pneumonia	81918 (019)	55d postdose 3/1d (R)
Apnea, dyspnea with neonatal jaundice	[24604] (011)	947 d postdose 3 [G+HB]/1d (R)	Transient tachypnea of newborn	81856 (019)	460d postdose 3/1d (R)
Transient tachypnea of newborn with jaundice, hypoglycemia	[84025] (019)	256d postdose3/1 & 11d (R)			

TABLE 67 (CONT.)
Studies HPV-013, -015, -018, and -019: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to test product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (New Data) [Excludes Congenital Anomalies] (12/2/07)**

Gardasil			Placebo		
Others					
Omphalitis, pneumonia	[25134] (011)	887 d postdose 3 [G+HBP]/15 d (R)	**Neoplasm**	**24923 (011)**	**791 d postdose 3 GP+HB/1d (F)**
GERD	42418 (015)	1037 d postdose 3/11d/(C)	Hypoglycemia	41733 (015)	1001 d postdose 3/28d (R)
Hypoglycemia	41724 (015)	971 d postdose 3/1d (R)	Rh isoimmunization	24574 (011)	877d postdose 3/1d (R)
Hypoglycemia	54819 (015)	1430d postdose 3/1d (R)	Eye infection	32246 (012)	1313d postdose 3/7d (R)
Viral infection	40877 (015)	959 d postdose 3/43d (R)	Hypoglycemia, hypothermia, NRDS	[30359] (012)	1288d postdose 3/1d (R)
Milk allergy	44479 (015)	921 d postdose 3/24d (R)	Umbilical cord prolapse	81061 (019)	306d postdose 3/1d (R)
Hypocalcemia (with prematurity and neonatal jaundice)	[57518] (015)	1085 d postdose 3/3d (R)			
Cerebral hemorrhage, hemorrhagic anemia, neonatal asphyxia, umbilical rupture, renal impairment	40305 (015)	1403d postdose 3/1d (R)			
Dyspnea, hypoglycemia, heart sounds abnormal	41351 (015)	1175 & 1177d postdose 3/1&3d/(R,R,NR)			
Necrotizing enterocolitis (with adrenal neopalsma)	80244 (019)	533d postdose 3/14d (NR)			
Polycythemia with fetal growth retardation, low weight	[82031] (019)	417d postdose 3/1d (R)			
Hypoglycemia with jaundice, transient tachypnea of newborn	[84025] (019)	256d postdose3/1 & 11d (R)			

[infant in more than one category]
Entire study period includes data from the beginning of the studies through 6/15/06 for HPV-013 and HPV-015, 10/3/06 for study HPV-007, and 10/24/06 for study HPV-018.
*For Protocol 016, the entire study period includes Day 1 through the end of the study (Month 12).
**Infant has SAE in post-neonatal period as well.
***Potentially Exposed = mother received study material and baby was born at any time after vaccination
R=Recovered
F=Fatal
C=Continuing
GP=Gardasil placebo; HB=hepatitis B vaccine; HBP=hepatitis B placebo
Source: STN 125126/0**,** Summary of Safety, Appendix 2.7.4:44, p. 920-934, 3/8/06 and p. 465-466;
STN 125126/419.0, Summary of Safety, Appendix 2.7.4:18, p. 920-926
STN 125126/-(b)(4)-, Summary of Safety, Appendix 2.7.4:99, p. 1125-

Serious Adverse Events were also noted outside the neonatal period.
The sponsor provided a summary table of events noted in time outside the neonatal period.

- A total of 56 infants born to study subjects who received Gardasil (representing 3.9% of live births among subjects who received Gardasil) experienced a Systemic-Other Serious Adverse Event. The 3 most common categories of Systemic-Other Serious Adverse Events observed in subjects who received Gardasil were: pneumonia/bronchopneumonia (9), bronchiolitis (8), and diarrhea and pyrexia (both 4).

- A total of 50 infants born to study subjects who received placebo (representing 3.5% of live births among subjects who received placebo) experienced a Systemic-Other Serious Adverse Event. The 3 most common categories of Systemic-Other Serious Adverse Events observed in subjects who received placebo were: pneumonia/bronchopneumonia (19), bronchiolitis (11), and convulsion/febrile convulsion (6).

SAEs which occurred outside the neonatal period are included in Table 68 below. It is noted that the proportions are comparable for the treatment groups. In this group of infants, the proportions of infants with a respiratory illness of bronchiolitis and pneumonia are slightly higher in the control group.

TABLE 68
Summary of Infant Adverse Experiences by System Organ Class Systemic – Other (Studies HPV-007, -013, -015, -016, -018, and -019)

SOC	Gardasil N=1447	Control N=1424
Blood and lymphatic system disorders	1 (0.1%)	1 (0.l%)
Cardiac Disorders	1 (0.1%)	4 (0.3%)
Congenital, familial, and genetic disorders	7 (0.5%)	7 (0.5%)
Ear and labyrinth disorders	1 (0.1%)	0 (0.0%)
Gastrointestinal disorders	9 (0.6%)	6 (0.4%)
General disorders and administration site disorders	9 (0.6%)	9 90.6%)
Infections and infestations	34 (2.3%)	46 (3.2%)
Bronchiolitis	8 (0.6%)	11 (0.8%)
Pneumonia/Bronchopneumonia	9 (0.6%)	19 (1.3%)
Injury, poisoning and procedural complications	2 (0.1%)	1 (0.1%)
Metabolism and Nutrition disorders	2 (0.1%)	2 (0.1%)
Nervous system disorders	1 (0.1%)	0 (0.0%)
Pregnancy, puerperium, and perinatal conditions	3 (0.2%)	2 (0.1%)
Renal and urinary disorders	1 (0.1%)	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders	4 (0.3%)	6 (0.4%)
Skin and subcutaneous disorders	0 (0.0%)	1 (0.1%)

Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Appendix 2.7.4:103, p. 1161-3

Reviewer's Comment: The time intervals between the time of vaccination and events were quite long in all instances of the additional events noted. The proportions were similar in each treatment group.

Serious Adverse Events in Infants who were Breastfeeding and potentially exposed to Gardasil

In the group that received Gardasil, 581 subjects in Protocols 013, 015, 016, and 019 indicated they were breastfeeding at any time during the study. Of these 581 subjects, 465 indicted they were breastfeeding during the vaccination phase.

- A total of 27 infants born to study subjects who received Gardasil (representing 1.9% of live births among subjects who received Gardasil) experienced a Systemic-Lactation Serious Adverse Experience. The 3 most common categories of Systemic-Lactation Serious Adverse Experiences observed in subjects who received Gardasil were: pneumonia/bronchopneumonia (11), bronchiolitis (6), and gastroenteritis (3).

In the group that received alum control, 551 subjects in Protocols 013, 015, and 019 indicated they were breastfeeding at any time during the study. Of these 551 subjects, 377 indicated they were breastfeeding during the vaccination phase.

- A total of 12 infants born to study subjects who received placebo (representing 0.8% of live births among subjects who received placebo) experienced a Systemic-Lactation Serious Adverse Experience. The 2 most common categories of Systemic-Lactation Serious Adverse Experiences observed in subjects who received placebo were: pneumonia/bronchopneumonia (3) and convulsion/febrile convulsion (2).

TABLE 69
Summary of Infant Adverse Experiences by System Organ Class
Systemic – Lactation (Studies HPV-007, -013, -015, -016, -018, and -019)

SOC	Gardasil N=1447	Control N=1424
Blood and lymphatic system disorders	1 (0.1%)	0 (0.0%)
Congenital, familial, and genetic disorders	1 (0.1%)	0 (0.0%)
Gastrointestinal disorders	2 (0.1%)	1 (0.1%)
General disorders and administration site disorders	1 (0.1%)	2 (0.1%)
Hepatobiliary disorders	0 (0.0%)	1 (0.1%)
Infections and infestations	24 (1.7%)	7 (0.5%)
Bronchiolitis	6 (0.4%)	1 (0.1%)
Pneumonia/Bronchopneumonia	11 (0.8%)	3 (0.2%)
Gastroenteritis	3 (0.2%)	2 (0.1%)
Injury, poisoning and procedural complications	1 (0.1%)	0 (0.0%)
Metabolism and Nutrition disorders	1 (0.1%)	0 (0.0%)
Nervous system disorders	1 (0.1%)	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders	2 (0.1%)	1 (0.1%)
Skin and subcutaneous disorders	1 (0.1%)	0 (0.1%)

Source: STN 125126/-(b)(4)-, Summary of Clinical Safety, Appendix 2.7.4:112, p. 1227

Reviewer's Comment: At the time of the original licensure, an imbalance was noted in the proportions of subjects with respiratory tract infections in infants who were potentially exposed to Gardasil through vaccinations of their mothers. In the 8 additional infants who developed a respiratory infection after potential exposure to Gardasil, seven (7) subjects were exposed at app. 10 months or greater after the mother was vaccinated. One of the subjects was exposed 27 days prior to the exposure in utero. This imbalance was noted at the time of original licensure, and such events were varied in intervals after dosing of the mother, and were not consistently noted after any specific dose. In infants reported at the time of original licensure, there was no report of these events recurring upon revaccination of the mothers. The number of respiratory events which occurred within 30 days of vaccination of the mothers were 6 in the Gardasil group as compared to 2 in the control. A complete listing of these events are noted in Tables 70 and 71.

TABLE 70

Studies HPV-013, -015, -016, -019: SAEs Reported in Infants of Vaccinated Subjects who were potentially Exposed to Gardasil (Entire Study Period-Lactation*) Safety Population**

Maternal AN (Study)	AE	Infant Age at AE	Days postdose	Duration of AE	Outcome
56355 (015)	Pneumonia (severe) Anomalous pulmonary venous malformation (severe) [EDCn 57 days postdose 2 see congenital anomalies]	69 days 71 days	19 days postdose 3 Gardasil 21 days postdose 3 Gardasil	19 days 21 days	Fatal
47942 (015)	Bronchopneumonia (moderate)	91 days	12 days postdose 1 Gardasil)	11 days	Recovered
60574 (016)	Pneumonia (severe)	277 days	20 days postdose 2 Gardasil	5 days	Recovered
24012 (011)	Bronchitis (moderate)	662 days	22 postdose 3 Gardasil + hep B placebo	146 days	Recovered
57048 (015)	Asthma (severe) Pneumonia (severe)	589 days	24 days postdose 3 Gardasil	8 days	Recovered
56572 (015)	Pneumonia (severe)	116 days	29 days postdose 1 Gardasil	8 days	Recovered
47369 (015)	URI (severe) Gastroenteritis (severe) Pneumonia (severe)	334 days 338 days 338 days	44 days postdose 1 Gardasil 48 days post above	20 days 16 days 16 days	Recovered Recovered
33654 (012)	Bronchiolitis (moderate)	305 days	112 days postdose 2 Gardasil	10 days	Recovered
47857 (015)	Pneumonia (moderate)	529 days	129 days postdose 2 gardasil	13 days	Recovered
32536 (012)	Bronchiolitis (moderate)	261 days	150 days postdose 3 Gardasil	3 days	Recovered
20420 (011)	Bronchial obstruction (severe) Diarrhea (severe)	201 days	155 days posdose 3 Gardasil + hep B vaccine	7 days 7 days	Recovered
25205 (011)	Pneumonia (severe) Gastroenteritis (moderate)	337 days 401 days	167 days postdose 3 Gardasil + hep B placebo 231 days post above	13 days 1 day	Recovered Recovered
31307 (012)	Cellulitis (moderate)	203 days	84 days postdose 2 Gardasil	12 days	Recovered
42699 (015)	Gastroenteritis (severe)	718 days	38 Days postdose 2 Gardasil	8 days	Recovered
56031 (015)	Head injury (severe)	346 days	23 days postdose 3 Gardasil	3 days	Recovered
47862 (015)	Dehydration (moderate)	263 days	201 days postdose 3 Gardasil	2 days	Recovered
56732 (015)	Diarrhea (moderate)	576 days	126 days postdose 3 Gardasil	3 days	Recovered
24866 (011)	*Bronchopneuomonia (mild)*	*216 days*	*1133 days postdose 3 Gardasil*	*24 hrs*	*Recovered*
31345 (012)	*Bronchiolitis (severe)*	*10 days*	*1178 days postdose 3 Gardasil*	*18 days*	*Recovered*
33516 (012)	*Apparent life-threatening event (severe)*	*26 days*	*1214 days postdose 3 Gardasil*	*13 days*	*Recovered*
54187 (015)	*Bronchopneumonia (moderate)*	*51 days*	*1287 days postdose 3 Gardasil*	*1 day*	*Recovered*
80620 (019)	*Bronchopneumonia (severe)*	*137 days*	*27 days postdose 2 Gardasil*	*7 days*	*Recovered*
82055 (019)	*Epilepsy (moderate)*	*34 days*	*381 days postdose 3 Gardasil*	*Cont.*	*Not recovered*
82071 (019)	*Bronchiolitis (moderate)*	*48 days*	*522 days postdose 3 Gardasil*	*6 days*	*Recovered*
81523 (019)	*Abscess, anemia, seborrheic dermatitis(moderate)*	*74-76 days*	*7, 8, and 9 days postdose 3 Gardasil*	*9, 106, 119 days*	*Recovered*
81977 (019)	*Bronchiolitis (severe)*	*64 days*	*356 days postdose 3 Gardasil*	*4 days*	*Recovered*
81999 (019)	*Bronchiolitis(moderate)*	*170 days*	*555 days postdose 3 Gardasil*	*11 days*	*Recovered*

BOLD-present at time of licensure

Italic-new data

*For Protocol 016, the entire study period includes Day 1 through the end of the study (Month 12). For Protocol s 011 and 012, the entire study period includes Day 1 through the primary fixed case analysis for Protocol 013 (15-Jul-2005). For Protocol 015, the entire study period includes Day 1 through the primary fixed case analysis (10-Jun-2005).;

** Potentially Exposed = mother received study material and baby was born at any time after vaccination

Source: From Appendix 2.7.4:195, p. 1076-9, Original BLA; STN 125126/-(b)(4)-, Appendix 2.7.4:110, p. 1220-1224.

TABLE 71

Studies HPV-013, -015, and -016: SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed to Placebo (Entire Study Period-Lactation) Safety Population**

Maternal AN (Study)	AE	Infant Age at AE	Days postdose	Duration of AE	Outcome
25169 (011)	Pneumonia (moderate)	302 d	3 d postdose 2	3 days	Recovered
47415 (015)	Bronchiolitis (moderate)	233 d	25 days postdose 3	8 days	Recovered
47374 (015)	Asthma (severe)	369 d	46 days postdose 1	2 days	Recovered
20442 (011)	Bronchopneumonia (moderate)	189 d	90d postdose 2	16 days	Recovered
54213 (015)	Pneumonia (mild)	209 d	135 days postdose 2	24 hours	Recovered
24639 (011)	Viral infection (moderate)	543 d	93 d postdose 2	3 days	Recovered
42394 (015)	Gastroenteritis (severe)	374 d	16 days postdose 3	2 days	Recovered
54218 (015)	Gastroenteritis (severe)	407 d	107 days postdose 2	2 days	Recovered
46022 (015)	Febrile convulsion (post wheezing with fever)	477 d	36 days postdose 3	12 days	Recovered
31528 (012)	*Hematemesis (mild)*	*6days*	*1210 days postdose 3*	*4 days*	*Recovered*
80944 (019)	*Pyrexia (severe)*	*191 days*	*40 days postdose 3*	*27 days*	*Recovered*
83436 (019)	*Hyperbilrubinemia (moderate)*	*8 days*	*742 days postdose 3*	*3 days*	*Recovered*

BOLD-present at time of licensure; *Italic-new data*

*For Protocol 016, the entire study period includes Day 1 through the end of the study (Month 12). For Protocol s 011 and 012, the entire study period includes Day 1 through the primary fixed case analysis for Protocol 013 (15-Jul-2005). For Protocol 015, the entire study period includes Day 1 through the primary fixed case analysis (10-Jun-2005).

** Potentially Exposed = mother received study material and baby was born at any time after vaccination

Source: From Appendix 2.7.4:195, p. 1076-9, original BLA; STN 125126/-(b)(4)-, Appendix 2.7.4:110, p. 1220-1224.

TABLE 72
Studies HPV-007, -013, -015, -016, -018, -019: Deaths in Infants Potentially Exposed* to Study Material During Follow-up of Phase III studies (12/2/07)

Gardasil			Placebo		
Event	AN	Time after dose/age	Event	AN	Time after dose/age
Congenital Anomalies					
Heart disease congenital, duodenal atresia, trisomy 21	47851	EDCn =33/postdose 1 Time of event = 304 days postdose 1 (1 day age)	Amniotic band syndrome	40330	EDCn = 343/postdose 3; Time to event = 469 days postdose 3 (stillborn)
Anomalous pulmonary venous connection (with pneumonia)	56355	EDCn = 57/postdose 2; Time to event = 407 days postdose 2 (app. 10 wks. Age)	Congenital anomaly	46561	EDCn = 498/postdose 3 Time to event = 659 days postdose 3 (stillborn)
Low set ears, limb malformation	24836	EDCn = 285/postdose 3; Time to event = 482 days postdose 3 (1 day age)	(Right Atrial Neoplasm)	24923	Time of event =17 months/postdose 3 (+ Hep B) (3 days of age)
			Fallot's tetrology	44067	Time to event = 1025 days postdose 3 (1 day)
Systemic Neonatal					
With prematurity, fetal growth retardation, bronchiolitis	[54184] (015)	Time of event = 270-298 d postdose 3/1d-28 d (1 day of age)	Prematurity	25312 (011)	Time of event = 643 d postdose 3/1d of age
Placental insufficiency	45312 (015)	Time to event = 1320 days postdose 3 (1 day of age)	Prematurity, NRDS	42392 (015)	Time to event = 1087 days postdose 3 (1 day of age)
Birth defects	81486 (019)	Time to event = 520 days postdose 3 (1 day of age)	Asphyxia, hepatic encephalopathy, sepsis	41304 (015)	Time to event = 1227 days postdose 3 (1 day of age)
Premature baby	31812 (012)	Time to event =1345 days postdose 3 (1 day of age)			
Premature baby, respiratory failure	49885 (015)	Time to event =937 days postdose 3 (1 day of age)			
Premature baby	54230 (015)	Time to event = 1147 days postdose 3 (1 day)			
Bacterial sepsis, cerebral hemorrhage, diabetes, jaundice, NRDS, small for dates, premature	54673 (015)	Time to event = 920 days postdose 3 (1 day of age)			
Outside Neonatal					
SIDS (previous E. coli infection, GE reflux, sleep apnea)	57822** (015)	Time of event = 16 months postdose 3 Gardasil)/5 months of age [one ot twins]	Bronchiolitis	20490 (011)	Time of event = 387 d postdose 3/58 d of age
SIDS	41768 (015)	Time of event = 463 d postdose 3/160 d of age	Pneumonia	45950 (015)	Time of event = 862 d postdose 3/85 d of age
Death (information not available)	57031 (015)	Time of event = 505 d postdose 3/44d of age	Pneumonia	49884 (015)	Time of event = 540 d postdose 3/89 d of age
			SIDS	56232 (015)	Time to event = 1161 days postdose 3 (Age =122 days)
TOTAL		**13**	**TOTAL**		**11**

* Potentially Exposed = mother received study material and baby was born at any time after vaccination
Source: Tables for infants deaths in this review and STN 125126/-(b)(4)-, Appendix 2.7.4: 98, 99, 101, 102, p. 1094-1133 and 1138-1160.

Reviewer's Comment: The total numbers of deaths in infants who were potentially exposed to product are comparable in the two treatment groups, and the times to events are rather lengthy between potential exposure to study material and event.

New Medical Conditions Reported in Subjects through Final Close-out data in studies HPV-007, 013, 015, 016, and 018

The first table presents the systemic clinical adverse events in the 15 days after vaccination for subjects in studies 007, 013, 015, 016, and 018 in the Detailed Safety Population (subjects 9-26 years of age). This was the group who were followed with Vaccine Report Cards.

TABLE 73
New Medical Conditions Days 1-15 after Any Vaccination in Studies HPV-007, -013, -015, -016, -018 in the Detailed Safety Population-Female Subjects (2/22/08 STN 125126/-(b)(4)- submission)

Event	Gardasil N=5088	Placebo N=3790
Subjects with follow-up	5012	3725
Subjects with systemic AE	3087 (61.6%)	2303 (61.8%)
Blood and Lymphatic system disorders	24 (0.5%)	17 (0.5%)
Cardiac	9 (0.2%)	5 (0.1%)
Ear and Labyrinth Disorders	58 (1.2%)	36 (1.0%)
Endocrine disorders	2 (0.04%)	0 (0.0%)
Eye disorders	49 (1.0%)	47 (1.3%)
Gastrointestinal disorders	928 (18.5%)	690 (18.5%)
Abdominal discomfort and pain	**340 (6.8%)**	**275 (7.0%)**
Diarrhea	182 (3.6%)	132 (3.5%)
Nausea	338 (6.7%)	243 (6.5%)
Vomiting	122 (2.4%)	69 (1.9%)
General disorders and Administration site conditions	954 (19.0%)	695 (18.7%)
Fatigue	143 (2.9%)	150 (4.0%)
Pyrexia	**654 (13.0%)**	**419 (11.2%)**
Hepatobiliary disorders	2 (0.04%)	2 (0.05%)
Immune system disorders	40 (0.8%)	24 (0.6%)
Hypersensitivity	13 (0.3%)	8 (0.2%)
Seasonal allergy	21 (0.4%)	8 (0.2%)
Infections and Infestations	944 (18.6%)	711 (19.1%)
Influenza	177 (3.5%)	152 (4.1%)
Nasopharyngitis	**318 (6.3%)**	**2367 (6.4%)**
Injury, Poisoning, and Procedural Complications	111 (2.2%)	78 (2.1%)
Investigations	16 (0.5%)	14 (0.4%)
Metabolism and Nutrition disorders	35 (0.7%)	34 (0.9%)
Musculoskeletal and Connective Tissue Disorders	437 (8.7%)	346 (9.3%)
Arthralgia	62 (1.2%)	35 (0.9%)
Back pain	110 (2.2%)	98 (2.6%)
Muscular weakness	5 (0.1%)	8 (0.2%)
Musculoskeletal pain/discomfort	23 (0.5%)	15 (0.4%)
Myalgia	97 (1.9%)	75 (2.0%)
Pain in extremity	100 (2.0%)	90 (2.4%)
Neoplasms, Benign, Maligant and Unspecified (Incl Cysts and Polyps)	2 (0.04%)	2 (0.05%)
Nervous System Disorders	1573 (31.4%)	1184 (31.8%)
Convulsion	1 (0.02%)	1 (0.03%)
Dizziness	198 (4.0%)	139 (3.7%)
Headache	**1411 (28.2%)**	**1058 (28.4%)**
Hyperaesthesia	2 (0.04%)	0 (0.0%)
Hypoaesthesia	12 (0.2%)	5 (0.1%)
Hypotonia	1 (0.02%)	1 (0.03%)
Migraine	33 (0.7%)	18 (0.5%)

TABLE 73 (CONT)
New Medical Conditions Days 1-15 after Any Vaccination in Studies HPV-007, -013, -015, -016, -018 in the Detailed Safety Population-Female Subjects (2/22/08 STN 125126/-(b)(4)- submission)

Event	Gardasil N=5088	Placebo N=3790
Subjects with follow-up	5012	3725
Subjects with systemic AE	3087 (61.6%)	2303 (61.8%)
Nervous System disorders (cont.)		
Paraesthesia	6 (0.1%)	2 (0.07%)
Somnolence	43 (0.9%)	42 (1.1%)
Syncope (includes vasovagal)	19 (0.4%)	19 (0.5%)
Pregnancy, puerperium, and Perinatal conditions	0 (0.0%)	1 (0.03%)
Pyschiatric disorders	99 (2.0%)	72 (1.9%)
Insomnia	59 (1.2%)	34 (0.9%)
Renal and Urinary disorders	17 (0.3%)	14 (0.4%)
Reproductive System and Breast disorders	348 (6.9%)	266 (7.1%)
Dysmenorrhea	178 (3.6%)	152 (4.1%)
Metrorrhagia	38 (0.8%)	20 (0.5%)
Pelvic pain	16 (0.3%)	23 (0.6%)
Vaginal hemorrhage	13 (0.3%)	6 (0.2%)
Respiratory, Thoracic, and Mediastinal disorders	408 (8.1%)	297 (8.0%)
Asthma	10 (0.2%)	4 (0.1%)
Bronchospasm	3 (0.06%)	1 (0.03%)
Cough	102 (2.0%)	55 (1.5%)
Epistaxis	20 (0.4%)	10 (0.3%)
Nasal congestion	53 (1.1%)	35 (0.9%)
Pharyngolaryngeal pain	220 (4.4%)	180 (4.8%)
Rhinorrhea	22 (0.4%)	26 (0.7%)
Skin and Subcutaneous Tissue disorders	184 (3.7%)	136 (3.7%)
Eczema	9 (0.2%)	7 (0.2%)
Leukocytoclastic vasculitis	1 (0.02%)	0 (0.0%)
Rash	55(1.1%)	42 (1.1%)
Urtciaria	10 (0.2%)	18 (0.5%)
Surgical and Medical Procedures	1 (0.02%)	0 (0.0%)
Vascular disorders	21 (0.4%)	23 (0.6%)
Circulatory collapse	21 (0.4%)	23 (0.6%)
Hypertension	2 (0.02%)	3 (0.08%)
Hypotension	8 (0.2%)	6 (0.2%)

Percentages are calculated based on number of subjects with follow-up
Subjects are counted once within each category

Reviewer's Comment: As noted in Table 73 above, the number of adverse events in each treatment group is comparable. The most common adverse events in either treatment group included headache, pyrexia, abdominal pain or discomfort, and nasopharyngitis. The proportions of subjects with each of these adverse events are bolded. When the original application was reviewed, focus was given to the subjects in the Detailed Safety group, because the proportions of subjects reporting a specific adverse event was higher than those reported in the entire safety population. The adverse events included in Table 73 above within each System Organ Classification represent the AEs that were reported most frequently in each group, or include adverse events that

were reported in the post-marketing period (so as to provide information about adverse events of interest which occurred during the clinical period). The table of systemic events in the revised package insert includes those in which the proportion of events was higher in the Gardasil group as compared to the control group, but even though headache occurred more often in the control group, it was felt important to include information about this event within the package insert.

The sponsor has also provided a table of injection site adverse events for subjects in the Detailed Safety Population in studies HPV-007, 013, 015, 016 and 018, and these were broken down by severity for each vaccination group.

TABLE 74
Injection Site Adverse Events in Gardasil Recipients (Female) of Detailed Safety Population (N=5088, 5012 subjects with follow-up) after any vaccination by Severity in Studies HPV-007, -013, -015, -016 and -018 (STN 125126/-(b)(4)-, 2/22/08)

Injection site AE	Total	Mild	Moderate	Severe
Injection Site Pain	4203 (83.9%)	2714 (54.2%) [64.6%]	1350 (26.9%) [32.1%]	138 (2.8%) [32.8%]
Injection Site Pruritus	158 (3.2%)	128 (2.6%) [81.0%]	29 (0.6%) [18.4%]	1 (0.02%) [0.63%]
Injection Site Bruising	140 (2.8%)	119 (2.4%) [85.0%]	17 (0.3%) [12.1%]	4 (0.1%) [2.9%]
Injection Site Reaction	39 (0.8%)	30 (0.6%) [76.9%]	8 (0.2%) [20.5%]	1 (0.02%) [2.6%]
Injection site hematoma	34 (0.7%)	27 (0.5%) [79.4%]	7 (0.1%) [20.6%]	0 (0.0%)
Injection Site Hypersensitivity	27 (0.5%)	21 (0.4%) [77.8%]	5 (0.1%) [18.5%]	1 (0.02%) [3.7%]

Source: STN 125126/-(b)(4)-, 2/22/08, Final Safety Tables, p. 65-66
(Proportions based on subjects with follow-up)
[Proportions based on number of specific adverse events]

TABLE 75
Injection Site Adverse Events in Alum Control or Saline Placebo Recipients (Female) of Detailed Safety Population (N=3470, 3410 subjects with follow-up) after any vaccination by Severity in Studies HPV-007, -013, -015, -016 and -018 (STN 125126/-(b)(4)-, 2/22/08)

Injection site AE	Total	Mild	Moderate	Severe
Injection Site Pain	2572 (75.4%)	1903 (55.8%) [74.0%]	623 (18.3%) [24.2%]	46 (1.3%) [1.8%]
Injection Site Bruising	110 (3.2%)	99 (2.9%) [90%]	11 (0.3%) [10%)	0 (0.0%)
Injection Site Pruritus	97 (2.8%)	81 (2.4%) [83.5%]	13 (0.4%) [13.4%]	3 (0.1%) [3/1%}
Injection Site Hypersensitivity	22 (0.6%)	17 (0.5%) [77.3%]	4 (0.1%) [18.2%]	1 (0.02%) [4.5%]
Injection Site hematoma	20 (0.6%)	17 (0.5%) [85%]	3 (0.1%) [15%]	0 (0.0%)
Injection Site Reaction	17 (0.5%)	13 (0.4%) [76.5%]	4 (0.1%) [23.5%]	0 (0.0%)

Source: STN 125126/-(b)(4)-, 2/22/08, Final Safety Tables, p. 68-69;
(Proportions based on subjects with follow-up)
[Proportions based on number of specific adverse events]

Reviewer's Comment: As noted from Tables 74 and 75 above, subjects who received Gardasil reported injection site pain more frequently as compared to subjects who received alum control or saline placebo, although the majority of these adverse events were rated as mild – moderate intensity in both treatment groups. It was noted in the original clinical review for Gardasil that in study HPV-018 (in which the injection site adverse events were compared in 9-15 year old girls and boys) that injection site reactions were reported less often as compared to subjects who received alum control in the other studies.

The sponsor has also presented tables in STN -(b)(4)- (2/22/08) which include the size of erythema and swelling. If there was measurable swelling or erythema, the majority of subjects had lesions 0 to ≤ 1 cm. These are presented for the Gardasil and control subjects in Tables 76 and 77 below.

TABLE 76
Injection Site Erythema and Swelling in Gardasil Recipients (Female) of Detailed Safety Population (N=5088, 5012 subjects with follow-up) by Size (in inches) in Studies HPV-007, -013, 015, -016 and -018 (STN 125126/-(b)(4)-, 2/22/08)

Injection site AE	0 to ≤ 1"	>1 to ≤ 2"	>2 to ≤ 3"	>3 to ≤ 4"	>4 to ≤ 5"	>5 to ≤ 6"
Injection site erythema	1041 (20.8%)	146 (2.9%) [14.0%]	36 (0.7%) [3.5%]	4 (0.1%) [3.8%]	1 (0.02%) [0.1%]	1 (0.02%) [0.1%]
Injection site swelling	942 (18.8%)	227 (4.5%) [24.1%]	79 (1.6%) [83.9%]	15 (0.3%) [1.6%]	1 (0.02%) [0.11%]	1 (0.02%) [0.11%]

Source: STN 125126/-(b)(4)-, Final Safety tables, p. 70
(Proportions based on subjects with follow-up)
[Proportions based on number of specific adverse events]

TABLE 77

Injection Site Erythema and Swelling in Alum Control or Saline Placebo Recipients (Female) of Detailed Safety Population (N=3470, 3410 subjects with follow-up) by Size (in inches) in Studies HPV-007, -013, -015, -016 and -018 (STN 125126/-(b)(4)-, 2/22/08)

Injection site AE	0 to ≤ 1"	>1 to ≤ 2"	>2 to ≤ 3"	>3 to ≤ 4"	>4 to ≤ 5"	>5 to ≤ 6"
Injection site erythema	556 (16.3%)	59 (1.7%) [10.6%]	11 (0.3%) [19.8%]	3 (0.1%) [0.54%]	0	0
Injection site swelling	444 (13.0%)	75 (2.2%) [16.9%]	16 (0.5%) [3.6%]	3 (0.1%) [0.68%]	1 (0.03%) [0.23%]	0

Source: STN 125126/-(b)(4)-, Final Safety tables, p. 74
(Proportions based on subjects with follow-up)
[Proportions based on number of specific adverse events]

Reviewer's Comment: There was a slightly lower proportion of control recipients who developed injection site swelling and erythema as compared to Gardasil recipients, but the majority of the measured reactions were ≤ 1 inch (as measured by Vaccine Report Card ruler by subjects or parents/guardians) in both treatment groups.

Temperature Elevation after any vaccination visit

A close-out table of temperature elevation is also provided for subjects who participated in studies HPV-007, 013, 015, 016, and 018. In the 5 days after any vaccination, in the Detailed Safety Population, there was a slightly higher proportion of subjects in the Gardasil treatment group [11.5%] with an elevated Temperature (≥ 100 deg F oral) as compared to the control group [10.0%]. The majority of elevated temperatures in both treatment groups were < 102 deg F oral. (See Table 78).

TABLE 78

Number (%) of Subjects With Elevated Temperatures by Vaccination Visit (Days 1 to 5 Following Any Vaccination Visit) Detailed Safety Population--Female Subjects (Studies HPV-007, -013, -015, -016 and -018)

	Gardasil N=5088	Placebo N=3790
Subjects with follow-up	4989	3714
Maximum T (Oral)		
<37.8 °C (< 100 °F) or normal	4413 (88.5%)	3345 (90.1%)
≥ 37.8 °C (≥ 100°F) and < 38.9 °C (< 102 ° F) or abnormal	510 (10.2%)	330 (8.9%)
≥ 38.9 °C (≥ 102°F) and < 39.9 °C (< 103.8 ° F)	56 (1.1%)	32 (0.9%)
≥ 39.9 °C (≥ 103.8°F) and < 40.9 °C (< 105.6 ° F)	9 (0.2%)	4 (0.1%)
≥ 40.9 °C (≥ 105.6°F)	1 (0.0%)	3 (0.1%)

Source: STN 125126/-(b)(4)-, Final Safety Tables, p. 76

The sponsor has also presented new medical conditions after Day 1 in the entire safety population for studies HPV-007, 013, 015, 016, and 018. These are presented in Table 79 below.

TABLE 79

New Medical Conditions After Day 1 in Studies HPV-007, -013, -015, -016, -018 in the Safety Population (Final Close-out data)

Event	Gardasil N=11778	Placebo N=9686
Subjects with new medical history	8628 (73.3%)	7390 (76.3%)
Blood and Lymphatic system disorders	344 (2.9%)	322 (3.3%)
Anemia	240 (2.0%)	243 (2.5%)
Lymphadenopathy/lymphadenitis	60 (0.5%)	47 (0.5%)
Cardiac	44 (0.4%)	40 (0.4%)
Arrythmia	7 (0.1%)	8 (0.1%)
Myocarditis	2 (0.02%)	0 (0.0%)
Palpitations	9 (0.1%)	11 (0.1%)
Pericarditis	1 (0.01%)	0 (0.0%)
Congenital, Facial and Genetic disorders	35 (0.3%)	32 (0.3%)
Ear and Labyrinth Disorders	122 (1.0%)	88 (0.9%)
Deafness/Unilateral deafness	2 (0.02%)	2 (0.02%)
Ear pain	46 (0.4%)	27 (0.3%)
Vertigo/Positional vertigo	26 (0.2%)	20 (0.2%)
Endocrine	79 (0.7%)	81 (0.8%)
Autoimmune thyroiditis	6 (0.1%)	1 (0.01%)
Basedow's disease	5 (0.09%)	2 (0.02%)
Goiter	11 (0.1%)	8 (0.1%)
Hyperprolactinemia	5 (0.09%)	10 (0.1%)
Hyperthyroidism	11 (0.1%)	10 (0.1%)
Hypothyroidism	34 (0.3%)	38 (0.4%)
Eye disorders	250 (2.1%)	210 (2.2%)
Conjunctivitis/Conjunctivitis allergic	158 (1.3%)	137 (1.4%)
Uveitis	3 (0.03%)	1 (0.01%)
Gastrointestinal disorders	1578 (13.4%)	1454 (15.0%)
Abdominal pain (discomfort)	516 (4.4%)	463 (4.7%)
Coeliac disease	10 (0.1%)	6 (0.1%)
Crohn's disease	4 (0.03%)	3 (0.03%)
Ulcerative colitis/colitis/proctitis ulcerative	7 (0.06%)	16 (0.16%)
Diarrhea	221 (1.9%)	188 (1.9%)
Gastritis	280 (2.4%)	270 (2.8%)
Irritable bowel syndrome	64 (0.5%)	82 (0.8%)
Nausea	159 (1.3%)	163 (1.7%)
Pancreatitis	3 (0.03%)	1 (0.01%)
Vomiting	114 (1.0%)	86 (0.9%)
General and Administration site conditions	444 (3.8%)	324 (3.3%)
Asthenia	18 (0.15%)	13 (0.13%)
Fatigue	59 (0.5%)	50 (0.5%)
Gait disturbance	0 (0.0%)	3 (0.03%)
Influenza like illness	41 (0.3%)	27 (0.3%)
Malaise	17 (0.14%)	8 (0.08%)
Pyrexia	165 (1.4%)	122 (1.3%)
Hepatobiliary disorders	41 (0.35%)	54 (0.56%)
Cholecystitis	9 (0.08%)	15 (0.15%)
Cholelithiasis	27 (0.23%)	28 (0.29%)
Immune system disorders	288 (2.4%)	247 (2.6%)
Anaphylactic reaction	5 (0.04%)	2 (0.02%)
Anaphylactic shock	2 (0.02%)	0 (0.0%)
Drug hypersensitivity	66 (0.6%)	64 (0.7%)

TABLE 79 (CONT)
New Medical Conditions After Day 1 in Studies HPV-007, -013, -015, -016, -018 in the Safety Population (Final Close out data)

Event	Gardasil N=11778	Placebo N=9686
Hypersensitivity	52 (0.44%)	48 (0.5%)
Infections and Infestations	6234 (52.9%)	5584 (57.7%)
Appendicitis	28 (0.2%)	30 (0.3%)
Bronchitis	309 (2.6%)	268 (2.8%)
Cervicitis	348 (3.0%)	357 (3.7%)
Cystitis	419 (3.6%)	407 (4.2%)
Ear infection	117 (1.0%)	89 (0.9%)
Gastroenteritis	306 (2.6%)	283 (2.9%)
Gyn Chlamydia infection	355 (3.0%)	408 (4.2%)
Mononucleosis	78 (0.7%)	56 (0.6%)
Influenza	627 (5.3%)	554 (5.7%)
Nasopharyngitis	1009 (8.6%)	897 (9.3%)
PID	300 (2.5%)	297 (3.1%)
Pharyngitis	398 (3.4%)	329 (3.4%)
Sinusitis	388 (3.3%)	359 (3.7%)
Tonsillitis	331 (2.8%)	287 (3.0%)
UTI	1004 (8.5%)	1037 (10.7%)
Vaginal candidiasis	1286 (10.9%)	1345 (13.9%)
Vaginal infection	372 (3.2%)	417 (4.3%)
Vaginitis bacterial	1151 (9.8%)	1129 (11.7%)
Vulvovaginal infections	676 (5.7%)	694 (7.2%)
Injury, Poisoning, and Procedural Complications	940 (8.0%)	654 (6.8%)
Investigations	1388 (11.8%)	1354 (14.0%)
Metabolism and Nutrition disorders	195 (1.7%)	162 (1.7%)
Musculoskeletal and connective tissue disorders	800 (6.8%)	632 (6.5%)
Arthralgia	122 (1.0%)	100 (1.0%)
Arthritis	12 (0.1%)	7 (0.1%)
Arthritis reactive	1 (0.01%)	1 (0.01%)
Arthropathy	7 (0.06%)	0 (0.0%)
Back disorder	267 (2.3%)	212 (2.2%)
JRA	1 (0.01%)	2 (0.02%)
Myalgia	45 (0.4%)	41 (0.4%)
Neoplasm, malignant, benign, including cysts	237 (2.0%)	189 (2.0%)
Hodgkin's disease	3 (0.03%)	0 (0.0%)
Benign neoplasm of thyroid	5 (0.04%)	1 (0.01%)
Fibroadenoma of breast	18 (0.2%)	19 (0.2%)
Nervous system disorders	1108 (9.4%)	861 (8.9%)
Carpal tunnel syndrome	10 (0.1%)	2 (0.02%)
Convulsion/epilepsy	11 (0.09%)	15 (0.15%)
Dizziness	87 (0.7%)	81 (0.8%)
Encephalitis	0 (0.0%)	2 (0.02%)
Headache	712 (6.0%)	523 (5.4%)
Hypoaesthesia	7 (0.06%)	10 (0.1%)
Migraine	146 (1.2%)	130 (1.3%)
Multiple sclerosis	2 (0.02%)	4 (0.04%)
Optic neuritis	2 (0.02%)	0 (0.0%)
Paresthesia	5 (0.04%)	6 (0.06%)
Syncope.vasovagal syncope	61 (0.5%)	54 (0.56%)
TIA	2 (0.02%)	0 (0.0%)

TABLE 79 (CONT)
New Medical Conditions After Day 1 in Studies HPV-007, -013, -015, -016, -018 in the Safety Population

Event	Gardasil N=11778	Placebo N=9686
Pregnancy, puerperium, and perinatal conditions	236 (2.0%)	255 (2.6%)
Psychiatric disorders	517 (4.4%)	473 (4.9%)
Bipolar disorder	14 (0.12%)	14 (0.14%)
Renal disorders	318 (2.7%)	295 (3.0%)
Glomerulonephritis	1 (0.01%)	1 (0.01%)
Nephritis	1 (0.01%)	4 (0.04%)
Reproductive and Breast Disorders	2916 (24.8%)	2812 (29.0%)
Respiratory, thoracic, and mediastinal disorders	651 (5.5%)	489 (5.0%)
Asthma	74 (0.6%)	68 (0.7%)
Pulmonary embolism	1 (0.01%)	2 (0.02%)
Skin and subcutaneous tissue disorders	876 (7.4%)	761 (7.9%)
Erythema multiforme	0 (0.0%)	1 (0.01%)
Erythema nodosum	2 (0.02%)	4 (0.04%)
Rash (multiple types)	77 (0.7%)	96 (1.0%)
Urticaria	51 (0.43%)	52 (0.54%)
Surgical Procedures	1200(10.2%)	1166 (12.4%)
Appendectomy	58 (0.5%)	56 (0.6%)
Vascular disorders	114 (1.0%)	127 (1.3%)
Deep vein thrombosis	3 (0.03%)	8 (0.08%)
Embolism	0 (0.0%)	1 (0.01%)
Hypertension	49 (0.4%)	37 (0.4%)
Hypotension/Orthostatic hypotension	14 (0.12%)	21 (0.22%)
Thrombosis	2 (0.02%)	3 (0.03%)

Source: STN 125126/-(b)(4)-, Table of Listing of Number (%) of Subjects With New Medical History (Incidence >0% in One or More Vaccination Groups) by System Organ Class (After Day 1) Safety Population (Protocols 007, 013, 015, 016 and 018)

Reviewer's Comment: As noted in Table 79 above, the proportions of subjects with any new medical condition after Day 1 were comparable in both treatment groups.

New Medical Conditions in HPV-018 (Gardasil compared to true saline placebo)
Because there was interest in direct comparison of new medical conditions in Gardasil recipients as compared to those who received normal saline, Table 80 is included below. Girls 9-15 years of age are included in the tables below, and show summary of new medical conditions which occurred after Month 7 to Month 30 in this younger age group. As can be noted, there was comparable proportions of subjects with these new medical conditions in each treatment group.

TABLE 80
New Medical Conditions Month 7 to Month 30 in Study HPV-018
Girls 9-15 years of age

Event	Gardasil N=591	Saline Placebo N=301
Subjects with new medical history	386 (65.3%)	202 (67.1%)
Blood and Lymphatic system disorders	6 (1.0%)	7 (2.3%)
Lymphadenopathy/lymphadenitis	5 (0.9%)	4 (1.3%)
Cardiac	0 (0.0%)	2 (0,7%)
Congenital, Familial and Genetic Disorders	2 (0.3%)	2 (0.7%)
Ear and Labyrinth Disorders	10 (1.7%)	14 (4.7%)
Endocrine disorders	7 (1.2%)	4 (1.3%)
Eye Disorders	22 (3.7%)	12 (4.0%)
Gastrointestinal disorders	71 (12.0%)	36 (12.0%)
Abdominal pain	30 (5.0%)	8 (2.7%)
Colitis	1 (0.2%)	4 (1.3%)
Nausea	8 (1.4%)	3 (1.0%)
Vomiting	9 (1.5%)	2 (0.7%)
General Disorders and Administration site Conditions	24 (4.1%)	13 (4.3%)
Hepatobiliary Disorders	0 (0.0%)	0 (0.0%)
Immune System disorders	12 (2.0%)	5 (1.7%)
Anaphylactic reaction*	1 (0.2%)	0 (0.0%)
Infections and Infestations	261 (44.2%)	138 (45.8%)
Injury, Poisoning and Proecdural Complications	87 (14.7%)	44 (14.6%)
Investigations	9 (1.5%)	9 (3.0%)
Metabolism and Nutritional Disorders	11 (1.9%)	7 (2.3%)
Musculoskeletal and Connective Tissue Disorders	62 (10.5%)	28 (9.3%)
Juvenile arthritis	1 (0.2%)	0 (0.0%)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	17 (2.9%)	11 (3.7%)
Nervous system disorders	45 (7.6%)	25 (8.3%)
Pregnancy, Puerperium And Perinatal Conditions	1 (0.2%)	0 (0.0%)
Psychiatric Disorders	28 (4.7%)	15 (5.0%)
Renal And Urinary Disorders	14 (2.4%)	1 (0.3%)
Dysuria	8 (1.4%)	0 (0.0%)
Reproductive System And Breast Disorders	48 (8.1%)	24 (8.0%)
Respiratory, Thoracic And Mediastinal Disorders	51 (8.6%)	35 (12.6%)
Skin And Subcutaneous Tissue Disorders	58 (9.8%)	34 (11.3%)
Eczema	3 (0.5%)	3 (1.0%)
Urticaria	3 (0.5%)	3 (1.0%)
Social Circumstances	3 (0.5%)	3 (1.0%)
Surgical And Medical Procedures	29 (4.9%)	18 (6.0%)
Vascular Disorders	2 (0.3%)	5 (1.7%)

One subject in the group that received Gardasil (AN 71028) reported a diagnosis of anaphylaxis at Month 18.
Source: STN 125126/419.8, CSR HPV-018 M30, Table 4-14, p. 41-83

Reviewer's Comment: The proportions of subjects in each System Organ Class were comparable. The most common conditions reported were pharyngitis, upper respiratory infections, and influenza. There was a higher proportion of subjects with abdominal pain in the Gardasil group (5.0%) as compared to the saline placebo group (2.7%).

A total of 6 subjects reported a diagnosis of a specific autoimmune condition in their Month 7 to Month 24 medical history. Of these: 2 subjects were in the group that received Gardasil (AN 70327, a 14-year-old boy with a diagnosis of Autoimmune

Thrombocytopenia reported at Month 18; AN 71311, a 14-year-old girl with a diagnosis of Juvenile Arthritis reported at Month 12); and 4 subjects were in the group that received placebo (AN 70434, a 12-year-old girl with a diagnosis of psoriatic arthritis diagnosed at Month 12; AN 71688, a 13-year-old boy diagnosed with psoriasis at Month 24; AN 71460, a 12-year-old girl with a diagnosis of psoriasis diagnosed at Month 18; and AN 70434, a 9-year-old girl with a diagnosis of Systemic Lupus Erythematosus at Month 24. Including the reported serious adverse experience in the subject who received Gardasil (ulcerative colitis), a total of 7 subjects were given a diagnosis consistent with an autoimmune disease. Thus, the cumulative incidences of such diagnoses were 3/945 (0.32%) in the boys and girls who received Gardasil and 4/482 (0.83%) in the boys and girls who received non-aluminum-containing placebo.

New Medical Conditions of Interest
Autoimmune Disorders

Further follow-up and reporting of autoimmune disorders was provided in the updated safety data (STN 125126/419.0). CBER requested that the sponsor conduct a meta-analysis across all HPV vaccine trials of specified autoimmune events to assess whether there was a statistical difference in the incidence of the prespecified events. Narratives were requested for review. The CBER statistician reviewed the proposed methodology and found it to be acceptable. Studies HPV-005, -007, -013, -015, -016, -018, and -019 were included, as well as non-IND studies and other VLP formulations. In this meta-analysis, there was no statistically significant difference in the incidence of events which were of potentially autoimmune nature. Table 81 includes all such events from studies HPV-007, -013, -016, and -018 as of the safety data cut-off dates which occurred in females 9-26 years of age. This table is included in the updated PI. It is noted that the sponsor has labeled several disease entities within one diagnosis.

TABLE 81

Summary of Subjects Who Reported an Incident Condition Potentially Indicative of Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL Regardless of Causality [Girls and Women 9-26 years of age]

Conditions	Gardasil (N=11778) [N=10706]	Alum Control or Saline Placebo (N=9686) [N=9412]
Arthralgias/Arthritis/Arthropathy*	(142/1.2%) [120/1.1%]	(108/1.1%) [98/1.0%]
Autoimmune thyroiditis	(6/0.1%) [4/0.1%]	(1/0.01%) [1/0.01%]
Coeliac disease	10 (0.1%)	6 (0.1%)
Diabetes mellitus insulin dependent	(5/0.04%) [2/0.02%]	(2/0.02%) [2/0.02%]
Erythema nodosum	2 (0.02%)	4 (0.04%)
Hyperthyroidism**	27 (0.2%)	21 (0.2%)
Hypothyroidism***	(36/0.3%) [35/0.3%]	38 (0.4%)
Inflammatory bowel disease€	7/0.1%	10 (0.1%)
Multiple sclerosis	2 (0.02%)	4 (0.04%)
Nephritis¥	2 (0.02%)	5 (0.05%)
Optic neuritis	2 (0.02%)	0 (0.0%)
Pigmentation disorders¶	4 (0.04%)	3 (0.03%)
Psoriasis±	13 (0.1%)	(16/0.2%) [15/0.2%]
Raynaud's phenomenon	3 (0.03%)	4 (0.04%)
Rheumatoid arthritis£	(7/0.1%) [6/0.1%]	(2/0.02%) [1/0.01%]
Scleroderma/morphea	2 (0.02%)	1 (0.01%)
Stevens Johnson syndrome	1 (0.01%)	0 (0.0%)
Systemic Lupus Erythematosus	1 (0.01%)	3 (0.03%)
Uveitis	3 (0.03%)	1 (0.01%)

*Arthralgia/Arthritis/Arthropathy includes the following terms: Arthralgia, Arthritis, Arthritis reactive, and Arthropathy

**Hyperthyroidism includes the following terms: Basedow's disease, Goitre, Toxic nodular goitre, and Hyperthyroidism

***Hypothyroidism includes the following terms: Hypothyroidism and thyroiditis

€Inflammatory bowel disease includes the following terms: Colitis ulcerative, Crohn's disease, and Inflammatory bowel disease

¥Nephritis includes the following terms: Nephritis, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative

¶Pigmentation disorder includes the following terms: Pigmentation disorder, Skin depigmentation, and Vitiligo

±Psoriasis includes the following terms: Psoriasis, Pustular psoriasis, and Psoriatic arthropathy

£Rheumatoid arthritis includes juvenile rheumatoid arthritis

N = Number of subjects enrolled

n = Number of subjects with specific new Medical Conditions

NOTE: Although a subject may have had two or more new Medical Conditions, the subject is counted only once within a category. The same subject may appear in different categories.

Alum Control = Amorphous Aluminum Hydroxyphosphate Sulfate

( )=Number of cases/percentage of total population with event

[ ]=Number of cases/percentage of girls and women 9-26 years of age with event.

Reviewer's Comment: For the entire population, the proportions of such events were similar in each of the treatment groups (2.3% Gardasil, 2.4% control). When only girls and women 9-26 years of age are considered, these proportions remain similar. There were 2 conditions in which a numerical imbalance was noted: autoimmune thyroiditis and rheumatoid arthritis. Narratives were requested for these events so that times to event could be noted as well. Tables were constructed to help compare total numbers of cases reported throughout the trial, and in all trials. Subjects who received the monovalent product and older women were included in the meta-analysis. It was noted that several of the subjects had some joint symptoms on the day of vaccination. Excluding the subjects who received monovalent product, those in the older age group, and those who may have had symptoms present on the day of vaccination, the numbers are consistent with those provided. The overall proportion of subjects with RA/JRA in the total dataset 0.1% in the Gardasil treatment group. These cases occurred over several years. The times to event were variable, and the event occurred in both treatment groups (although at a higher rate in the Gardasil as compared to the control group). For autoimmune thyroiditis, in post-marketing reports, there were 2 cases reported in the PSUR submitted to the BLA. At the time of original licensure, as part of the post-marketing safety study (44,000 subjects) in a Managed Care Organization, the sponsor committed to conduct a short-term surveillance study, and conditions including those of potential autoimmune nature and thyroiditis would be specifically studied (in addition to all medically attended events), with comparison in the selected time period before and after the 60 days after vaccination. This study is underway at the ----------(b)(4)----------, and the study was scheduled to complete enrollment at the end of 2008, with results available in 2009. In addition, the CDC via the Vaccine Safety Datalink is also conducting a surveillance study to assess events of interest which occur after vaccination with Gardasil.

For the diagnosis of Rheumatoid Arthritis/Juvenile Rheumatoid Arthritis in the entire safety population, the following was noted: in the Gardasil group, one subject was diagnosed with RA/JRA at 130 days after dose 2 (although symptoms began 40 days postdose 2); one subject at Month 12; one subject at Month 24; and two other subjects at Month 36. One other subject was included in the totals, although and she was diagnosed at Month 6, although she had pains in her arms, fingers, and knees at Day 1. In the control group, there were two subjects who were diagnosed with RA (one at Month 36 and one at Month 48). It is unclear that cases which developed at a longer time period after vaccination are associated with vaccination.

For autoimmune thyroiditis in the entire safety population, there was a higher number of subjects with autoimmune thyroiditis in the Gardasil treatment group as compared to the control group. For the cases reported in the Gardasil group, the times to diagnosis ranged from one subject was diagnosed at Month 2; 2 were diagnosed at Month 12; 1 at Month 24; and 3 at Month 48. For the case reported in the control group, the subject was diagnosed at Month 36. The reported annual incidence in the literature is variable, and ranges from 30-150 cases/100,000. With the 7 subjects diagnosed during the studies, the incidence was app. 60/100,000.

Siegrist et al (2007)[9] reported on a cohort study conducted at the Northern California Kaiser Permanente (NCKP) HMO in 2005 (prior to licensure of Gardasil). In that cohort study within a database of female adolescents (n =214,896) and young adults (n= 221,472) followed in the pre-HPV vaccine era (2005), computing rates of emergency consultations, hospitalizations and outpatient consultations, and estimation of risks of coincident associations. Immune-mediated conditions were a frequent cause (10.3%) of emergency room consultation by adolescent girls. Nonallergic immune-mediated conditions affected 86 per 100,000, diabetes ranking first. In 2005, 53 per 100,000 adolescents and 389 per 100,000 women were hospitalized for diseases of presumed autoimmune origin, thyroiditis being the most frequent diagnosis. Other diagnoses identified in this cohort study included ulcerative colitis, systemic lupus erythematosus, regional enteritis, Juvenile rheumatoid arthritis, autoimmune disorders (not specified), optic neuritis, multiple sclerosis, acute polyneuritis, thyroid disorders, rheumatoid arthritis, and multiple sclerosis. This report demonstrates that many of the diagnoses of interest accounted for app. 10% of illnesses and these occurred in subjects of similar sex and age within the Kaiser Permanente HMO (and prior to introduction of Gardasil). The adverse events that have been reported within the studies warrant further analysis, and the post-marketing study that is ongoing at the -----(b)(4)---- may help identify a safety signal with more certainty, in addition to the study ongoing by the VSD of CDC and VAERS.

Thryoid nodules were also noted as diagnoses identified in the safety datasets after Day 1. There were 7 incidence cases in the Gardasil group and 2 in the control group. These were all benign. Two of the Gardasil recipients had concurrent hyperthyroidism. In the post-marketing reports to VAERS, no reports were identified. The times to events in the Gardasil group were M6-2, M18-2, M24-2, and M48-1. In the control group, both events were reported at M12.

In the extension study of HPV-007, in the table of new medical history, there was 1 subject with **myocarditis** reported at Day 1 postdose 4 (she had received 3 doses of Gardasil in the primary series in late 2000-early 2001, and the 4th dose 12/05. The subject felt feverish and had symptoms of increased heart rate. She was seen by a cardiologist and reportedly had an increased heart rate but an ECG was reported as normal. The cardiologist diagnosed the event as myocarditis, and it was assessed as not serious, related to prolonged flu. The subject was never hospitalized.

Postmarketing Safety Reports

Deaths have been reported after vaccination with Gardasil. No consistent cause of death has been identified in the post-marketing period, but further analyses are in progress to ascertain if there is any identifiable pattern not yet noted.

The sponsor has provided the Postmarketing Safety Update Report within the BLA. The post-marketing experience with Gardasil is summarized from the International Birthdate 12/1/06 through 9/30/07. Gardasil was first licensed on 6/2/06 in Mexico. More than ----(b)(4)--- doses of Gardasil were distributed as of 9/30/07. The post licensure experiences with Gardasil were collected through passive reporting of

[9] Siegrist C et al. Pediatric Infectious Disease Journal 2007; 26(11):979-84.

spontaneous adverse experiences to Merck & Co., Inc. Two 6-month Periodic Safety Update Reports (PSURs) for Gardasil for the periods of 6/1/06 through 11/30/06 and 12/1/06 through 5/31/07 are complete.

To permit safety surveillance for its products, Merck & Co., Inc. maintains the New Worldwide Adverse Experience System (NWAES) database. Postmarketing safety surveillance is a worldwide, passive, spontaneous, and voluntary reporting system. At Merck & Co. Inc., the WAES database contains all spontaneous adverse experience reports from the marketed environment, serious reports from clinical trials, and reports from the medical literature. Adverse experience information is updated continuously. The retrieval of data is provided as a snapshot in time.

All of the reports are entered into NWAES and are coded using the terminology of the reporter. The Medical Dictionary for Regulatory Activities (MedDRA) is the dictionary used to code adverse experience terms in the NWAES database. Inclusion of the report in the database implies only a temporal association and not necessarily a causal association. Each report represents one individual who may experience one or more adverse experiences. Since each adverse experience is coded to a body system, one report may contain multiple adverse experiences in the same or different body systems. Routine Pharmacovigilance practices include continuous monitoring of the safety profile of approved products. Data from the NWAES database are routinely reviewed as individual reports and in aggregate. The purpose of the review is to evaluate adverse experience reports for possible safety signals, to determine if further investigation is warranted to clarify the safety profile of the product, and to ensure completeness of safety information in worldwide package circulars.

For submission of this report to the Gardasil Licensing Application, the NWAES database was queried as of 10/14/07 for all marketed adverse experience reports temporally associated with the administration of Quadrivalent HPV vaccine received from health care providers (HCP) for the period 6/1/07 through 9/30/07. Table 82 below lists the total number of reports and number of adverse experiences reported during this time period. Of the 8611 reports received, 660 reports (8%) were considered serious. Although the majority (6968 or 81%) of reports originated in the United States, reports originated in the following countries as well: Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Colombia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Lebanon, Malaysia, Malta, Mexico, Netherlands, New Zealand, Peru, Philippines, Poland, Portugal, Puerto Rico, Singapore, Slovakia, Slovenia, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Arab Emirates, United Kingdom and Venezuela.

TABLE 82
Spontaneous Adverse Experience Reports Temporally Associated with Administration of Quadrivalent HPV Vaccine 6/1/06 to 9/30/07

Total Number	Serious	Non-serious	Total
AE Reports	660	7951	8611
Adverse Events	1778	16733	18511

Source: Summary of Clinical Safety, STN 125126/-(b)(4)-, submitted 1/11/08, p. 135

An additional table is presented which includes the listing of the specific spontaneously reported AEs by System Organ Class (SOC) (See Table 83). The VAERS group has been following adverse events that have been reported through passive reporting.

For each System Organ Class, specific diagnoses are also provided. From June 2006 to September 2007, there were 2 spontaneous reports of rheumatoid arthritis, 2 spontaneous reports of juvenile arthritis, and 2 spontaneous reports of autoimmune thyroiditis.

TABLE 83
Number of Spontaneous Adverse Experience Reports by System Organ Class
6/1/06 to 9/30/07

System Organ Class	Total # of Reports	% of Total Reports	Total # of Serious Reports	% of Serious Reports
Blood and lymphatic system disorders	121	1	26	4
Cardiac disorders	70	1	19	3
Congenital, familial and genetic disorders	9	0	8	1
Ear and labyrinth disorders	48	1	13	2
Endocrine disorders	2	0	1	0
Eye disorders	152	2	33	5
Gastrointestinal disorders	830	10	84	13
General disorders and administration site conditions	3787	44	146	22
Hepatobiliary disorders	6	0	3	0
Immune system disorders	98	1	29	4
Infections and infestations	302	4	49	7
Injury, poisoning and procedural complications	3787	44	57	9
Investigations	198	2	31	5
Metabolism and nutrition disorders	54	1	21	3
Musculoskeletal and connective tissue disorders	661	8	95	14
Neoplasms benign, malignant and unspecified (including cysts and polyps)	10	0	3	0
Nervous system disorders	2211	26	314	48
Pregnancy, puerperium and perinatal conditions	80	1	56	8
Psychiatric disorders	180	2	32	5
Renal and urinary disorders	26	0	11	2
Reproductive system and breast disorders	185	2	11	2
Respiratory, thoracic and mediastinal disorders	313	4	73	11
Skin and subcutaneous tissue disorders	1187	14	87	13
Social circumstances	8	0	4	1
Surgical and medical procedures	84	1	27	4
Vascular disorders	291	3	38	6
Total Number of Distinct Reports	**8611**	-	**660**	-

*A single report may include adverse events in one or more System Organ Classes. Therefore, the sum of reports from all System Organ Classes can be greater than the total distinct number of reports. Percentages are the percent of distinct number of reports for events in that System Organ Class.

Source: Summary of Clinical Safety, STN 125126/-(b)(4)-, p. 136

In addition to data provided by sponsor, adverse events continue to be reported to the VAERS group. In the early post-marketing period, syncope was the most commonly reported adverse event, sometimes with serious traumatic injury. The original data was

re-reviewed, and no imbalance between treatment groups was noted in data provided in the clinical study reports.

Reviewer's Comment:
As post-marketing reports of adverse events were reported to VAERS, review of those events which occurred during the clinical trials was also conducted. These events are noted below, and data reported include proportions of subjects in each treatment group reported to the Biologics Licensing Application in the updated safety tables (submitted 2/22/08) was utilized.

Anaphylaxis: There was one report of anaphylaxis in the control group reported during the clinical studies (as a serious adverse event). In the post-marketing period, anaphylactic reactions after vaccination with Gardasil have been reported. These events are being analyzed as for the expected rate in the general population.

Urticaria:
In the post-marketing period, one subject developed chronic urticaria 1 month after dose 3. From the clinical trial data:

- In Days 1-15 after any vaccination in Detailed Safety population (Vaccine Report Card), there were 10/5088 subjects Gardasil group and 18/3790 control subjects who reported urticaria. One of the subjects who discontinued from study 015 received dose 1 of Gardasil and developed urticaria the day after.
- In the entire safety population, there was no apparent difference in proportions of subjects who reported urticaria as a new medical condition after day 1:
  - Solar urticaria: 2/11778 Gardasil [0.017%] and 0/9686 control [0.0%]
  - Urticaria: 49/11778 Gardasil [0.42%] and 50/9686 control [0.52%]
  - Urticaria generalized: 2/11778 [0.017%] and 1/9686 control [0.01%]
  - Urticaria localized: 0/11778 Gardasil [0.0%] and 1/9686 control [0.01%]

If we total all the urticaria categories, there were 53/11778 in the Gardasil group [0.45%] and 52/9686 [0.54%].
As noted, the rates are similar in the two treatment groups.

Neurologic Disorders
Guillain-Barre syndrome (GBS): No cases of GBS were reported during the clinical studies. However, reports of GBS, including the Miller-Fisher variant of GBS, with and without receipt of other vaccines, have been received in the post-marketing period. The analyses to date by VAERS have not indicated that the rate of reports exceeds the expected rates in the general population. This event was already added as an event reported in the post-marketing period within the label.

In the post-marketing period, a 14 year old girl was reported to have developed progressive motor atrophy at 1-4 months after dose 3 Gardasil. No similar events were reported during the clinical trials. However, terms relating to neurological events were searched in the updated safety tables, and narratives for subjects were requested, and these narratives were reviewed. The narratives did not reveal subjects with diagnosis of progressive motor atrophy or ALS. However, further evaluation of such rare serious

adverse events is ongoing in the CDC and VAERS and this process is ongoing. In addition, reports of subjects with convulsions were made to VAERS.

Ageusia (loss of taste): 1/11778 Gardasil [0.01%] and 0/9686 [0.0%] control. This event was attributed to poisoning of non-specified etiology at month 48.

Amnesia: 1/11778 Gardasil [0.01%] and 1/9686 control [0.01%]. The Gardasil recipient had a concussion and headache at Month 6 and the event was reported as not active. The control subject had this at Month 7 and it was reported as active, but of questionable etiology.
Balance disorder: 1/11778 [0.01%] Gardasil and 0/9686 [0.0%] control. The Gardasil recipients developed this at M24, and had a history of hearing impairment at D1.

Benign Intracranial hypertension (pseudotumor cerebri): 0/11778 Gardasil [0.0%] and 1/9686 control [0.01%]. This event occurred at Month 6.

Carpal tunnel syndrome: 10/11778 [0.08%] Gardasil 2/9686 [0.02%] control. The times to events for the Gardasil recipients were: M2-1, M7-1, M12-1, M24-4, M30-1, M36-2, and M48-1. The times to events in the control subjects were: M24-1 and M48-1.

Cerebral hemorrhage: 0/11778 Gardasil [0.0%] and 1/9686 control [0.01%]. This event occurred at Month 24; history migraine Day 1.

Cerebrovascular spasm Right cerebral artery Month 3 to Month 6) and anti-phospholipid syndrome, with history of migraine at Day 1. Received 2 doses of Gardasil and discontinued from study. 1/11778 Gardasil [0.01%] and 0/9686 control [0.0%]. [AN 32454, 23 year old female Colombia, study 012]

Convulsion/Epilepsy/Myoclonic epilepsy: 12-6 active, 6 not active/11778 Gardasil [0.1%] and 14-8 active, 6 not active/9686 [0.14%] control. The times to events were variable in both treatment groups. In the Gardasil group were as follows: M2-3, M12-1, M18-2, M24-2, M30-2, and M48-2. The times to events in the control group were as follows: M2-1, M6-1, M12-2, M18-2, M24-3, M36-4, M48-1. The proportions of convulsions/epilepsy as new medical condition were comparable.

Cranial nerve palsy: 1/11778 [0.01%] Gardasil and 0/9686 [0.0%] control. The Gardasil recipient had a diagnosis of intracranial hypotension and required an epidural patch (after epidural tear post-procedure).

Cubital tunnel syndrome: 2/11778 Gardasil [0.02%] and 0/9686 [0.0%] control. One subject developed this at Month 24; one subject developed it at Month 48 with a history of injury and slipped cervical disc.

Dysaesthesia: 2/11778 [0.02%] Gardasil and 1/9686 [0.01 %] control. One Gardasil recipient had burning sensation in her feet at M2 and back muscle spasms and lumbar pain at a later time. She received 3 doses of Gardasil. The other Gardasil recipient had a

feeling disturbance at M24 (not active). The control subject developed dysaesthesia at M7.

Encephalitis: 0/11778 Gardasil [0.0%] and 2/9686 control [0.02%]. One control subject suffered meningitis and pneumonia with this event at Month 48 and was no longer active, and the other control recipient had convulsions with the encephalitis at Month 36, but was no longer active.

Extrapyramidal disorder and dyskinesia: 1/11778 [0.01%] Gardasil and 1/9686 [0.01%] control. The event in the Gardasil recipient was attributed to use of Wellbutrin. The control subject was on concomitant psychotropic meds.

Facial palsy/paresis: 9-2 active, 7 not active/11778 [0.08%] Gardasil and 11-3 active, 8 not active/9686 [0.11%] control. The times to events were variable for both groups, with M2-1, M6-2, M12-1, M18-3, M24-1, M30-1 for the Gardasil recipients; the times to events were M2-1, M7-1, M12-1, M18-2, M24-3, M30-1, M36-1, and M48-1. Again, occurrence of these events during clinical trials was comparable.

Hypersomnia/somnolence: 14/11778 [0.012%] Gardasil and 9/9686 [0.01%] control. The times to event were variable for both groups. In the Gardasil, the times to events were M2-2, M3-1, M6-1, M7-2, M12-1, M12-24-2, M24-2, M24-36-1, M36-481, M48-1. In the control group, the times to events were M2-3, M6-2, M7-1, M12-24-1, and M36-2.

Hydrocephalus: 1/11778 Gardasil [0.01%] and 1/9686 control [0.01%]. Both events were associated with CNS infection.

Hypoaesthesia: 8/11778 [0.07%] Gardasil and 10/9686 [0.10%] control. The times to events were again variable in both treatment groups. In the Gardasil recipients, these were: M6-1, M7-1, M18-1, M24-3, M36-1, and M48-1. The times to events in the control subjects were: M6-1, M7-1, M12-1, M24-3, M30-1, M36-2, and M48-1.

Muscular weakness: 3/11778 Gardasil [0.017%] and 2/9686 [0.2%] control. One subject in study 018 received saline placebo. Identified episodes lasted 1-2 days, and resolved spontaneously.

Myasthenia gravis: 0/11778 [0.0%] Gardasil and 1/9686 [0.01%] control (M24).

Mycolonus: 0/11778 [0.0%] Gardasil and 1/9686 [0.01%] control (M7-12).

Neuritis/neuralgia: 4/11778 [0.03%] Gardasil and 2/9686 [0.02%] control.

Nerve compression: 3/11778 [0.03%] Gardasil and 0/9686 [0.0%] control. These three events were related to pinched nerve.

Nerve degeneration high frequency ears: 1/11778 [0.01%] Gardasil and 0/9686 [0.0%] control. The etiology of this event in the Gardasil recipient at M24 was not known.

Paresthesias: 5/11778 [0.04%] Gardasil and 5/9686 [0.05%] control. In the Gardasil group, the times to events were M6-3 (one subject with acromegaly at Day 1) and M24-2. In the control group, the times to events were M7-1, M18-1, M24-1, M30-1, and M48-1. In each treatment group, 2 were listed as active.

Peripheral neuropathy: 1/11778 [0.01%] Gardasil and /9686 [0.015] control.
Pseudoparalysis, paresis and monoparesis: 2/11778 [0.02%] Gardasil (pseudoparalysis) and 1/9686 [0.01%] control (monoparesis). The Gardasil recipient had pseudoparalysis which lasted < 24 hours at M36 and the subject was pregnant at the time, and was subsequently diagnosed with schizophrenia. The other Gardasil recipient with paresis of her arms and legs at M6 experienced the event after alcohol use, and it resolved. The control recipient with monoparesis noted left leg paralysis and paresthesias of the left arm at M12 and was subsequently diagnosed with MS.

Restless leg syndrome: 1/11778 [0.01%] Gardasil and 3/9686 [0.03%] control. The Gardasil recipient was diagnosed at M12; the control recipients were diagnosed at M2, M36, and M48.

Sciatica: 8/11778 [0.07%] Gardasil and 6/9686 [0.06%].

Syncope/vasovagal syncope/Presyncope: 63/11778 Gardasil [0.53%] and 50/9686 [0.52%] control. The times to events were variable, and the majority of events were reported as not temporally related to vaccination. For Gardasil, the times to events were: D1 (prior to vaccination), M2-4, M3-4, M6-5 (one received JE vaccine and typhoid vaccine and cholera vaccine), M7-8 (one after blood test), M12-14, M18-2, M24-16, M-30-4, M36-4, and M48-3. For control recipients, the times to events were: D1 (with pregnancy), M2-3, M6-6, M7-4, M12-11, M18-2, M24-9, M36-4, and M48-9.

Transient ischemic attacks: 2/11778 [0.02%] Gardasil and 0/9686 [0.0%] control. One Gardasil recipient with a TIA at M2 had a history of migraines, and subsequently received the last 2 doses without adverse events. The other subject developed the TIA at M24 and the event was assessed as no longer active.

Tremor: 4/11778 [0.03%] Gardasil and 4/9686 [0.04%] control.
Visual field defect: 1/11778 Gardasil [0.01%] at Month 48 and 0/9686 [0.0%] control. The etiology in the Gardasil recipient was unknown at the time of reporting.

Other Events reported in the post-marketing period:
Pancreatitis: 3/11778 [0.03%] Gardasil and 1/9686 [0.01%] control. In the Gardasil group, 1 subject developed this event at M30 (also with ruptured ovarian cyst), and 2 at M48 (one with gallstones and one with GERD and gastritis). In the control group, the 1 event occurred at Month 48 and was associated with gallstones.

Hodgkin's disease: 3/11778 [0.03%] Gardasil and 0/9686 [0.0%] control. The 3 events which occurred during the trials included 1 case diagnosed at M6, recovered, and went onto participate in the extension study of 015 (father with history of 'lymphogranulomadosis' or Hodgkin's disease years earlier); 1 case occurred at M12 and subject went onto complete study; and one subject was diagnosed at M48 (no additional information reported).

Conclusions from Safety Data

- The rates of deaths were comparable between the Gardasil group and the control group, and none appeared to be related to receipt of study material.
- The rates of serious adverse were comparable between the Gardasil group and control group.
- The rates of subjects who discontinued due to an adverse event were comparable in the Gardasil group as compared to the control group.
- The updated pregnancy outcomes demonstrate a comparable rate of spontaneous abortions within each treatment group (18.2% Gardasil, 19.5% control). These rates were similar for the groups with an estimated date of conception within 30 days of vaccination (18.3% Gardasil, 21.0% control).
- Regarding congenital anomalies, there was a higher number of subjects in the Gardasil group who delivered a child with a congenital anomaly (40 total) as compared to the control group (30 total). Four of the infants in the Gardasil group and three infants in the control group were diagnosed with inherited defects, so the totals are 36 for Gardasil and 27 for control subjects. In pregnancies in which the estimated date of conception was within 30 days of vaccination, there were 5 congenital anomalies in infants born to mothers who received Gardasil and 1 in an infant born to a mother who received control. In an expert review of these anomalies provided by the sponsor (5 experts), none of the expert teratologists assessed any of the congenital anomalies as related to study material (both in a blinded and unblinded assessment). Gardasil is not recommended for routine use during pregnancy, and the subjects in the clinical trials who became unintentionally pregnant were all followed for outcomes. The congenital anomalies which developed were varied in nature. A post-marketing commitment includes a pregnancy registry to follow subjects who may become pregnant after vaccination with Gardasil.
- In subjects who were pregnant after vaccination with Gardasil, the comparative rates of systemic and injection site adverse event rates were similar to those seen in the general study population, i.e., there was a higher rate of injections site adverse events in the Gardasil group as compared to control group, but a similar proportion of subjects with a systemic adverse event in each of the two treatment groups.
- The proportions of infants born to mothers participating in the studies with serious adverse events were similar in each of the two treatment groups, both in the neonatal period and outside the neonatal period.
- The proportion of infants with an adverse event born to a mother who was breastfeeding was slightly higher in the Gardasil group (1.9%) as compared to infants born to mothers who received control (0.8%). The imbalance was primarily due to an imbalance in the proportion of infants with a respiratory disorder (17 Gardasil

compared to 4 control). This imbalance was noted at the time of the original licensure, although the number of events was smaller at the original licensing action. The majority of the additional events which occurred in the Gardasil group since the time of original licensure occurred at an interval between vaccination and event that was >10 months. The number of infants with respiratory events which occurred within 30 days of vaccination is 6 in the Gardasil group and 2 in the control group. In an earlier review of the original cases, there was no recurrence of a similar event after revaccination of the mother, and the events occurred at varying times after each dose.

- The most common systemic adverse events in the 15 days after vaccination are headache, pyrexia, abdominal pain or discomfort, and nasopharyngitis, and the rates are comparable in each treatment group.
- The most common injection site adverse events in the 5 days after receipt of Gardasil was pain, erythema, and swelling, and these occurred at higher rates in the Gardasil group as compared to the control group. The majority of these injection site adverse events were rated as mild in each treatment group.
- There was a slightly higher rate of fever (most <102 ºF) in the 5 days after receipt of Gardasil (10.2%) as compared to the alum control or saline placebo (8.9%).
- Although not found to be statistically significantly different in a meta-analysis across all studies, there was a higher number of subjects with a new diagnosis of Rheumatoid arthritis/Juvenile rheumatoid arthritis in the Gardasil group (7) as compared to the control group (2). These cases occurred at varying times after vaccination. In addition, there was a higher number of cases of autoimmune thyroiditis in the Gardasil group (6) as compared to the control group (1), which was also not found to be statistically significant in a meta-analysis across all studies. In a recent cohort study of adolescent girls and young women conducted in a large HMO in the year before Gardasil was licensed, autoimmune events such as these occurred in approximately 10% of females in this age group who sought medical attention. The overall proportion of subjects with a potentially autoimmune event were similar between the two treatment groups (2.3% Gardasil, 2.4% control). These data are being provided in the updated package insert. A post-marketing safety surveillance study in the ----------(b)(4)---------- is underway in 44,000 subjects, and this study is near completion. This study may help identify if the rates of such autoimmune events are increased as compared to the rate expected in the vaccinated population.
- In the post-marketing period, several serious adverse events have been reported, including transverse myelitis, primary motor atrophy, amyotrophic lateral sclerosis, pancreatitis, Guillain-Barre syndrome, anaphylaxis, and death. Some of the deaths were ascribed to other causes, and some could not be confirmed, while several were still being reviewed (VAERS and CDC). The review has included comparison to expected rates of such events in the population, and to date, none have exceeded these rates, although analyses continue to be conducted.

10.4.1 Immunogenicity

In supplements 419, -(b)(4)-, and -(b)(4)-, follow-up immunogenicity data is provided. In addition, in the Month 24 and Month 30 reports for subjects participating in study HPV-018, follow-up immunogenicity reports ate also provided.

Study HPV-007-010
Immunogenicity data out to Month 60 was included. Three populations were considered for immunogenicity. In order to be eligible for inclusion in any of the 3, subjects must have received a 3-dose primary series of Gardasil or placebo and a dose of Gardasil at Month 60 and have serology data from the Month 61 visit.

The main analysis population for immunogenicity was the Extension Per-Protocol Immunogenicity (Extension PPI) Population. This population included all subjects enrolled in the extension phase, regardless of general protocol violations, which had the Month 61 serum sample collected within an appropriate day range relative to the Month 60 vaccination and were seronegative to the appropriate HPV type(s) at Day 1 and PCR negative to the appropriate HPV type(s) at Day 1 and through Month 60. Unlike the Per Protocol Immunogenicity (PPI) population used for the primary immunogenicity analysis in the main study of Protocol 007, no day range criteria for the vaccinations (primary series or fourth dose) were used to determine eligibility for analysis.

Plots of anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs from Day 1 through Month 60 are included in this review, because the anti-HPV 6, 11, 16, and 18 antibodies were similar to those observed at Month 24. These plots are included for each of the vaccine HPV types in Figures 7, 8, 9 and 10, respectively. Each figure includes 3 lines, one for subjects in the Extension PPI Population who received a primary series of Gardasil, one for subjects in the Extension PPI Population who received Placebo, and one for Placebo subjects who were seropositive and PCR-negative to the relevant HPV type at Day 1. The subject included the last group to provide a comparison of vaccine-induced anti-HPV levels with anti-HPV levels present in subjects with evidence of exposure to a vaccine HPV type prior to enrollment.

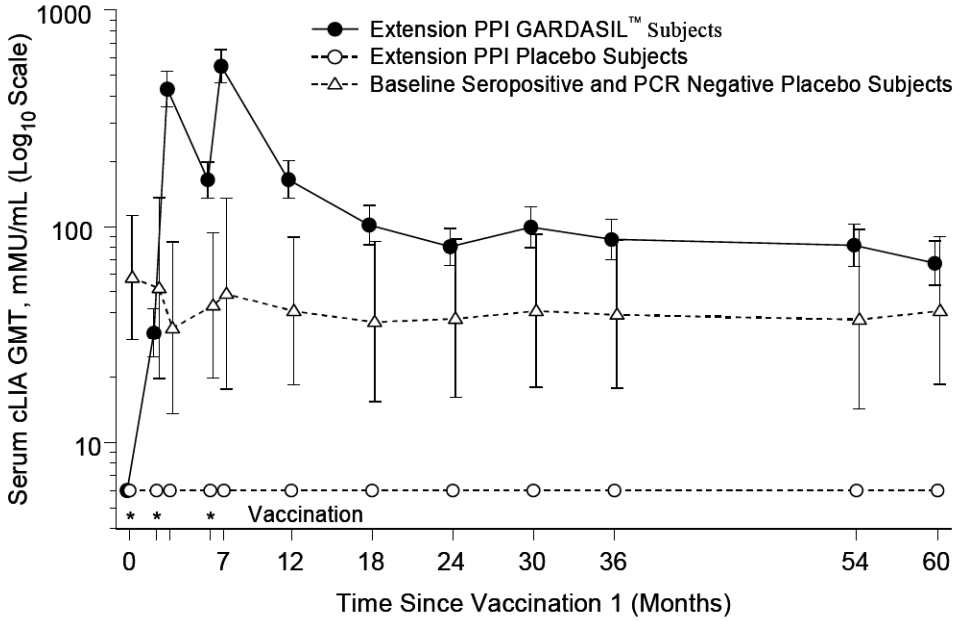
For all 4 HPV types, the highest anti-HPV levels among subjects in the Extension PPI Population who received Gardasil were observed at Month 7 (1 month Postdose 3). Thereafter, anti-HPV GMTs declined until Month 18 and then remained fairly steady through Month 60. For anti-HPV 6, 16, and 18 responses, the antibody levels observed from Month 18 through Month 60 in subjects who received Gardasil within the Extension PPI population remained higher than those observed in subjects who had evidence of exposure to the relevant vaccine HPV type prior to Day 1. For anti-HPV 11 responses, the observed GMTs from Month 24 through Month 60 among subjects in the Extension PPI population were lower than those observed in subjects who had evidence of exposure to the HPV 11 prior to Day 1; however, the sample sizes in the latter group were too small to calculate meaningful confidence intervals, making such comparisons difficult. Seropositivity rates among subjects in the Extension PPI Population who received a primary series of 3 doses of Gardasil remained above 89% for HPV Types 6, 11, and 16 through Month 60 (89.9%, 91.1%, and 98.8% for HPV Types 6, 11, and 16, respectively). Seropositivity rates for HPV 18 in the same subjects declined more rapidly than the rates for the other three vaccine HPV types, but remained above 64% at Month 60. Of note, there were no cases of HPV 18 infection among subjects who received Gardasil and who became HPV 18-seronegative during the Post-Month 7 follow-up period (there was one case of persistent HPV 18 in the group that received Gardasil in the PPE population; however, that subject remained anti-HPV 18 positive prior to and during

the course of her infection; she became seronegative only after her infection had already resolved). On the other hand, in the placebo group within the PPE population, 11 subjects developed persistent HPV 18 infection. For all 4 HPV types, seropositivity rates in Extension PPI Population subjects who received 3 primary doses of Gardasil and a fourth dose of GARDASIL at Month 60 were >96% by 1 Week Postdose 4.

During the course of the 60 month follow-up, 10.6%, 9.4%, 13.7%, and 8.7% of placebo subjects within the Extension PPI Population became anti-HPV 6, 11, 16, and 18 seropositive, respectively, on at least one visit. None of these subjects were found to have had a persistent HPV 6, 11, 16, or 18 infection, respectively, at or prior to the visit in which seropositivity was first detected.

FIGURE 5

Longitudinal Plot of Anti-HPV 6 Serum cLIA GMTs (and 95% Confidence Intervals) From Day 1 Through Month 60

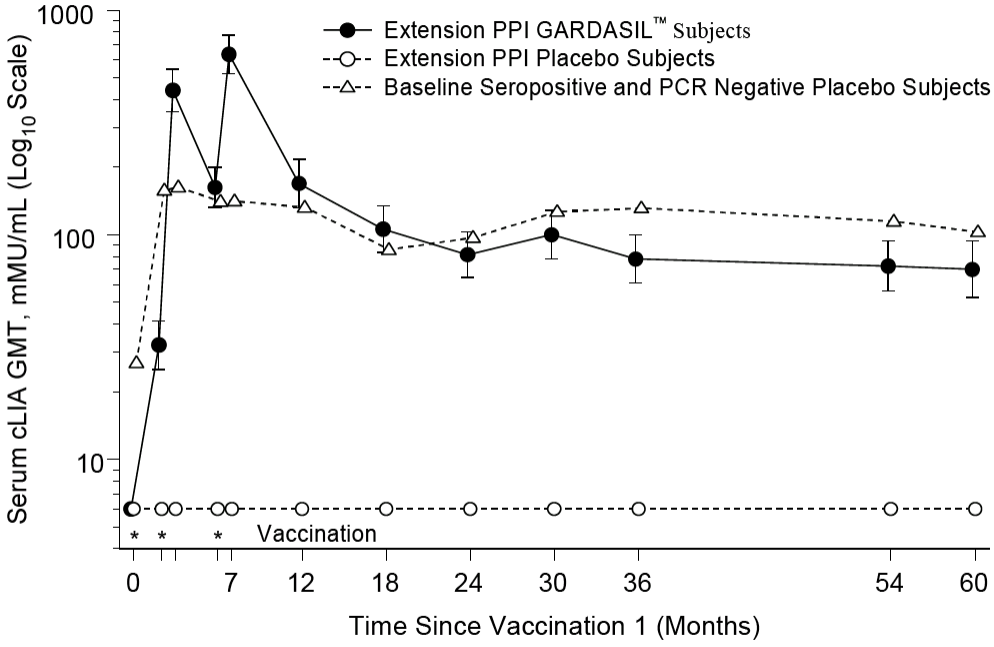


HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titers; mMU = Milli Merck unit; PPI = Per-protocol immunogenicity; PCR = Polymerase chain reaction.

Source: STN 125126/419.9, CSR 007-010, Figure 4-3, p. 80

FIGURE 6

Longitudinal Plot of Anti-HPV 11 Serum cLIA GMTs (and 95% Confidence Intervals) From Day 1 Through Month 60

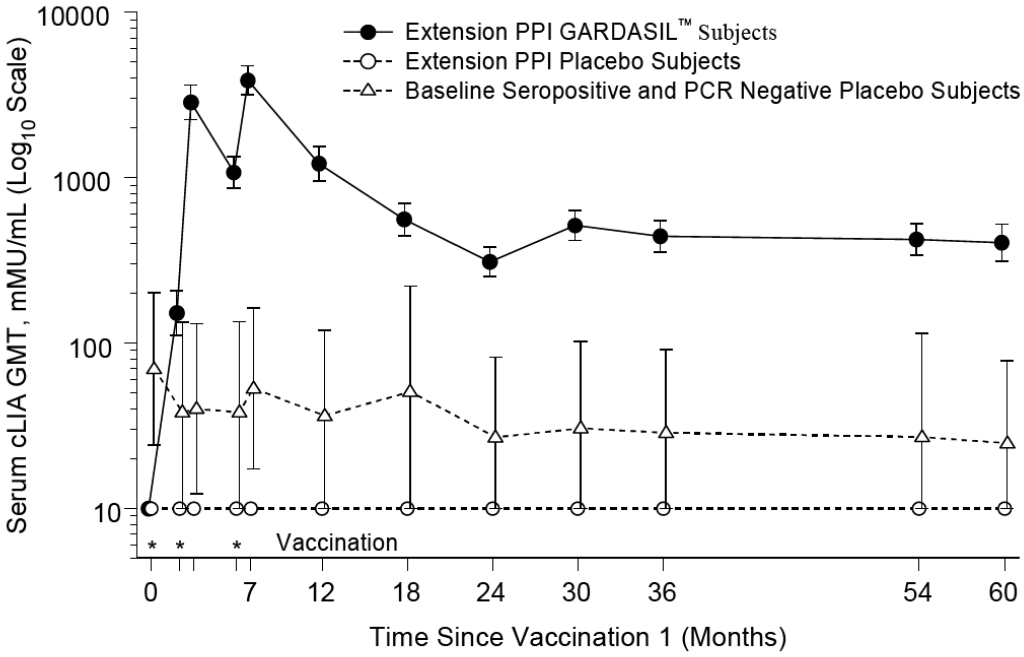


HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titers; mMU = Milli Merck unit; PPI = Per-protocol immunogenicity; PCR = Polymerase chain reaction.

Source: STN 125126/419.0, CSR 007-010, Figure 4-4, p. 81

FIGURE 7

Longitudinal Plot of Anti-HPV 16 Serum cLIA GMTs (and 95% Confidence Intervals) From Day 1 Through Month 60

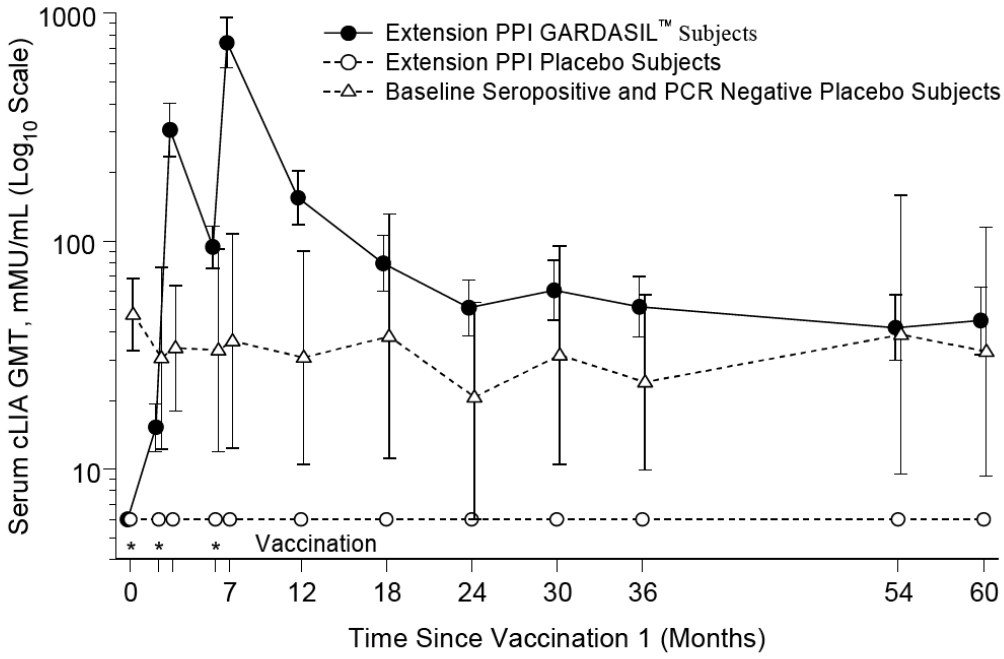


HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titers; mMU = Milli Merck unit; PPI = Per-protocol immunogenicity; PCR = Polymerase chain reaction.

Source: STN 125126/419.0, CSR 007-010, Figure 4-5, p. 82

FIGURE 8

Longitudinal Plot of Anti-HPV 18 Serum cLIA GMTs (and 95% Confidence Intervals) From Day 1 Through Month 60



HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titers; mMU = Milli Merck unit; PPI = Per-protocol immunogenicity; PCR = Polymerase chain reaction.

Source: STN 125126/419.0, CSR 007-010, Figure 4-6, p. 83

The sponsor notes that the observed anti-HPV 16 and anti-HPV 18 Geometric Mean Titers (GMTs) one month following a fourth dose of Gardasil, among subjects who received 3 primary doses of Gardasil, were higher than those 1 month following a first dose of Gardasil, among subjects who received 3 primary doses of placebo. There is no documented need for a 4th dose of Gardasil at this time, and actual efficacy data is lacking for recommendation for a 4th dose. A post-marketing study is in progress to follow long term efficacy and duration of effect of vaccination.

The actual summaries of GMTs and seropositivity rates for subjects who received 3 doses of Gardasil as their primary series in study HPV-007, and then went onto receive a 4th dose of Gardasil at Month 60 is shown in Tables 84, 85, 86, 87, 88, 89, 90, and 91.

TABLE 84
Study HPV-007: Summary of Anti-HPV 6 cLIA Geometric Mean Titers by Vaccination Group (Extension Per-Protocol Immunogenicity Population)

	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™		
Study Time	n	GMT (mMU/mL)	(95% CI)
Day 1	80	<8	(<8, <8)
Month 02	80	32.1	(24.8, 41.7)
Month 03	80	431.4	(357.2, 521.0)
Month 06	80	164.1	(135.6, 198.5)
Month 07	80	549.2	(460.6, 654.7)
Month 12	80	164.8	(135.0, 201.3)
Month 18	80	101.7	(82.6, 125.1)
Month 24	80	80.7	(66.2, 98.3)
Month 30	80	99.3	(79.6, 123.8)
Month 36	80	87.2	(70.3, 108.1)
Month 54	73	81.9	(65.4, 102.6)
Month 60	79	67.7	(53.5, 85.7)
Month 60 + 1 Week	79	503.3	(344.2, 736.1)
Month 61	80	693.2	(451.9, 1,063.3)

† The Extension Per-Protocol Immunogenicity Population includes all extension subjects who received three primary series injections of Gardasil and a fourth dose of Gardasil at Month 60, were seronegative and PCR-negative at Day 1 and PCR-negative through Month 60 to the respective HPV type(s), and had valid serology data 4 weeks Postdose 4.
n = Number of subjects contributing to the analysis.
Source: STN 125126/419.0, CSR 007-010, Table 7-6, p. 173

TABLE 85

Study HPV-007: Summary of HPV 6 cLIA Seropositivity Rates by Vaccination Group (Extension Per-Protocol Immunogenicity Population)

	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™			
		Seropositive		
Study Time	n	m	Percent	(95% CI)
Day 1	80	0	0.0	(0.0%, 4.5%)
Month 02	80	59	73.8	(62.7%, 83.0%)
Month 03	80	80	100	(95.5%, 100%)
Month 06	80	80	100	(95.5%, 100%)
Month 07	80	80	100	(95.5%, 100%)
Month 12	80	80	100	(95.5%, 100%)
Month 18	80	78	97.5	(91.3%, 99.7%)
Month 24	80	76	95.0	(87.7%, 98.6%)
Month 30	80	76	95.0	(87.7%, 98.6%)
Month 36	80	76	95.0	(87.7%, 98.6%)
Month 54	73	69	94.5	(86.6%, 98.5%)
Month 60	79	71	89.9	(81.0%, 95.5%)
Month 60 + 1 Week	79	76	96.2	(89.3%, 99.2%)
Month 61	80	76	95.0	(87.7%, 98.6%)

† The Extension Per-Protocol Immunogenicity Population includes all extension subjects who received three primary series injections of Gardasil and a fourth dose of Gardasil at Month 60, were seronegative and PCR-negative at Day 1 and PCR-negative through Month 60 to the respective HPV type(s), and had valid serology data 4 weeks Postdose 4.

n = Number of subjects contributing to the analysis.

m=Number of subjects who were seropositive

Source: STN 125126/419.0, CSR 007-010, Table 7-10, p. 177

TABLE 86

Study HPV-007: Summary of Anti-HPV 11 cLIA Geometric Mean Titers by Vaccination Group (Extension Per-Protocol Immunogenicity Population)

	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™		
		GMT	
Study Time	n	(mMU/mL)	(95% CI)
Day 1	80	<8	(<8, <8)
Month 02	80	32.3	(25.1, 41.4)
Month 03	80	439.4	(352.7, 547.3)
Month 06	80	162.6	(132.3, 199.8)
Month 07	80	635.5	(521.3, 774.9)
Month 12	76	169.1	(132.1, 216.6)
Month 18	80	105.7	(83.4, 134.0)
Month 24	78	81.4	(64.4, 102.8)
Month 30	80	100.1	(77.9, 128.6)
Month 36	74	78.0	(61.0, 99.9)
Month 54	73	72.5	(56.0, 93.9)
Month 60	79	70.1	(52.5, 93.7)
Month 60 + 1 Week	79	1,417.5	(1,009.0, 1,991.4)
Month 61	80	2,652.4	(1,956.7, 3,595.3)

† The Extension Per-Protocol Immunogenicity Population includes all extension subjects who received three primary series injections of Gardasil and a fourth dose of Gardasil at Month 60, were seronegative and PCR-negative at Day 1 and PCR-negative through Month 60 to the respective HPV type(s), and had valid serology data 4 weeks Postdose 4.

n = Number of subjects contributing to the analysis.

Source: STN 125126/419.0, CSR 007-010, Table 7-7, p. 174

TABLE 87

Study HPV-007: Summary of HPV 11 cLIA Seropositivity Rates by Vaccination Group (Extension Per-Protocol Immunogenicity Population)

	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™			
		Seropositive		
Study Time	n	m	Percent	(95% CI)
Day 1	80	0	0.0	(0.0%, 4.5%)
Month 02	80	62	77.5	(66.8%, 86.1%)
Month 03	80	80	100	(95.5%, 100%)
Month 06	80	79	98.8	(93.2%, 100%)
Month 07	80	80	100	(95.5%, 100%)
Month 12	76	75	98.7	(92.9%, 100%)
Month 18	80	78	97.5	(91.3%, 99.7%)
Month 24	78	73	93.6	(85.7%, 97.9%)
Month 30	80	77	96.3	(89.4%, 99.2%)
Month 36	74	72	97.3	(90.6%, 99.7%)
Month 54	73	66	90.4	(81.2%, 96.1%)
Month 60	79	72	91.1	(82.6%, 96.4%)
Month 60 + 1 Week	79	78	98.7	(93.1%, 100%)
Month 61	80	79	98.8	(93.2%, 100%)

† The Extension Per-Protocol Immunogenicity Population includes all extension subjects who receive three primary series injections of Gardasil and a fourth dose of Gardasil at Month 60, were seronegative and PCR-negative at Day 1 and PCR-negative through Month 60 to the respective HPV type(s), and had valid serology data 4 weeks Postdose 4.
n = Number of subjects contributing to the analysis.
m=Number of subjects who were seropositive

Source: STN 125126/419.0, CSR 007-010, Table 7-11, p. 178

TABLE 88

Study HPV-007: Summary of Anti-HPV 16 cLIA Geometric Mean Titers by Vaccination Group (Extension Per-Protocol Immunogenicity Population)

	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™		
		GMT	
Study Time	n	(mMU/mL)	(95% CI)
Day 1	82	<12	(<12, <12)
Month 02	82	151.7	(111.2, 207.0)
Month 03	82	2,848.1	(2,236.4, 3,627.1)
Month 06	81	1,074.9	(863.5, 1,337.9)
Month 07	82	3,870.0	(3,157.0, 4,744.0)
Month 12	69	1,212.6	(950.9, 1,546.3)
Month 18	75	557.9	(443.6, 701.7)
Month 24	79	310.1	(252.3, 381.2)
Month 30	82	512.2	(415.2, 631.8)
Month 36	82	441.6	(353.5, 551.5)
Month 54	74	423.2	(339.8, 527.0)
Month 60	82	404.2	(312.9, 522.1)
Month 60 + 1 Week	81	4,466.4	(3,095.2, 6,445.0)
Month 61	81	5,714.0	(3,829.7, 8,525.4)

† The Extension Per-Protocol Immunogenicity Population includes all extension subjects who received three primary series injections of Gardasil and a fourth dose of Gardasil at Month 60, were seronegative and PCR-negative at Day 1 and PCR-negative through Month 60 to the respective HPV type(s), and had valid serology data 4 weeks Postdose 4.
n = Number of subjects contributing to the analysis.

Source: STN 125126/419.0, CSR 007-010, Table 7-8, p. 175

TABLE 89

Study HPV-007: Summary of HPV 16 cLIA Seropositivity Rates by Vaccination Group (Extension Per-Protocol Immunogenicity Population)

	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™			
		Seropositive		
Study Time	n	m	Percent	(95% CI)
Day 1	82	0	0.0	(0.0%, 4.4%)
Month 02	82	77	93.9	(86.3%, 98.0%)
Month 03	82	82	100	(95.6%, 100%)
Month 06	81	81	100	(95.5%, 100%)
Month 07	82	82	100	(95.6%, 100%)
Month 12	69	69	100	(94.8%, 100%)
Month 18	75	75	100	(95.2%, 100%)
Month 24	79	79	100	(95.4%, 100%)
Month 30	82	82	100	(95.6%, 100%)
Month 36	82	82	100	(95.6%, 100%)
Month 54	74	74	100	(95.1%, 100%)
Month 60	82	81	98.8	(93.4%, 100%)
Month 60 + 1 Week	81	81	100	(95.5%, 100%)
Month 61	81	80	98.8	(93.3%, 100%)

† The Extension Per-Protocol Immunogenicity Population includes all extension subjects who received three primary series injections of Gardasil and a fourth dose of Gardasil at Month 60, were seronegative and PCR-negative at Day 1 and PCR-negative through Month 60 to the respective HPV type(s), and had valid serology data 4 weeks Postdose 4.

n = Number of subjects contributing to the analysis.

m=Number of subjects who were seropositive

Source: STN 125126/419.0, CSR 007-010, Table 7-12, p. 179

TABLE 90

Study HPV-007: Summary of Anti-HPV 18 cLIA Geometric Mean Titers by Vaccination Group (Extension Per-Protocol Immunogenicity Population)

	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™		
		GMT	
Study Time	n	(mMU/mL)	(95% CI)
Day 1	86	<8	(<8, <8)
Month 02	86	15.2	(11.9, 19.3)
Month 03	86	306.8	(234.1, 402.0)
Month 06	86	94.1	(76.2, 116.2)
Month 07	86	741.2	(576.8, 952.4)
Month 12	86	154.7	(117.9, 202.9)
Month 18	86	79.7	(60.1, 105.7)
Month 24	86	50.9	(38.4, 67.3)
Month 30	86	60.7	(44.7, 82.4)
Month 36	86	51.4	(37.9, 69.8)
Month 54	78	41.6	(29.9, 57.9)
Month 60	85	44.7	(31.8, 62.8)
Month 60 + 1 Week	84	1,033.2	(753.9, 1,415.8)
Month 61	86	1,230.0	(904.5, 1,672.5)

† The Extension Per-Protocol Immunogenicity Population includes all extension subjects who received three primary series injections of Gardasil and a fourth dose of Gardasil at Month 60, were seronegative and PCR-negative at Day 1 and PCR-negative through Month 60 to the respective HPV type(s), and had valid serology data 4 weeks Postdose 4.

n = Number of subjects contributing to the analysis.

Source: STN 125126/419.0, CSR 007-010, Table 7-9, p. 176

TABLE 91
Study HPV-007: Summary of HPV 18 cLIA Seropositivity Rates by Vaccination Group (Extension Per-Protocol Immunogenicity Population)

	Primary Series of GARDASIL™ + Challenge Dose of GARDASIL™			
		Seropositive		
Study Time	n	m	Percent	(95% CI)
Day 1	86	0	0.0	(0.0%, 4.2%)
Month 02	86	28	32.6	(22.8%, 43.5%)
Month 03	86	84	97.7	(91.9%, 99.7%)
Month 06	86	82	95.3	(88.5%, 98.7%)
Month 07	86	85	98.8	(93.7%, 100%)
Month 12	86	80	93.0	(85.4%, 97.4%)
Month 18	86	73	84.9	(75.5%, 91.7%)
Month 24	86	62	72.1	(61.4%, 81.2%)
Month 30	86	65	75.6	(65.1%, 84.2%)
Month 36	86	63	73.3	(62.6%, 82.2%)
Month 54	78	50	64.1	(52.4%, 74.7%)
Month 60	85	55	64.7	(53.6%, 74.8%)
Month 60 + 1 Week	84	82	97.6	(91.7%, 99.7%)
Month 61	86	84	97.7	(91.9%, 99.7%)

The Extension Per-Protocol Immunogenicity Population includes all extension subjects who received three primary series injections of Gardasil and a fourth dose of Gardasil at Month 60, were seronegative and PCR-negative at Day 1 and PCR-negative through Month 60 to the respective HPV type(s), and had valid serology data 4 weeks Postdose 4.
n = Number of subjects contributing to the analysis.
m=Number of subjects who were seropositive
Source: STN 125126/419, CSR 007-010, Table 7-13, p. 180

The sponsor also presented the end of study immunogenicity results for subjects who participated in studies HPV-013 and HPV-015.

In review, for study HPV-013, the Per Protocol Immunogenicity (PPI) population included subjects who received all 3 vaccinations within the day ranges prespecified in the data analysis plan did not deviate from the study protocol in ways that could have interfered with the effects of the vaccine or detection of the immunogenicity endpoint; did not have DNA detection of the relevant HPV type(s) between Day 1 and Month 7, inclusive, were seronegative to the relevant HPV type(s) at Day 1, and underwent specimen collection within the day ranges prespecified in the data analysis plan. The PPI analysis population differed from the PPE population in that it included only subjects who received all 3 vaccinations within acceptable day ranges and had the Month 7 serum sample collected within an acceptable day range. A summary of GMTs in the "all type-specific HPV-naïve subjects with serology data" cohort was also provided as a supplement to the PPI analyses.

Immunogenicity data summaries are presented for the following time points: month 7, month 12, month 24 and 'End of Study'. The latter time point refers to all timepoints within 6 months of 44 months. The reason for this approach is that, per the DSMB mandate, the month 48 visits were scheduled early and many subjects had immunogenicity data collected before month 48. Almost all subjects in the Gardasil group had seroconverted to each vaccine HPV type by Month 7, and the percent of subjects who were seropositive to HPV 6, HPV 11, and HPV 16 remained high at Month

24. The seropositivity rates decreased over time, especially for HPV type 18. For HPV types 6, 11 and 16 the seropositivity rate at 'End of study' was above 90% but for HPV type 18, it was 62%.

Despite the decreasing seroconversion rate for HPV type 18, there were no cases of HPV type 18-related CIN or EGL observed in any of the populations analyzed. Protective efficacy despite seronegativity has been observed for Hepatitis B vaccine. The sponsor postulates that Gardasil induces immune memory and that protective anti-HPV levels, including HPV 18, may similarly develop in response to exposure. Longer term follow-up will be required to evaluate the duration of efficacy for each component of Gardasil.

Summaries of the anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 serum cLIA seropositivity and GMTs in the PPI population are presented in Tables 92 and 93. At this time, no universally accepted reference standards exist, and absolute anti-HPV cLIA levels across the 4 HPV types are not comparable. The GMTs decrease over time, although the reductions between Month 24 and Month 48 are modest. For HPV type 18, the percentage drop in GMTs from Month 7 to 'End of Study' for HPV type 18 was larger than for the other HPV types.

Longitudinal plots of the GMTs for each vaccine HPV type in the PPI analysis population are presented in Figures 9-12. For comparison, the anti-HPV serum cLIA GMTs for the baseline seropositive and PCR negative subjects who received placebo are also plotted. These are subjects who had presumably been infected with the relevant vaccine HPV type, mounted an immune response to the infection, and then cleared that infection prior to enrollment. These subjects were also required to have their Day 1 serology and PCR samples collected within acceptable day ranges, to have a Month 7 serology sample collected within an acceptable day range, to have received the correct clinical material, and to have received all 3 vaccinations. The GMTs observed in these subjects provide a reference against which to evaluate vaccine-induced anti-HPV responses. At Month 7, anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs in Gardasil recipients in the PPI population were substantially higher than the corresponding GMTs in those presumably naturally infected subjects. At the end of the study, the anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs in subjects in Gardasil group in the PPI population remained higher than the GMTs in the presumably naturally infected subjects.

Of note, seropositivity increased over time in placebo subject. This finding reflects the development of new HPV 6, 11, 16, and 18 infections among placebo subjects, which has been shown to result in seroconversion in approximately 50 to 70% of cases.

The results in the "all type-specific HPV-naïve subjects with serology data" are similar to those in the PPI population; GMTs declined between Month 7 and 'End of Study' for all HPV types. The seropositivity rates are also similar in the "all type-specific HPV naïve subjects with serology data" are similar to those in the PPI population.

TABLE 92
Summary of Anti-HPV cLIA Seropositivity Rates by Vaccination Group (Per-Protocol Immunogenicity Population) (Study HPV-013)

Assay (cLIA)	Time Point	qHPV Vaccine (N=2,717)			
			Seropositive		
		n	m	Percent	95% CI
Anti-HPV 6	Month 07	1,582	1,576	99.6%	(99.2%, 99.9%)
	Month 12	1,501	1,490	99.3%	(98.7%, 99.6%)
	Month 24	1,447	1,382	95.5%	(94.3%, 96.5%)
	End of Study‡	1,436	1,300	90.5%	(88.9%, 92.0%)
Anti-HPV 11	Month 07	1,605	1,598	99.6%	(99.1%, 99.8%)
	Month 12	1,520	1,511	99.4%	(98.9%, 99.7%)
	Month 24	1,477	1,448	98.0%	(97.2%, 98.7%)
	End of Study‡	1,459	1,392	95.4%	(94.2%, 96.4%)
Anti-HPV 16	Month 07	1,559	1,554	99.7%	(99.3%, 99.9%)
	Month 12	1,458	1,451	99.5%	(99.0%, 99.8%)
	Month 24	1,425	1,417	99.4%	(98.9%, 99.8%)
	End of Study‡	1,422	1,406	98.9%	(98.2%, 99.4%)
Anti-HPV 18	Month 07	1,664	1,652	99.3%	(98.7%, 99.6%)
	Month 12	1,558	1,394	89.5%	(87.8%, 91.0%)
	Month 24	1,539	1,139	74.0%	(71.7%, 76.2%)
	End of Study‡	1,520	944	62.1%	(59.6%, 64.6%)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
m=number of subjects who were seropositive
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units.
‡End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months\ of the approximate mean interval of 44 months.
Source: STN 125126/-(b)(4)-, CSR 013-010, Table 11-32, p. 82

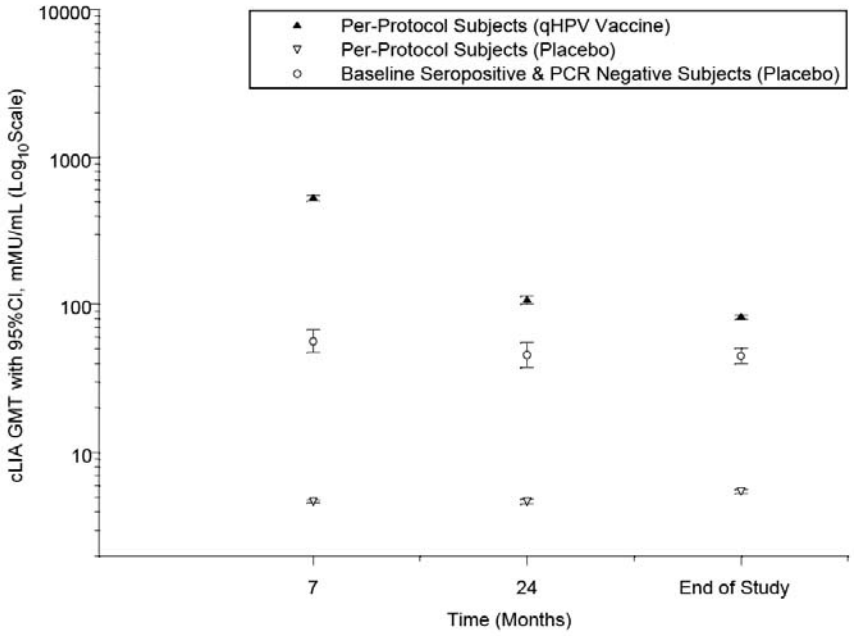
TABLE 93
Summary of Anti-HPV cLIA Geometric Mean Titers by Vaccination Group (Per-Protocol Immunogenicity Population) (Study HPV-013)

Assay (cLIA)	Time Point	qHPV Vaccine (N=2,717)		
		n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Month 07	1,582	547.1	(524.8, 570.2)
	Month 12	1,501	208.0	(198.8, 217.7)
	Month 24	1,447	117.5	(111.7, 123.5)
	End of Study‡	1,436	77.9	(73.9, 82.1)
Anti-HPV 11	Month 07	1,605	773.5	(737.8, 810.9)
	Month 12	1,520	261.6	(249.2, 274.7)
	Month 24	1,477	150.2	(142.8, 158.0)
	End of Study‡	1,459	93.3	(88.5, 98.3)
Anti-HPV 16	Month 07	1,559	2,208.8	(2,070.3, 2,356.6)
	Month 12	1,458	901.7	(851.9, 954.5)
	Month 24	1,425	476.8	(450.8, 504.3)
	End of Study‡	1,422	347.6	(327.6, 369.0)
Anti-HPV 18	Month 07	1,664	463.2	(439.6, 488.2)
	Month 12	1,558	114.0	(106.9, 121.5)
	Month 24	1,539	56.2	(52.3, 60.4)
	End of Study‡	1,520	36.1	(33.6, 38.8)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis; CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units ; ‡End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months.
Source: STN 125126/-(b)(4)-,CSR 013-010

FIGURE 9
Study HPV-013

Longitudinal Plot of Anti-HPV 6 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)

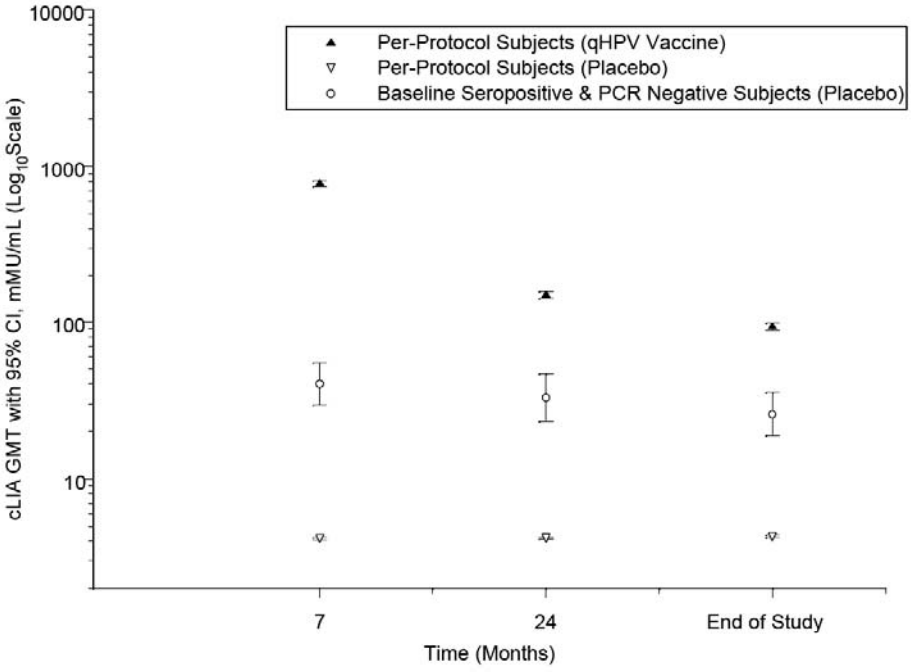


cLIA=Competitive luminex assay; GMT=Geometric mean titer; HPV=Human papillomavirus; PCR=Polymerase chain reaction; End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months

Source: STN 125126/-(b)(4)-, CSR 013-010, Figure 11-1, p. 255

FIGURE 10
Study HPV-013

Longitudinal Plot of Anti-HPV 11 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)

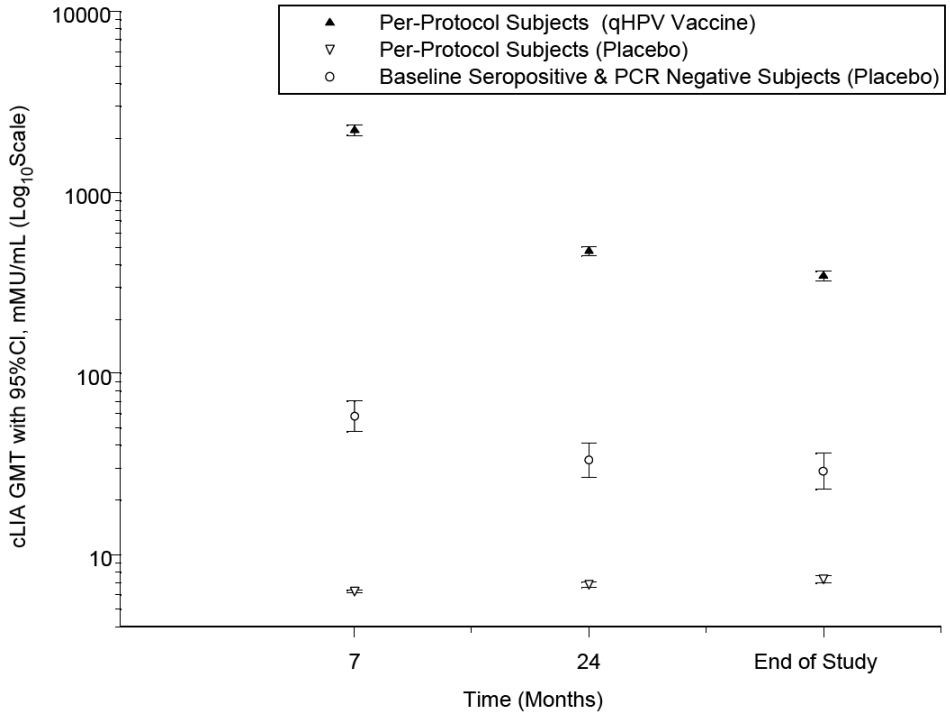


cLIA=Competitive luminex assay; GMT=Geometric mean titer; HPV=Human papillomavirus; PCR=Polymerase chain reaction; End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months

Source: STN 125126/-(b)(4)-, CSR 015-010, Figure 11-2, p. 256

FIGURE 11
Study HPV-013

Longitudinal Plot of Anti-HPV 16 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)

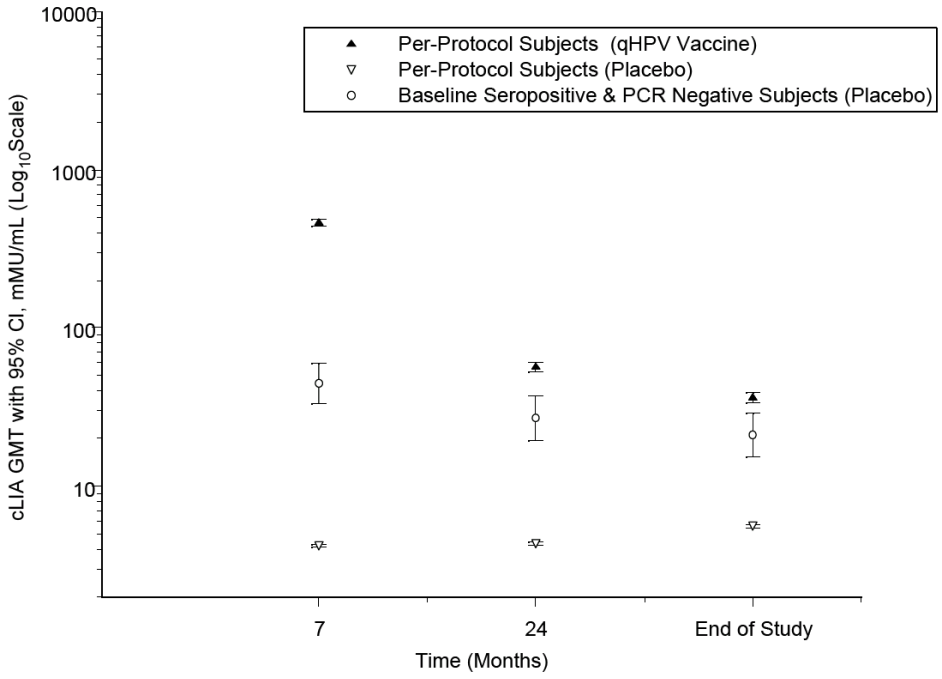


cLIA=Competitive luminex assay; GMT=Geometric mean titer; HPV=Human papillomavirus; PCR=Polymerase chain reaction; End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months

Source: STN 125126/-(b)(4)-, CSR 015-010, Figure 11-3, p. 257

FIGURES 12
Study HPV-013

Longitudinal Plot of Anti-HPV 18 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)



cLIA=Competitive luminex assay; GMT=Geometric mean titer; HPV=Human papillomavirus; PCR=Polymerase chain reaction; End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months

Source: STN 125126/-(b)(4)-, CSR 015-010, Figure 11-4, p. 258

The sponsor also presented immune responses in subjects who were seropositive and PCR negative, seropositive and PCR positive, and seronegative and PCR positive, in addition to those who were seronegative and PCR negative. In general, subjects who were seropositive to the relevant vaccine HPV type at baseline (Day 1) had higher GMTs at month 07, month 24 and 'End of Study' than those who were seronegative (regardless of PCR status at Day 1) to the same vaccine HPV type(s) at Day 1. The difference between groups based on baseline serostatus and PVR status appears to diminish at the time of "end of study" analysis.

TABLE 94

End of Study‡ Anti-HPV cLIA Geometric Mean Titers by Day 1 Serostatus and PCR Status (Study HPV-013)

HPV Type	Cohort		qHPV Vaccine (N=2,717)		
				GMT (mMU/mL)	
	Day 1 Serostatus	Day 1 PCR Status	n	GMT	(95% CI)
HPV 6	Negative	Negative	1,879	79.4	(75.9, 83.1)
	Negative	Positive	41	102.1	(76.5, 136.3)
	Positive	Negative	133	370.4	(309.1, 444.0)
	Positive	Positive	24	348.0	(243.8, 496.7)
HPV 11	Negative	Negative	1,879	95.8	(91.5, 100.3)
	Negative	Positive	10	105.2	(62.7, 176.6)
	Positive	Negative	41	541.3	(366.8, 798.9)
	Positive	Positive	5	500.3	(230.4, 1,086.1)
HPV 16	Negative	Negative	1,780	363.1	(344.6, 382.7)
	Negative	Positive	99	445.1	(369.2, 536.8)
	Positive	Negative	155	787.7	(661.9, 937.3)
	Positive	Positive	85	719.6	(563.5, 918.9)
HPV 18	Negative	Negative	1,993	35.7	(33.5, 38.0)
	Negative	Positive	53	52.4	(35.2, 77.9)
	Positive	Negative	60	178.4	(121.8, 261.3)
	Positive	Positive	14	274.9	(189.2, 399.4)

Subjects were required to have completed the vaccination regimen, received the correct clinical material, and have the Month 7 serum sample collected within an acceptable day range.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.; n = Number of subjects evaluable in the given cohort.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; NA = Vaccine efficacy and confidence interval not computed; mMU = Milli Merck units; PCR = Polymerase chain reaction;

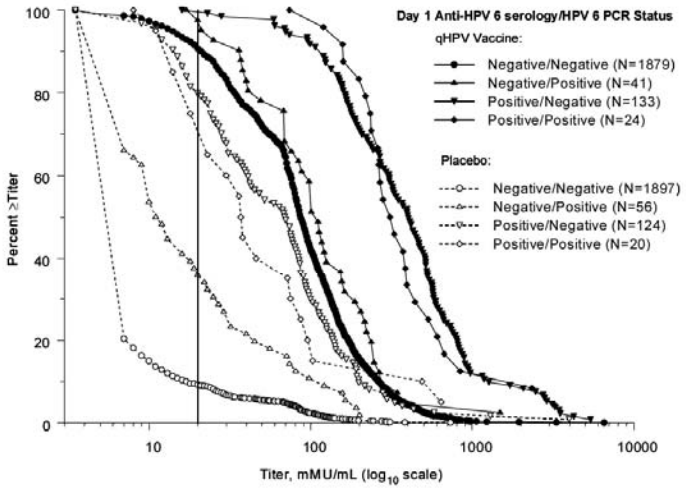
‡End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months.

Source: STN 125126/-(b)(4)-, Table 11-33, CSR 013-010, p. 262

Reverse cumulative distribution function (RCDF) plots of 'End of study' anti-HPV serum cLIA responses are included in Figures 13-16 for HPV types 6, 11, 16, and 18, respectively. Subjects were required to have their Day 1 serum and PCR samples collected within acceptable day ranges, to have a Month 7 serum sample collected within an acceptable day range, to have received the correct clinical material, and to have received all 3 vaccinations. Unlike subjects in the PPI population, subjects in the seronegative and PCR negative cohort were not required to be PCR negative through Month 7 for the relevant HPV type(s). For summaries presented for subjects who were seronegative to HPV 6 or HPV 11, subjects were required to be seronegative to both HPV 6 and HPV 11 at baseline (Day 1) due to the potential cross-reaction of antibody to these 2 HPV types. Likewise, for summaries presented for subjects who were PCR negative to HPV 6 or HPV 11, subjects were required to be PCR negative to both HPV 6 and HPV 11 at baseline (Day 1).

FIGURE 13
Study HPV-013

Reverse Cumulative Distribution Plot of 'End of study' Anti-HPV 6 cLIA Levels

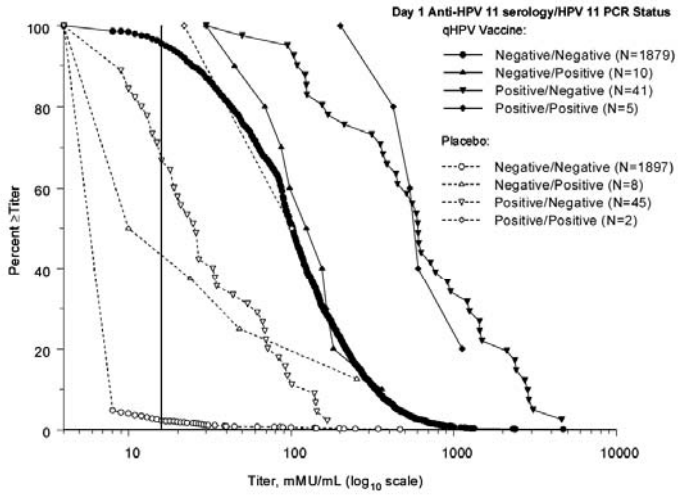


Note: The vertical line corresponds to the anti-HPV 6 cLIA cutoff value for being seropositive to HPV 6.
cLIA = Competitive luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months

Source: STN 125126/-(b)(4)-, CSR 013-010, Figure 14-6, p. 469

FIGURE 14
Study HPV-013

Reverse Cumulative Distribution Plot of 'End of study' Anti-HPV 11 cLIA Levels

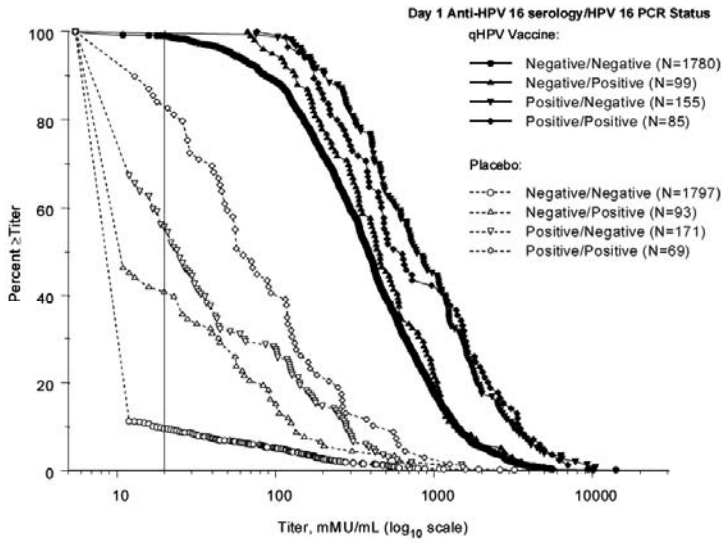


Note: The vertical line corresponds to the anti-HPV 6 cLIA cutoff value for being seropositive to HPV 6.
cLIA = Competitive luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months

Source: STN 125126/-(b)(4)-, CSR 013-010, Figure 14-7, p. 470

FIGURE 15
Study HPV-013

Reverse Cumulative Distribution Plot of 'End of study' Anti-HPV 16 cLIA Levels

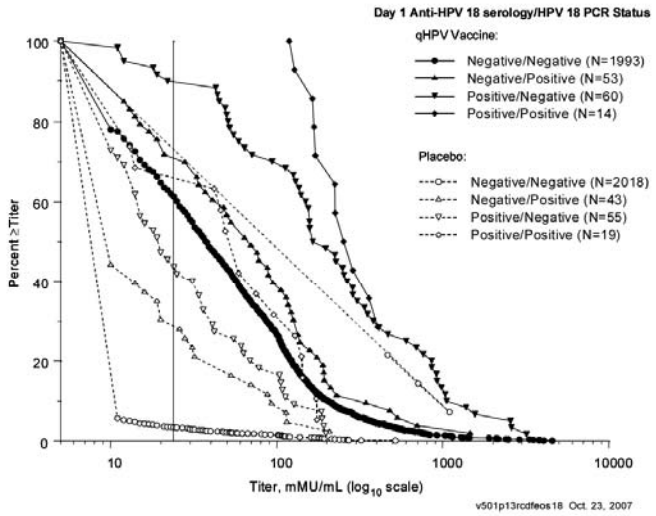


Note: The vertical line corresponds to the anti-HPV 6 cLIA cutoff value for being seropositive to HPV 6.
cLIA = Competitive luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months

Source: STN 125126/-(b)(4)-, CSR 013-010, Figure 14-8, p. 471

FIGURE 16
HPV-013

Reverse Cumulative Distribution Plot of 'End of study' Anti-HPV 18 cLIA Levels



Note: The vertical line corresponds to the anti-HPV 6 cLIA cutoff value for being seropositive to HPV 6.
cLIA = Competitive luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months

Source: STN 125126/-(b)(4)-, CSR 013-010, Figure 14-9, p. 472

For Study HPV-015, findings were similar to those seen in study HPV-013. Table 95 summarizes anti-HPV seropositivity or seroconversion) percentages by vaccination group in the PPI population for each time point. In the Gardasil group, the proportions of subjects remaining seropositive through the end of study remained high for HPV types 6, 11 and 16. For HPV 18, 62.9% of subjects in the Gardasil group were seropositive at the end of study visit. Summaries of the anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 serum cLIA GMTs in the PPI population are presented in Table 96, along with 95% confidence intervals for each vaccination group, HPV vaccine type, and time point. By the end of study visit, GMTs in the Gardasil group had declined to between 76% to 93% of their Month 24 value, depending on HPV type. For all HPV types, the lower bound of the 95% CI for the end of study GMT remained above the serostatus cutoff value. Despite the decreasing seroconversion rate for HPV type 18, there was only a single case of HPV type 18-related CIN , and no cases of HPV type 18-related EGL observed in the per-protocol population.

Longitudinal plots of the GMTs for each vaccine HPV type in the PPI analysis population are presented in Figures 17-20. In the Gardasil group, GMTs remained at or above the level of subjects naturally infected with HPV prior to the start of the study. Seropositivity increased over time in placebo subjects. This finding reflects the development of new HPV 6, 11, 16, and 18 infections among placebo subjects, which results in seroconversion in approximately 50 to 70% of cases.

TABLE 95
Summary of Anti-HPV cLIA Seropositivity Rates by Vaccination Group (Per-Protocol Immunogenicity Population) (Study HPV-015)

		qHPV Vaccine (N=6,082)			
			Seropositive		
Assay (cLIA)	Time Point	n	m	Percent	95% CI
Anti-HPV 6	Month 07	1,056	1,054	99.8%	(99.3%, 100%)
	Month 24	1,041	995	95.6%	(94.1%, 96.7%)
	End of Study‡	3,878	3,522	90.8%	(89.9%, 91.7%)
Anti-HPV 11	Month 07	1,057	1,054	99.7%	(99.2%, 99.9%)
	Month 24	1,041	1,014	97.4%	(96.2%, 98.3%)
	End of Study‡	3,879	3,689	95.1%	(94.4%, 95.8%)
Anti-HPV 16	Month 07	1,017	1,014	99.7%	(99.1%, 99.9%)
	Month 24	1,006	999	99.3%	(98.6%, 99.7%)
	End of Study‡	3,752	3,704	98.7%	(98.3%, 99.1%)
Anti-HPV 18	Month 07	1,140	1,133	99.4%	(98.7%, 99.8%)
	Month 24	1,125	763	67.8%	(65.0%, 70.5%)
	End of Study‡	4,163	2,617	62.9%	(61.4%, 64.3%)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units.
‡End-of-study visits were generally scheduled earlier than Month 48. This time point includes all visits occurring within six months of the approximate mean interval of 44 months.
Source: STN 125126/-(b)(4)-, CSR 015-010, Table 11-23, p. 215

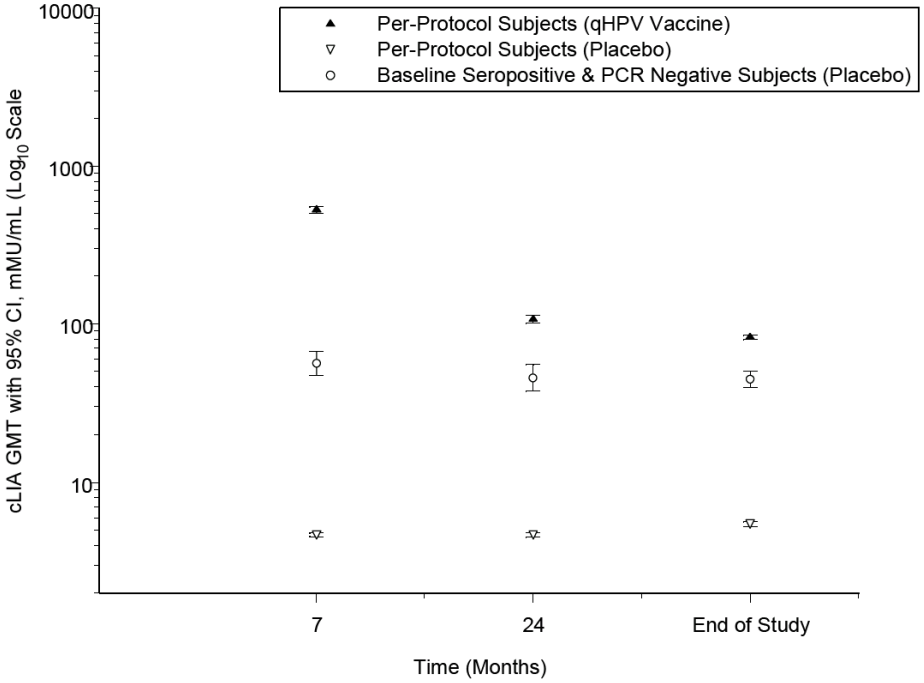
TABLE 96
Summary of Anti-HPV cLIA Geometric Mean Titers by Vaccination Group (Per-Protocol Immunogenicity Population) (Study HPV-015)

Assay (cLIA)	Time Point	qHPV Vaccine (N=6,082) n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Month 07	1,056	528.8	(504.2, 554.5)
	Month 24	1,041	106.5	(100.4, 113.0)
	End of Study‡	3,878	82.0	(79.4, 84.7)
Anti-HPV 11	Month 07	1,057	732.8	(694.6, 773.1)
	Month 24	1,041	135.4	(127.3, 144.0)
	End of Study‡	3,879	102.3	(98.9, 105.7)
Anti-HPV 16	Month 07	1,017	2,388.7	(2,215.8, 2,575.1)
	Month 24	1,006	435.2	(407.7, 464.6)
	End of Study‡	3,752	405.6	(391.4, 420.4)
Anti-HPV 18	Month 07	1,140	451.6	(425.4, 479.4)
	Month 24	1,125	46.2	(42.4, 50.3)
	End of Study‡	4,163	37.7	(36.1, 39.4)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units.
‡End-of-study visits were generally scheduled earlier than Month 48. This time point includes all visits occurring within six months of the approximate mean interval of 44 months.
Source: STN 125126/-(b)(4)-, CSR 015-010, Table 11-24, p. 216

FIGURE 17
Study HPV-015

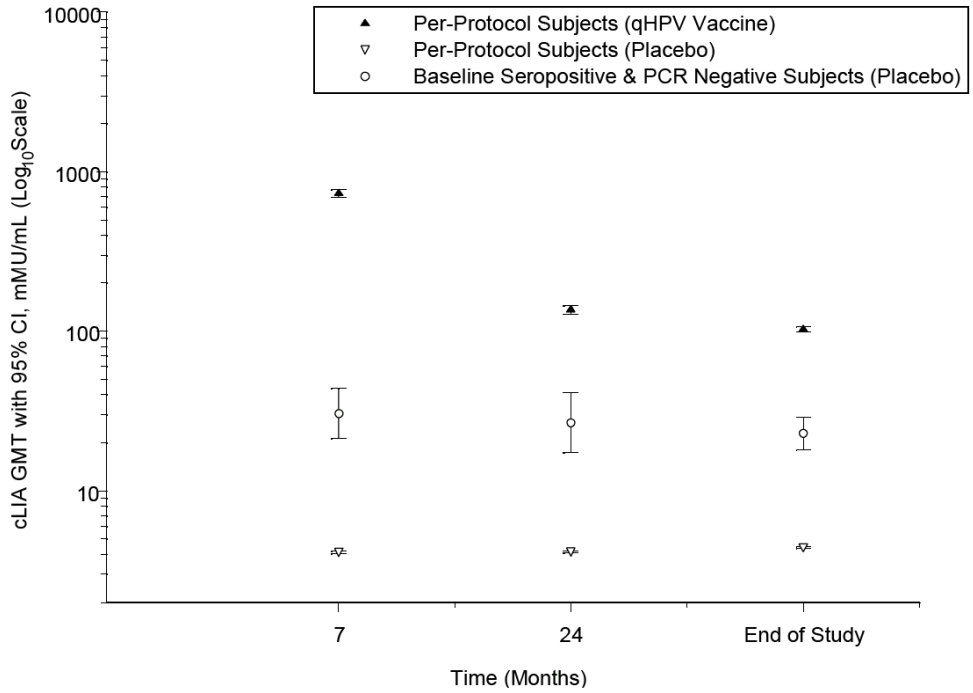
Longitudinal Plot of Anti-HPV 6 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)



Source: STN 125126/-(b)(4)-, CSR 015-010, Figure 11-3, p. 217

FIGURE 18
Study HPV-015

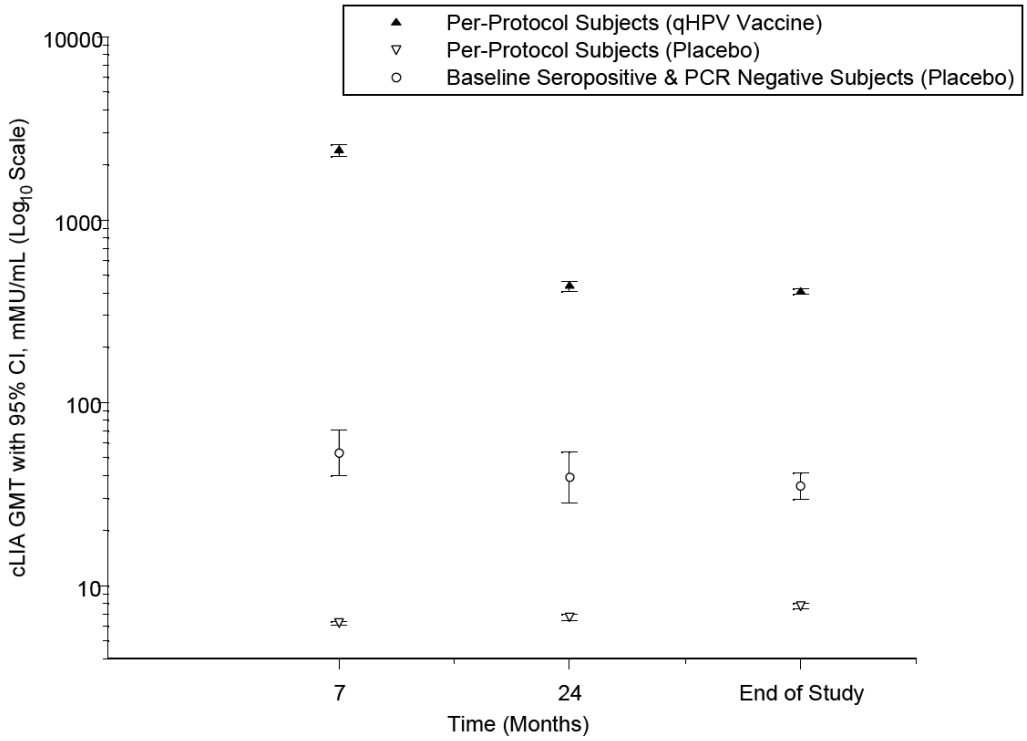
Longitudinal Plot of Anti-HPV 11 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)



Source: STN 125126/-(b)(4)-, CSR 015-010, Figure 11-4, p. 218

FIGURE 19
Study HPV-015

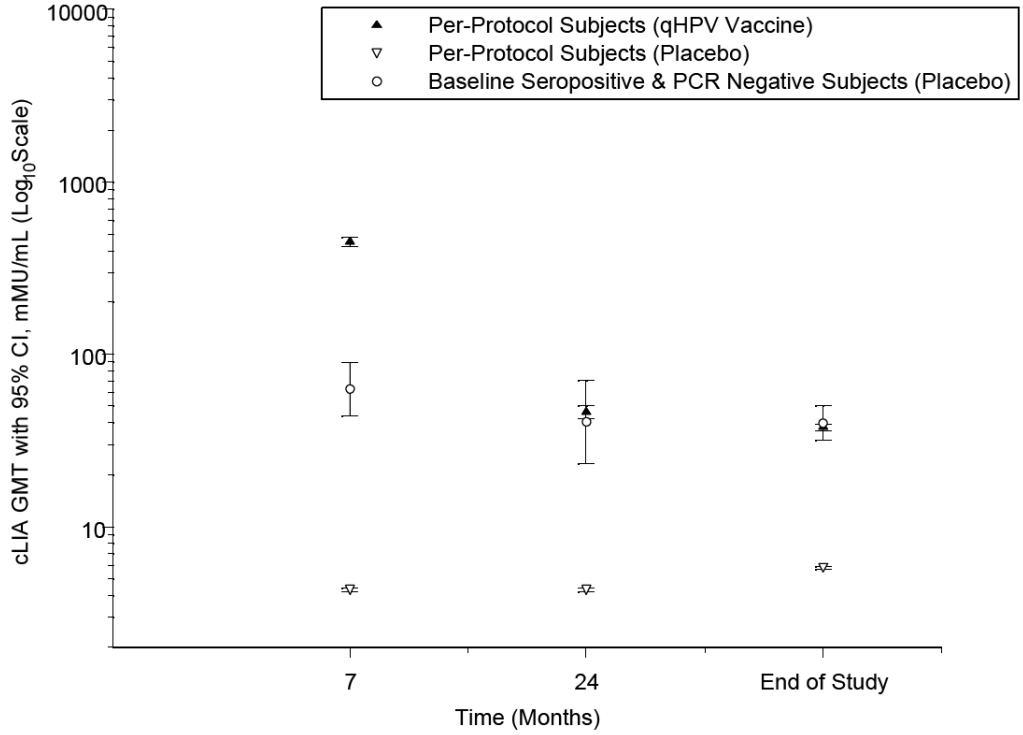
Longitudinal Plot of Anti-HPV 16 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)



Source: STN 125126/-(b)(4)-, CSR 015-010, Figure 11-5, p. 219

FIGURE 20
Study HPV-015

Longitudinal Plot of Anti-HPV 18 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)



Source: STN 125126/-(b)(4)-, CSR 015-010, Figure 11-6, p. 220

As noted in study HPV-013, subjects who were seropositive to the relevant vaccine HPV type at baseline (Day 1) had higher GMTs at 'End of Study' than those who were seronegative (regardless of PCR status at Day 1) to the same vaccine HPV type(s) at Day 1.

TABLE 97

End of Study‡ Anti-HPV cLIA Geometric Mean Titers by Day 1 Serostatus and PCR Status (Study HPV-015)

	Cohort		qHPV Vaccine (N=6,082)		
				GMT (mMU/mL)	
HPV Type	Day 1 Serostatus	Day 1 PCR Status	n	GMT	(95% CI)
HPV 6	Negative	Negative	4,230	82.5	(80.0, 85.1)
	Negative	Positive	121	111.6	(95.7, 130.1)
	Positive	Negative	301	376.1	(328.6, 430.6)
	Positive	Positive	95	255.5	(204.8, 318.8)
HPV 11	Negative	Negative	4,231	102.8	(99.6, 106.1)
	Negative	Positive	19	187.2	(147.9, 236.9)
	Positive	Negative	66	452.7	(331.1, 619.1)
	Positive	Positive	16	239.4	(135.8, 421.9)
HPV 16	Negative	Negative	4,088	408.0	(394.1, 422.3)
	Negative	Positive	234	423.0	(369.7, 484.0)
	Positive	Negative	290	785.4	(679.4, 908.0)
	Positive	Positive	204	777.2	(674.6, 895.3)
HPV 18	Negative	Negative	4,522	38.0	(36.4, 39.6)
	Negative	Positive	131	77.5	(62.6, 95.9)
	Positive	Negative	122	211.0	(162.4, 274.2)
	Positive	Positive	51	291.5	(219.0, 387.9)

Subjects were required to have completed the vaccination regimen, received the correct clinical material, and have the Month 7 serum sample collected within an acceptable day range.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.; n = Number of subjects evaluable in the given cohort.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; NA = Vaccine efficacy and confidence interval not computed; mMU = Milli Merck units; PCR = Polymerase chain reaction;

‡End-of-study visits were generally scheduled earlier than Month 48. This timepoint includes all visits occurring within six months of the approximate mean interval of 44 months.

Source: STN 125126/-(b)(4)-, CSR 015-010, Table 11-25, p. 222

In study HPV-018 (which included subjects 9-15 years of age), immunogenicity results were reported at the Month 30 time point. Month 7 GMTs were higher in the younger age group compared to the older age group, and remained higher through Month 30, for all 4 HPV types, although the age-related differences in anti-HPV GMTs were less pronounced. Longitudinal plots comparing the GMTs in the 2 age groups are displayed in Figure 21. For both age groups, the predominant decrease in GMT occurred from the peak at Month 7 to Month 18. After Month 18, there was a further slight decrease through Month 30.

Over 90% of subjects in the PPI population who received Gardasil were anti-HPV 6, anti-HPV 11, and HPV 16 seropositive at Month 30. Anti-HPV 18 seropositivity showed a greater decline than for the other 3 types, and the decline was most marked at Month 30 in the older age group. The proportions of subjects who were anti-HPV seropositive were comparable between the age groups, with the exception of anti-HPV 18 seropositivity at Month 30, which was lower in the older age group compared with the younger age group.

Results in the all HPV Naïve Subjects with Serology Data Population were similar to those seen in the Population in study HPV-018.

TABLE 98

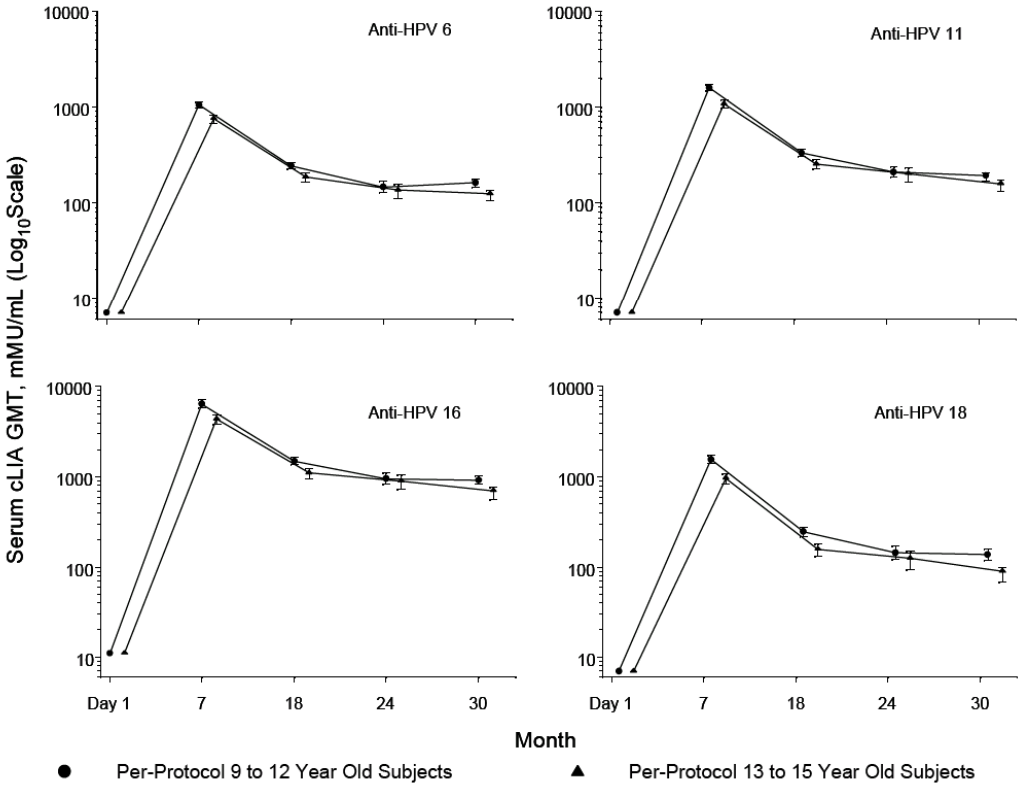
Summary of HPV cLIA Geometric Mean Titers by Age Group Among Female Subjects Who Received Gardasil (Per-Protocol Immunogenicity Population) (Study HPV-018)

		qHPV Vaccine								
		9 to 12 Years of Age at Enrollment			13 to 15 Years of Age at Enrollment			Total		
Assay (cLIA)	Time Point	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Day 1	294	<8	(<8, <8)	197	<8	(<8, <8)	491	<8	(<8, <8)
	Month 07	294	1,078.4	(976.0, 1,191.6)	197	649.1	(564.3, 746.7)	491	879.7	(808.3, 957.4)
	Month 18	287	250.2	(225.2, 277.8)	194	167.1	(143.7, 194.3)	481	212.6	(194.5, 232.3)
	Month 24	136	176.8	(147.7, 211.6)	79	126.6	(101.7, 157.6)	215	156.4	(135.9, 179.8)
	Month 30	250	179.6	(159.8, 201.8)	156	109.7	(91.7, 131.3)	406	148.6	(134.2, 164.5)
Anti-HPV 11	Day 1	294	<8	(<8, <8)	197	<8	(<8, <8)	491	<8	(<8, <8)
	Month 07	294	1,674.9	(1,517.1, 1,849.0)	197	951.4	(818.9, 1,105.3)	491	1,334.8	(1,222.8, 1,457.1)
	Month 18	287	352.7	(314.4, 395.6)	194	236.9	(202.5, 277.2)	481	300.4	(273.3, 330.2)
	Month 24	136	236.9	(198.3, 282.9)	79	188.3	(146.1, 242.8)	215	217.7	(188.2, 251.9)
	Month 30	250	208.9	(183.5, 237.8)	156	145.0	(118.6, 177.3)	406	181.6	(162.3, 203.0)
Anti-HPV 16	Day 1	291	<12	(<12, <12)	197	<12	(<12, <12)	488	<12	(<12, <12)
	Month 07	291	6,382.4	(5,603.2, 7,270.0)	197	3,415.3	(2,867.6, 4,067.6)	488	4,958.6	(4,450.8, 5,524.4)
	Month 18	284	1,517.4	(1,348.9, 1,707.0)	194	941.3	(802.8, 1,103.8)	478	1,250.1	(1,134.3, 1,377.7)
	Month 24	132	1,027.4	(831.3, 1,269.6)	79	829.7	(649.1, 1,060.5)	211	948.4	(807.7, 1,113.6)
	Month 30	248	960.9	(847.9, 1,089.0)	156	572.6	(461.9, 709.8)	404	786.8	(701.2, 882.8)
Anti-HPV 18	Day 1	295	<8	(<8, <8)	198	<8	(<8, <8)	493	<8	(<8, <8)
	Month 07	295	1,451.3	(1,283.1, 1,641.5)	198	765.7	(644.3, 909.9)	493	1,122.6	(1,011.1, 1,246.3)
	Month 18	288	226.3	(192.7, 265.7)	195	129.7	(106.0, 158.8)	483	180.8	(159.1, 205.4)
	Month 24	135	155.4	(123.6, 195.5)	80	113.4	(84.4, 152.4)	215	138.2	(115.4, 165.6)
	Month 30	251	126.4	(105.8, 151.0)	157	73.6	(58.0, 93.4)	408	102.6	(88.8, 118.6)

n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus.

Source: STN 125126/-(b)(4)-, CSR 018 30 months, Table 4-5, p. 22

FIGURE 21
Longitudinal Plot of HPV 6, 11, 16, and 18 cLIA Geometric Mean Titers
With 95% Confidence Intervals by Age Group
Among Subjects Who Received qHPV Vaccine
(Per-Protocol Immunogenicity Population)



Source: STN 125126/-(b)(4)-, CSR 018 30 months, Figure 4-1, p. 24

TABLE 99

Summary of HPV cLIA Seropositivity Rates by Age Group Among Female Subjects Who Received Gardasil (Per-Protocol Immunogenicity Population) (Study HPV-018)

		qHPV Vaccine											
		9 to 12 Years of Age at Enrollment				13 to 15 Years of Age at Enrollment				Total			
	Time		Seropositive				Seropositive				Seropositive		
Assay (cLIA)	Point	n	m	Percent	95% CI	n	m	Percent	95% CI	n	m	Percent	95% CI
Anti-HPV 6	Month 07	294	294	100%	(98.8%, 100%)	197	196	99.5%	(97.2%, 100%)	491	490	99.8%	(98.9%, 100%)
	Month 18	287	286	99.7%	(98.1%, 100%)	194	185	95.4%	(91.4%, 97.9%)	481	471	97.9%	(96.2%, 99.0%)
	Month 24	136	133	97.8%	(93.7%, 99.5%)	79	75	94.9%	(87.5%, 98.6%)	215	208	96.7%	(93.4%, 98.7%)
	Month 30	250	249	99.6%	(97.8%, 100%)	156	143	91.7%	(86.2%, 95.5%)	406	392	96.6%	(94.3%, 98.1%)
Anti-HPV 11	Month 07	294	294	100%	(98.8%, 100%)	197	196	99.5%	(97.2%, 100%)	491	490	99.8%	(98.9%, 100%)
	Month 18	287	286	99.7%	(98.1%, 100%)	194	191	98.5%	(95.5%, 99.7%)	481	477	99.2%	(97.9%, 99.8%)
	Month 24	136	134	98.5%	(94.8%, 99.8%)	79	76	96.2%	(89.3%, 99.2%)	215	210	97.7%	(94.7%, 99.2%)
	Month 30	250	247	98.8%	(96.5%, 99.8%)	156	147	94.2%	(89.3%, 97.3%)	406	394	97.0%	(94.9%, 98.5%)
Anti-HPV 16	Month 07	291	291	100%	(98.7%, 100%)	197	196	99.5%	(97.2%, 100%)	488	487	99.8%	(98.9%, 100%)
	Month 18	284	284	100%	(98.7%, 100%)	194	193	99.5%	(97.2%, 100%)	478	477	99.8%	(98.8%, 100%)
	Month 24	132	129	97.7%	(93.5%, 99.5%)	79	78	98.7%	(93.1%, 100%)	211	207	98.1%	(95.2%, 99.5%)
	Month 30	248	247	99.6%	(97.8%, 100%)	156	150	96.2%	(91.8%, 98.6%)	404	397	98.3%	(96.5%, 99.3%)
Anti-HPV 18	Month 07	295	295	100%	(98.8%, 100%)	198	196	99.0%	(96.4%, 99.9%)	493	491	99.6%	(98.5%, 100%)
	Month 18	288	272	94.4%	(91.1%, 96.8%)	195	170	87.2%	(81.7%, 91.5%)	483	442	91.5%	(88.7%, 93.8%)
	Month 24	135	124	91.9%	(85.9%, 95.9%)	80	71	88.8%	(79.7%, 94.7%)	215	195	90.7%	(86.0%, 94.2%)
	Month 30	251	226	90.0%	(85.6%, 93.5%)	157	122	77.7%	(70.4%, 84.0%)	408	348	85.3%	(81.5%, 88.6%)

Seropositive is defined as anti-HPV serum cLIA levels ≥ 20, 16, 20, and 24 mMU/mL, for HPV types 6, 11, 16, and 18, respectively.
n = Number of subjects contributing to the analysis.
m = Number of seropositive subjects.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus.

Source: STN 125126/-(b)(4)-, CSR 018 30 months, Table 4-8, p. 30

Reviewer's Comment: As noted in the original application, the immune response is more robust in the younger age population, in terms of GMTs and seropositivity rates. For HPV 18, the seropositivity rate in younger girls 9-15 years of age is higher (85.5% for girls and women 9-15 years of age) as compared to women studied in study HPV-013 (74%) and study HPV-015 (68%).

Immunogenicity Conclusions:

- No immune correlate of protection has been demonstrated with the additional data.
- The immune responses elicited by Gardasil (anti-HPV 6, anti-HPV 11, anti-HPV 16, or anti-HPV 18) have remained fairly stable since approximately Month 24, with seropositivity rates of approximately 90% for HPV 6, 95% for HPV 11, 98-99% for HPV 16 at the end of the study, although the seropositivity rate for HPV 18 decreased to approximately to 62%. Nonetheless, there has been no evidence of breakthrough cases at approximately Month 42 due to this decrease in seropositivity rates for HPV 18.
- The immune responses elicited in younger subjects (9-15 years of age) remain higher than those elicited in older females at Month 30.
- At this time, there is no indication that there is need for a booster dose, since there has been no indication of breakthrough cases. One post-marketing study will follow subjects on a long-term basis to follow for evidence of waning immunity.

10.4.2 Human Carcinogenicity: No additional testing conducted since time of original licensure.

10.4.3 Withdrawal Phenomena/Abuse Potential: Not applicable

10.4.4 Human Reproduction and Pregnancy Data:
Please see discussion under Safety regarding pregnancy data. Also, preclinical toxicology studies and reproductive toxicology studies were conducted with Gardasil. These studies were reviewed in detail in the original application.

10.4.5 Assessment of Effect on Growth: No additional testing was conducted since time of original licensure.

10.4.6 Overdose Experience: In the original application, when subjects were inadvertently given 0.75 mL Gardasil, most of the AEs were injection site AEs (mild to moderate), and of short duration. Systemic AEs were also mild to moderate and of short duration. Subjects who received Hepatitis B vaccine overdose experienced predominantly local injection site reactions (mild to moderate in severity). (Source: Appendix 2.7.4: 197, p. 1093-5, not shown here)

10.4.7 Person-to-Person Transmission, Shedding: This product is not a live viral product, so there is no issue of vaccine shedding or person-to-person transmission.

10.4.8 Post-Marketing Experience: Please see discussion under Safety discussion.

10.5 Safety Conclusions

In the close-out safety data provided to the Gardasil license application, in females 9-26 years of age, Gardasil, when administered in a 3 dose regimen at 0, 2, and 6 months, adverse event profiles in those who received placebo (alum and saline) were comparable with a few exceptions.

As noted in the original review, there was a somewhat higher proportion of Gardasil recipients as compared to placebo recipients with an injection site adverse event in the 5 days after any vaccination, and there was a somewhat higher proportion of Gardasil recipients with a complaint that was moderate or severe as compared to placebo recipients. Pain, swelling, and erythema were the most common injection site adverse events.

The rates of deaths were comparable between the Gardasil group and the control group, and none appeared to be related to receipt of study material.

The rates of serious adverse were comparable between the Gardasil group and control group.

The rates of subjects who discontinued due to an adverse event were comparable in the Gardasil group as compared to the control group.

The updated pregnancy outcomes demonstrate a comparable rate of spontaneous abortions within each treatment group (18.2% Gardasil, 19.5% control). These rates were similar for the groups with an estimated date of conception within 30 days of vaccination (18.3% Gardasil, 21.0% control).

Regarding congenital anomalies, there was a higher number of subjects in the Gardasil group who delivered a child with a congenital anomaly (40 total) as compared to the control group (30 total). Four of the infants in the Gardasil group and three infants in the control group were diagnosed with inherited defects, so the totals are 36 for Gardasil and 27 for control subjects. In pregnancies in which the estimated date of conception was within 30 days of vaccination, there were 5 congenital anomalies in infants born to mothers who received Gardasil and 1 in an infant born to a mother who received control. In an expert review of these anomalies provided by the sponsor (5 experts), none of the expert teratologists assessed any of the congenital anomalies as related to study material (both in a blinded and unblinded assessment). Gardasil is not recommended for routine use during pregnancy, and the subjects in the clinical trials who became unintentionally pregnant were all followed for outcomes. The congenital anomalies which developed were varied in nature. A post-marketing commitment includes a pregnancy registry to follow subjects who may become pregnant after vaccination with Gardasil.

In subjects who were pregnant after vaccination with Gardasil, the comparative rates of systemic and injection site adverse event rates were similar to those seen in the general study population, i.e., there was a higher rate of injections site adverse events in the Gardasil group as compared to control group, but a similar proportion of subjects with a systemic adverse event in each of the two treatment groups.

The proportion of infants born to mothers participating in the studies with serious adverse events were similar in each of the tow treatment groups, both in the neonatal period and outside the neonatal period.

The proportion of infants with an adverse event born to a mother who was breastfeeding was slightly higher in the Gardasil group (1.9%) as compared to infants born to mothers who received control (0.8%). The imbalance was primarily due to an imbalance in the proportion of infants with a respiratory disorder (17 Gardasil compared to 4 control). This imbalance was noted at the time of the original licensure, although the number of events was smaller at the original licensing action. The majority of the additional events which occurred in the Gardasil group since the time of original licensure occurred at an interval between vaccination and event that was >10 months. The number of infants with respiratory events which occurred within 30 days of vaccination is 6 in the Gardasil group and 2 in the control group. In an earlier review of the original cases, there was no recurrence of a similar event after revaccination of the mother, and the events occurred at varying times after each dose, and no definitive relationship was established.

The most common systemic adverse events in the 15 days after vaccination are headache, pyrexia, abdominal pain or discomfort, and nasopharyngitis, and the rates are comparable in each treatment group.

The most common injection site adverse events in the 5 days after receipt of Gardasil was pain, erythema, and swelling, and these occurred at higher rates in the Gardasil group as compared to the control group. The majority of these injection site adverse events were rated as mild in each treatment group.

There was a slightly higher rate of fever (most <102 ºF) in the 5 days after receipt of Gardasil (10.2%) as compared to the alum control or saline placebo (8.9%).

Although not found to be statistically significantly different in a meta-analysis across all studies, in all subjects, there was a higher number of subjects with a new diagnosis of Rheumatoid arthritis/Juvenile rheumatoid arthritis in the Gardasil group (7) as compared to the control group (2). These cases occurred at varying times after vaccination. In addition, there was a higher number of cases of autoimmune thyroiditis in the Gardasil group (6) as compared to the control group (1), which was also not found to be statistically significant in a meta-analysis across all studies. In a recent cohort study of adolescent girls and young women conducted in a large HMO in the year before Gardasil was licensed, autoimmune events such as these occurred in approximately 10% of females in this age group who sought medical attention. The overall proportion of subjects with a potentially autoimmune event were similar between the two treatment groups (2.3% Gardasil, 2.4% control). These data are being provided in the updated package insert. A post-marketing safety surveillance study in the ----------(b)(4)---------- in -------- (b)(4)-------- is underway in 44,000 subjects, and this study is expected to be completed within the next year. This study may help identify if the rates of such autoimmune events are increased as compared to the rate expected in the vaccinated population.

In the post-marketing period, several serious adverse events have been reported, including transverse myelitis, primary motor atrophy, amyotrophic lateral sclerosis, pancreatitis, Guillain-Barre syndrome, anaphylaxis, and death. Some of the deaths were ascribed to other causes, and some could not be confirmed, while several were still being reviewed (VAERS and CDC). The review has included comparison to expected rates of such events in the population, and to date, none have exceeded these rates, although analyses continue to be conducted.

11. Additional Clinical Issues: No additional issues not discussed in this review.

11.1 Directions for Use: Gardasil is supplied as a single dose vial or as a prefilled syringe. The vaccine should be used as supplied. No dilution or reconstitution is necessary. The vaccine should be thoroughly agitated prior to administration.

11.2 Dose Regimens and Administration: Gardasil should be administered intramuscularly as 3 separate 0.5 mL doses according to the following schedule: First dose: at elected date; Second dose: 2 months after the first dose; Third dose: 6 months after the first dose. The same dose is administered to ages 9-26 year old females. Gardasil should be administered intramuscularly in the deltoid region of

the upper arm or in the anterolateral area of the thigh.

In view of the reports of syncope after vaccination in the post-marketing period, some with traumatic injury after falling, a warning was added to the revised label that subjects should be observed for 15 minutes after vaccination. No imbalance in proportions of subjects who received Gardasil or control or placebo in the clinical trials was noted. The reason for this syncope noted in clinical practice may be related to a shorter observation time in use in general practice as compared to the clinical trials, where subjects were observed for 30 minutes as specified by the procedures in the clinical trials.

11.3 Special Populations: Safety and effectiveness has not been established in subjects with severe immunosuppresssion or HIV infection by the sponsor.

11.4 Pediatrics: CBER has agreed that the sponsor defer pediatric studies for Gardasil in boys and girls less than 9 years of age. However, specific studies were not specified at the present time because it is not known the ultimate duration of immune response elicited by Gardasil, nor long term safety. Studies of long term immunogenicity, safety and efficacy are in progress.

11.5 Women 27-45 years of age: Data are insufficient to establish effectiveness of Gardasil in women 27-45 years of age.

11.6 Geriatrics: No studies have been conducted in subjects older than 45 years of age.

12. **Conclusions – Overall**

Available data support the efficacy of Gardasil in prevention of vulvar and vaginal cancer related to HPV 16 and/or 18 if the subject is naïve for the relevant vaccine HPV type. It is important to understand that not all cases of vulvar and vaginal cancer are related to HPV infection, and that cases of vulvar and vaginal cancer are rare. The prevention is believed to be related to prevention of the dysplastic lesions, VIN 2/3 or VaIN 2/3 related to HPV 16 and/or 18 if the subject is naïve for the relevant vaccine HPV type.

Available data support the continued safety and efficacy of Gardasil in females 9-26 years of age who are naïve to the specific vaccine HPV type. The conclusion regarding efficacy in prevention of vaccine related CIN, AIS, and external genital lesions in females 16-26 years of age is based on 4 efficacy trials which utilized histopathololgical endpoints which included identification of the vaccine HPV type within the same specimen. Efficacy was inferred in the 9-15 year old female group because of immune responses that were non-inferior to those seen in the 16-23 year old female population. Females who are naïve to vaccine HPV types are expected to derive the most benefit from the vaccine in prevention of vaccine related HPV disease.

In the close out data, efficacy was maintained and point estimates of efficacy increased slightly, and 95% CIs narrowed. In the close-out data, efficacy was not demonstrated in prevention of histopathological events (CIN 2/3) related to a non-vaccine HPV type, even if the subject was naïve for the non-vaccine HPV type. Any possible benefit appeared to be associated with protection of CIN 2/3 related to a vaccine HPV type for which the subject was also naïve.

There was no apparent evidence of benefit in prevention of CIN 2/3 related to a vaccine or non-vaccine HPV type for which a subject was already infected.

Safety issues have been discussed in the Safety conclusions above, and other clinical issues also discussed within the overall sections on efficacy and immunogenicity.

13. Recommendations

13.1 Approval Recommendations

The clinical data provided support approval of Gardasil in females 9-26 years of age for the prevention of some vulvar and vaginal cancers related to HPV 16 and/or 18.

13.2 Recommendations on Postmarketing Actions

The sponsor completed the postmarketing commitments of the submission of the final data and study reports from studies 007, 013 and 015, as reviewed in this and other supplements. The sponsor has other postmarketing commitments as part of the original approval in 2006, and these studies are still underway. Please refer to the approval letter and clinical review of the original BLA for information about the postmarketing commitments as part of the original BLA.

13.3 Labeling

There were multiple communications (including two telecons) with the sponsor to work on the label in order to achieve consistency with CBER's current guidance on the Physicians Labeling Rule for package inserts. The new indication for prevention of HPV 16 and 18 related vulvar and vaginal cancer was added to the package insert. The indications for prevention of cervical cancer and adebocarcinoma in situ or worse were made more specific to include prevention of these lesions related to HPV types 16 and 18. Similarly, the indication for prevention of genital warts was made more specific to include prevention of these lesions related to HPV types 6 and 11. The limitations of the vaccine's efficacy are now included within the new highlights section, under Warnings and precautions. These facts were included within the original package insert, but these items are now placed in a more prominent location according to the Physcian's Labeling Rule. Additional post-marketing adverse events were added, and the language was strengthened to caution about the syncopal episodes which have been associated with falling and traumatic events, sometimes severe. In addition, the Patient Package Information sheet was updated to conform with the updated package insert.

Since the time of the original approval for Gardasil in 2006 and the present package insert, there were three labeling supplements (submitted as Changes Being Effected). These include:

125126/428: CBE (adding syncope and vomiting to PI; additional language regarding syncope added to Dosage and Administration section). This was approved 10/2/07.

125126/578: CBE (adding Guillian-Barre Syndrome, lymphadenopathy, and headache to the PI; changing the generic name to Human Papillomavirus Quadravalent (Types 6, 11, 16, 18) Vaccine, Recombinant at the request of CBER). This was approved 1/11/08.

125126/714: CBE ("a composite of circular 9682305" submitted on July 12, 2007 amending the PPI section "What are the possible side effects of Gardasil?" to make it consistent with the PI). This was approved 3/12/08.

125126/758: CBE (addition of post-marketing adverse reactions: arthralgia, myalgia, asthenia, fatigue, malaise; revision of Dosage and Administration section: wording for syncope was modified to clarify and an image of the syringe minus the safety guard was included, also for clarification). This was approved 6/16/08.

14. **Comments and questions for the applicant**

The sponsor provided responses to reviewer questions during the course of the BLA review.