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Christine Walsh, R.N.
FDA/CBER/DSAC/HFM-71
5515 Security Lane
Rockwall II Building, Room 1113
Rockville, MD 20852

Dear Ms.Walsh:

GARDASIL™
Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine
STN 125126

Find enclosed 35 copies of the final briefing document for the upcoming GARDASIL™ Vaccines and Related Biological Products Advisory Committee meeting to be held on May 18, 2006. By receipt of this letter Merck & Co., Inc. hereby grants permission to allow the Food and Drug Aministration (FDA) to make this document public and to allow the FDA to post is on the FDA website without redaction. A Compact Disc is also being provided for the sole purpose of posting on the aforementioned website.

Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

Questions concerning this application should be directed to me at (484-344-7883) or, in my absence, to Ercem Atillasoy at (484-344-7811).

Sincerely,

Patrick Brill-Edwards, M.D.
Director
Worldwide Regulatory Affairs
Vaccines/Biologics

Attachments

DHL

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GARDASIL®
(Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine)

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

Presented to VRBPAC on
18-May-2006

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse experience
AIN	Anal intraepithelial neoplasia
AIS	Adenocarcinoma in situ
ASC-H	Atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of unknown significance
BLA	Biologics Licensing Application
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
cLIA	Competitive Luminex immunoassay
cRIA	Competitive radioimmunoassay
CSR	Clinical study report
DAP	Data analysis plan
DNA	Deoxyribonucleic acid
ECC	Endocervical curettage
EGL	External genital lesion
EOP	Estimated onset of pregnancy
GMT	Geometric mean titer
H&E	Hematoxylin and Eosin
hCG	Human chorionic gonadotropin
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
LEEP	Loop electroexcision procedure
LSIL	Low-grade squamous intraepithelial lesion
mAb	Monoclonal antibody
MITT	Modified intention-to-treat
mMU/mL	Milli Merck units per milliliter
MRL	Merck Research Laboratories
Pap	Papanicolaou's test
PCR	Polymerase chain reaction
PPE	Per-protocol efficacy
PPI	Per-protocol immunogenicity
PV	Papillomavirus
RRP	Recurrent respiratory papillomatosis
SIL	Squamous intraepithelial lesion
SUR	Safety update report
VaIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia
VLP	Virus-like particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VRC	Vaccination report card

1. Introduction and Organization of the Document

An original Biologics Licensing Application (BLA) for the use of GARDASIL®[1] (human papillomavirus [Types 6, 11, 16, 18] recombinant vaccine) was filed by Merck & Co., Inc. in December 2005. The application has received priority review status. This document provides a summary of the safety, efficacy, and immunogenicity data to support licensure of this vaccine.

GARDASIL® is a vaccine intended to prevent anogenital cancers and their precursor lesions, genital warts, and infection caused by the human papillomavirus (HPV) types 6, 11, 16, and 18. These HPV types cause the majority of genital HPV disease in the United States.

The clinical development program for GARDASIL® included girls and women 9 to 26 years of age and boys 9 to 15 years of age at the start of vaccination. This range covers the period just prior to sexual debut through the period of peak risk for HPV infection. Subjects were enrolled regardless of baseline HPV status, as vaccination programs will be population-based (no HPV screening prior to vaccination). Inclusion of subjects with prior or ongoing HPV infection also allowed for an evaluation of the impact of such infection on the efficacy, immunogenicity, and safety of GARDASIL®. The clinical program was conducted in 5 continents and 33 countries, providing diversity that justifies the application of study findings to the general population of 9- to 26-year-old subjects worldwide.

Efficacy was assessed in 4 randomized, double-blind, placebo-controlled studies. Together, these trials randomized 20,887 16- to 26-year-old adolescent and young adult women, of whom 20,845 subjects received at least one dose of vaccine (GARDASIL®, HPV 16 L1 VLP vaccine component of GARDASIL®, or placebo). Overall, 19,321 subjects (92.7% of subjects who received at least one dose of vaccine) continued in the study from the time of enrollment through the date at which each study's database was closed.

The immunogenicity studies for GARDASIL® evaluated anti-HPV responses 1 month after the completion of the 3-dose vaccination regimen and for up to 3.5 years thereafter. In these trials, 12,344 subjects (9- to 26-year-old girls and women; 9- to 15-year-old boys) were randomized to receive GARDASIL® or placebo. Of these, 11,726 completed the vaccination phase of the studies. Trials that enrolled 9- to 15-year-old subjects served 2 purposes: (1) to bridge efficacy findings from mostly sexually active 16- to 26-year-old subjects in whom efficacy was evaluated to adolescents prior to sexual debut in whom efficacy trials are not feasible; and (2) to demonstrate that anti-HPV responses induced by GARDASIL® in boys are non-inferior to those generated in girls (gender-neutral vaccination programs will be needed to induce herd immunity). Other trials were

[1] GARDASIL is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

designed to: (1) show that GARDASIL® can be given concomitantly with hepatitis B vaccine (both vaccines are given to adolescents); (2) show the consistency of manufacture of GARDASIL®; and (3) provide data to support dose justification for manufactured lots of GARDASIL®.

The safety of GARDASIL® and its monovalent precursors was assessed in 12 studies in which 16,014 subjects received at least one dose of HPV L1 VLP vaccines (of these, 11,792 subjects receiving GARDASIL®). The safety of GARDASIL® was evaluated with regard to: (1) injection-site and systemic tolerability; (2) impact on long-term health status; and (3) interaction with pregnancy and lactation, events that are likely to occur in the population for which GARDASIL® will be indicated.

The clinical program for GARDASIL® has shown that the vaccine is highly efficacious in preventing the development of cervical cancer, vulvar cancer, vaginal cancer, the dysplastic lesions preceding these cancers, and genital warts caused by vaccine HPV types in a broad population of subjects who were representative of the population in which GARDASIL® is intended. Efficacy was durable through at least 2.5 years postvaccination with respect to infection and disease caused by HPV 6, HPV 11, and HPV 18, and at least 3.5 years postvaccination with respect to infection and disease caused by HPV 16. Phase III study subjects in the Nordic Region will be followed for up to 15 years to define the longer-term efficacy of GARDASIL®. Because these subjects completed their vaccinations in 2003, the longer-term duration of efficacy of the vaccine will be known well in advance of the time needed to implement booster vaccinations in the general population (if such boosters are required).

GARDASIL® was highly immunogenic in all populations tested, inducing robust anti-HPV responses regardless of gender, ethnicity, national origin, body mass index (BMI), smoking status, Day 1 Papanicolaou (Pap) test result, lifetime number of sexual partners at enrollment, and method of contraception used prior to vaccination. Based on the numerically superior and statistically non-inferior anti-HPV responses induced by GARDASIL® in 10- to 15-year-old boys and girls compared with 16- to 23-year-old adolescent and young adult women, the efficacy of GARDASIL® can be bridged from 16- to 23-year-old female subjects in whom efficacy was evaluated with virginal adolescents in whom an efficacy evaluation was not feasible. Concomitant administration of GARDASIL® with RECOMBIVAX HB®[2] (hepatitis B vaccine, recombinant) resulted in anti-HPV levels and anti-HBs levels that were comparable to those observed when these vaccines are administered nonconcomitantly.

The clinical program has shown that GARDASIL® has an excellent safety profile. GARDASIL® was generally well tolerated in all groups tested. Vaccine-related serious adverse experiences occurred in <0.1% of subjects. There was no safety signal with respect to allergic reactions or other immune-mediated diseases. The proportions of

[2] RECOMBIVAX HB is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

subjects reporting new medical conditions through up to 2.5 years Postdose 3 were comparable between subjects who received GARDASIL® and placebo subjects. Baseline HPV status did not impact vaccine safety. Use of GARDASIL® did not impact overall pregnancy outcomes. Administration of GARDASIL® to nursing mothers did not affect the health of the mother or the nursing child.

The proposed prescribing information for GARDASIL® includes the following indications:

GARDASIL® is a vaccine indicated for the prevention of cancer, precancerous or dysplastic lesions, genital warts, and infection caused by the HPV types targeted by the vaccine.

GARDASIL® is indicated for the prevention of the following caused by HPV 16 and HPV 18:

- cervical, vulvar, and vaginal cancer;
- cervical adenocarcinoma *in situ* (AIS);
- cervical intraepithelial neoplasia (CIN) grade 2 and grade 3;
- vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3; and
- vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3.

GARDASIL® is indicated for the prevention of the following caused by HPV 6, HPV 11, HPV 16, and HPV 18:

- cervical intraepithelial neoplasia (CIN) grade 1;
- genital warts (condyloma acuminata);
- VIN grade 1 and VaIN grade 1; and
- HPV infection.

Since the submission of the Original Application, additional safety data from Phase III trials have been obtained. These data were submitted in a Safety Update Report (SUR) on 03-Apr-2006. This briefing document presents cumulative safety data comprised of data presented in the Original Application and data from the SUR. This document is organized as follows:

Section 1 Introduction and Organization of the Document

Section 2 Background

Section 3 Clinical Efficacy

Section 4 Immunogenicity

Section 5 Clinical Safety

2. Background

2.1 HPV Infection and Clinical Disease

Over 50% of sexually active adults become infected with HPV during their lifetime [1; 2]. HPV infection can cause: (1) epithelial dysplasia and cancer, most commonly in the cervix; and (2) benign tumors of the genitalia (condyloma acuminata) and the larynx (recurrent respiratory papillomatosis [RRP]).

HPV infection is necessary for the development of squamous cell cervical cancer [3] (and its precursor lesions Cervical Intraepithelial Neoplasia [CIN] 1 and CIN 2/3) and cervical adenocarcinoma (and its precursor lesion adenocarcinoma *in situ* [AIS]). HPV also causes a subset of vulvar, vaginal, and anal cancers and their precursor lesions Vulvar Intraepithelial Neoplasia (VIN), Vaginal Intraepithelial Neoplasia (VaIN), and Anal Intraepithelial Neoplasia (AIN), respectively. HPV 16 and HPV 18 cause ~70% of cervical, anal, and HPV-related vulvar and vaginal cancers.

HPV 6 and HPV 11 cause dysplasia that rarely progresses to cancer. These types cause >90% of genital wart and RRP cases and 10 to 15% of low-grade dysplastic lesions of the cervix, vagina, and vulva (CIN 1, VaIN 1, VIN 1, respectively) [1; 4].

HPV infection is generally transmitted via sexual contact. The risk of HPV infection (and cervical dysplasia/cancer) is closely correlated with the lifetime number of sexual partners. The peak risk for HPV infection occurs within the first 10 years following sexual debut.

HPV infection is generally asymptomatic; thus, it is not recognized until patients are diagnosed with cervical dysplasia/cancer or genital warts.

2.1.1 Public Health Burden of HPV-Related Clinical Disease

Cervical Cancer. Cervical cancer is the second most common cancer in women worldwide. Every year, ~500,000 women are diagnosed with cervical cancer, and 290,000 die due to the disease [5; 6]. The impact of cervical cancer is accentuated relative to other cancers because it affects women in their 30s to 50s, when they are at the peak of family life and productivity [7]. In developed countries, screening programs using the Pap test have reduced cancer rates by 75% [8; 9; 10]. The success of Pap testing has largely shifted the burden of HPV disease from managing the morbidity of cervical cancer to managing a large burden of pre-malignant cervical lesions. Every year, ~3,500,000 women in the United States have an abnormal result on a routine Pap test. Of these women ~1,400,000 receive a diagnosis of CIN 1 on follow-up and ~330,000 receive a diagnosis of CIN 2/3 [11; 12]. Despite screening, ~10,000 women in the United States are diagnosed with cervical cancer annually [13].

Cervical adenocarcinoma is not well detected by screening; the incidence of this cancer is increasing [14]. In developing countries, the lack of sustainable screening programs has resulted in a high incidence of cervical cancer. Over 80% of deaths resulting from cervical cancer worldwide occur in these countries [15].

Other Cancers. HPV causes ~50% of all vulvar and vaginal cancers, primarily in women below age 50. In the United States, ~3500 women are diagnosed with HPV-related vulvar or vaginal cancers, and ~1100 women die from these cancers annually [5].

HPV-Related Vulvar Cancer. The epidemiology of this cancer mirrors that of cervical cancer: (1) HPV is detected in 75 to 100% of all cancers in young women; (2) vulvar cancer in young women is strongly associated with a previous diagnosis of condyloma acuminata, or CIN; (3) cancer is preceded by dysplastic lesions of varying severity, termed Vulvar Intraepithelial Neoplasia (VIN) grades 1, 2, and 3. The incidence of vulvar cancer in young women has increased over the past 25 years.

HPV-Related Vaginal cancer is also closely associated with cervical cancer [16; 17; 18], suggesting that these cancers share a common etiology. In the Thames (London) Cancer Registry, women with CIN 3 had an 18.5-fold increased risk of vaginal cancer compared to the general population. In a large study in Seattle, HPV DNA was detected in 82% of biopsies diagnosed with VaIN 3 and in 64% of invasive cancers [19]. HPV-related vaginal cancer is preceded by precancerous lesions (Vaginal Intraepithelial Neoplasia, or VaIN), which are classified into 3 categories based on severity that are analogous to those used to classify cervical lesions). Left untreated, high-grade VaIN will progress to cancer [19]. Even with treatment, cancer risk is high [18].

HPV infection can cause anal, penile, and some oral cancers [20; 21]. The incidences of HPV-related vulvar and anal cancer have increased in the United States over the past 2 decades [5].

Overall, HPV infections account for ~35,000 cancers per year in the United States, of which ~25,000 occur in women and ~10,000 occur in men.

Condyloma Acuminata (Genital Warts). In the United States, ~1,000,000 men and women develop new genital wart cases annually [22]. The lifetime risk for acquisition of genital warts exceeds 10% [23]. Although these lesions are benign, individuals who develop genital warts have a high incidence of depression, sexual dysfunction, and disruptions to long-term relationships [24; 25]. Ablation causes regression of the lesions in ~70% of subjects, but 30% of lesions recur [26]. On average, clearance of genital warts requires 3 treatment rounds [27].

Recurrent Respiratory Papillomatosis (RRP). RRP is characterized by warty tumors in the respiratory tract (primarily in the larynx). The disease has a juvenile variant caused by maternal to infant transmission, and an adult variant whose mode of transmission has not been characterized. In the United States, ~5900 cases are reported yearly in children and

adults. The disease causes hoarseness, choking, and recurrent infections. During the disease's active periods, patients undergo 4 surgeries per year on average to maintain airway patency [28].

2.1.2 Pathophysiology of HPV Infection

Virology. HPV is a nonenveloped capsid virus containing double-stranded deoxyribonucleic acid (DNA) [4]. The viral genome contains ~8000 base pairs divided into 6 early (E) genes, 2 late (L) genes, and a noncoding long control region. E genes encode for proteins involved in DNA synthesis. The E6 and E7 proteins induce excessive and disordered cell proliferation by disrupting cell cycle control proteins [29]. L genes encode for viral capsid proteins.

HPV is an epitheliotropic virus that infects mucosal basal cells, preferentially at squamo-columnar junctions. These junctions are in a constant cycle of growth, injury, and repair leading to metaplasia (transformation from one mature cell type to a different cell type). The metaplastic area, called a transformation zone, is the primary location for HPV-induced tumorigenesis. The presence of such junctions in the cervical/genital tract, the anal canal, the oral cavity, and the larynx explains the predominance of HPV-related lesions in these organs [28; 30].

The HPV family consists of >90 related viruses, 40 of which infect the genital tract [31]. All HPVs can disrupt cell cycle regulatory mechanisms, but only a subset of HPV types are oncogenic. HPV types are divided into high-risk types that can cause cancer (e.g., HPV 16, HPV 18) and low-risk types that cause dysplasia that rarely leads to cancer (e.g., HPV 6, HPV 11) [32].

An effective vaccine targeting HPV 6, HPV 11, HPV 16, and HPV 18 should substantially reduce the overall burden of clinical HPV disease. HPV 16 and 18 cause ~70% of cervical cancers. The contributions of HPV 16 and HPV 18 to high-grade CIN and to HPV-related vulvar, vaginal, and anal cancers are similar to those seen in cervical cancer [20; 4]. HPV 6, 11, 16 and 18 together cause ~35% of CIN 1 cases. HPV 6 and HPV 11 cause >90% of genital warts and RRP cases [1; 4].

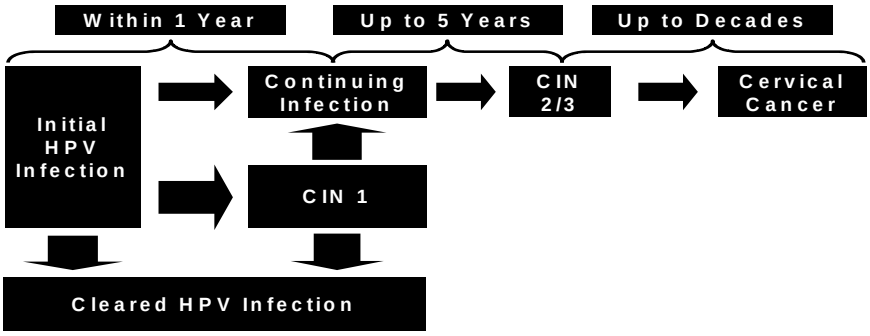
2.1.3 Epidemiology of HPV Infection – Impact on Clinical Trial Design

2.1.3.1 Endpoints for Use in Clinical Trials of Prophylactic HPV Vaccines

Cervical Cancer. The natural history of cervical HPV infection is displayed in Figure 1.

Figure 1

Natural History of Infection With High-Risk HPV Types (Such as HPV 16 and HPV 18)



CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus.

High-risk HPV infection is the first, necessary step in the development of squamous cell carcinoma of the cervix and its precursor lesion CIN 2/3 and adenocarcinoma of the cervix and its precursor lesion AIS.

Most HPV infections are self-limited (Table 1). Early HPV infection often manifests itself as low-grade dysplasia (CIN 1). Such lesions often resolve spontaneously. CIN 1 caused by low-risk HPV types (e.g., HPV 6, HPV 11) is indistinguishable from CIN 1 caused by high-risk HPV types (e.g., HPV 16, HPV 18). CIN 1 lesions are managed by instituting frequent Pap testing with a low threshold for repeat colposcopy and excision or ablation.

HPV infection can cause moderate/high-grade cervical dysplasia (CIN 2/3), AIS, and cancer. CIN 2/3 is the immediate and obligate precursor to cervical squamous cell cancer. AIS is the immediate and obligate precursor to cervical adenocarcinoma. CIN 2/3 and AIS are treated by excision. While surgery is often curative, it can limit fertility [33]. After surgery, women remain at risk of recurrent CIN and vulvar and vaginal cancer [34]. Excisional cervical surgery represents a major economic burden [35].

Table 1

Lifetime Risk of Developing Cervical Cancer or Cervical Cancer Precursors in Women Worldwide

HPV-Related Pathologic State	Approximate Lifetime Risk
HPV Infection	1 in 2 (50%)
CIN 1	1 in 6 (17%)
CIN 2/3 or AIS	1 in 25 (4%)
Cervical Cancer (Under No Pap Test Screening Conditions)	1 in 31 (3%)
Cervical Cancer (Under Current Pap Test Screening Conditions)	1 in 123 (0.8%)

HPV = Human papillomavirus; CIN = Cervical intraepithelial neoplasia; Pap = Papanicolaou test; AIS = Adenocarcinoma in situ.

[1; 5]

The licensure of prophylactic HPV vaccines would ideally be predicated on a demonstration of the efficacy of the vaccine against invasive cervical cancer caused by vaccine HPV types. However, a Phase III trial using an invasive cervical cancer endpoint is not feasible because the time from acquisition of infection to the development of cancer often exceeds 20 years, and the standard of care is to screen for and excise CIN 2/3 or AIS lesions to prevent invasion. Thus, clinical trials to evaluate the impact of an HPV vaccine on invasive cervical cancer risk must use earlier lesions as efficacy endpoints. Such pathologic states must be sufficiently robust to ensure that a demonstration of efficacy with regard to this state will necessarily translate into a reduction in risk of invasive cervical cancer. Such a state must meet the following criteria: (1) it is a necessary step in the development of invasive cervical cancer; (2) it is sequentially close to invasive cervical cancer; (3) it confers a high risk for development of invasive cervical cancer; and (4) prevention of the pathologic state, or treatment of that state, has been shown to reduce cervical cancer mortality.

Pap test results are not appropriate primary endpoints for HPV vaccine trials, as the Pap test is a screening tool, and definitive diagnosis is made by histologic review of biopsies.

HPV 16/18 infection, HPV 16/18-related CIN 1, and HPV 16/18-related CIN 2/3 are pathologic states that have served as candidate endpoints for demonstrations of the efficacy of GARDASIL® against cervical cancer. Table 2 displays a categorization of the suitability of these states as the key proof of efficacy for HPV vaccine licensure.

CIN 2/3 and AIS are the immediate and obligate precursors of invasive cervical cancer. Pap testing reduces cervical cancer rates by detecting such lesions so that they can be removed before they become invasive cancer. Therefore, CIN 2/3 and AIS are the best surrogate markers for invasive cervical cancer for use in clinical efficacy studies of HPV vaccines.

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the Center for Biologics Evaluation and Research (CBER) met in 2001 to consider appropriate endpoints for licensure of prophylactic HPV vaccines. The committee and CBER concluded that the licensure of prophylactic HPV vaccines in the United States requires a definitive demonstration that such vaccines reduce the incidence of CIN 2/3 and AIS caused by vaccine HPV types (surrogate of cervical cancer efficacy) [36].

The pivotal efficacy studies of GARDASIL® were designed to meet the criteria set by VRBPAC and CBER for licensure of vaccines for cervical cancer prevention. The primary efficacy endpoints of these studies were limited to CIN 2/3, AIS, or cancer. Studies with primary endpoints that included HPV infection were used as a proof-of-concept for vaccine efficacy. Studies with primary endpoints that included CIN (including CIN 1, CIN 2/3, and AIS) were used to define the impact of the vaccine on the burden of cervical HPV disease.

Table 2

Suitability of Candidate Intermediate Endpoints as Surrogate Markers for Vaccine Efficacy in Trials of Vaccines Targeting HPV 16 and HPV 18

Criterion	HPV Infection	CIN 1	CIN 2/3 or AIS
Obligate precursor for cervical cancer	Yes	No	Yes
Temporally close to cervical cancer	No	No	Yes
Risk for cervical cancer	Low	Low/Moderate	High
Treatment or prevention shown to reduce the risk for cervical cancer	No	No	Yes
Use in the Clinical Development Program for GARDASIL®	Phase IIa Proof of Concept	Health Economics	Regulatory + Public Health Approval

CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ;
HPV = Human papillomavirus.

HPV-Related Vaginal and Vulvar Disease. Genital warts are caused by low-risk HPV types. Low-grade vulvar and vaginal lesions (VIN 1 and VaIN 1, respectively) can be caused by both high-risk and low-risk HPV types. High-grade vulvar and vaginal lesions (VIN 2/3 and VaIN 2/3, respectively) are caused by high-risk HPV types. Clinical management involves watchful waiting (low-grade lesions) or ablation/excision (genital warts, recurrent low-grade lesions; high grade lesions). Recurrences are common as lesions tend to be multifocal and nearby normal-appearing tissue may also be infected. Clearance requires ~3 rounds of therapy [27].

Study Endpoints - HPV 16/18-Related Vulvar and Vaginal Cancer. The efficacy of vaccines to prevent HPV 16- and HPV 18-related vulvar and vaginal cancers can be evaluated by measuring the impact of vaccination on the combined incidence of HPV 16- and HPV 18-related VIN 2/3, VaIN 2/3, vulvar cancer, or vaginal cancer.

HPV 16- and HPV 18-related VIN 2/3 is a suitable surrogate marker for HPV-related vulvar cancer: (1) vulvar cancer in young women arises from a field of VIN 3 [37]; (2) up to 20% of VIN 3 lesions will be found to be microinvasive on intensive review of biopsy blocks [37]; (3) left untreated, VIN 3 lesions will progress to invasive cancer (in a large case series of VIN 3, 16% of untreated lesions progressed to invasive cancer over a period of 3.9 years) [37]; and (4) even among treated subjects, 2 to 7% will develop vulvar cancer due to recurrent disease [37].

HPV 16- and HPV 18-related VaIN 2/3 is a suitable surrogate marker for HPV-related vaginal cancer: (1) vaginal cancer in young women arises from a field of high grade VaIN 3 [18]; (2) following treatment for high grade VaIN, recurrences are common, including invasive cancer [18].

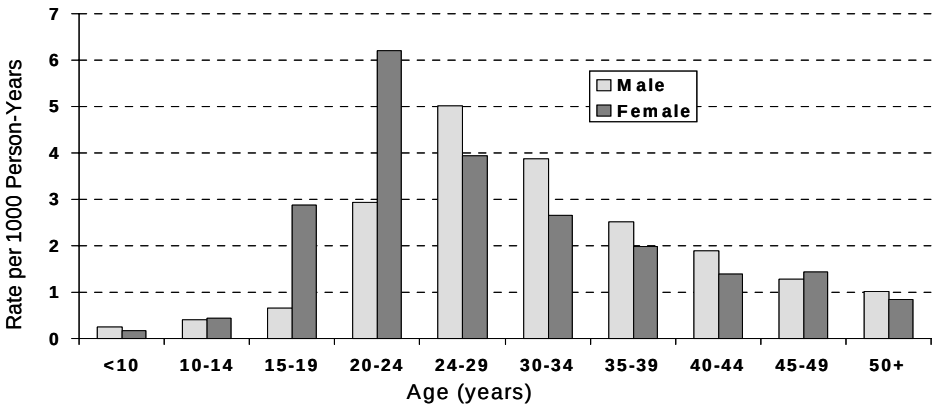
Study Endpoints - HPV 6/11/16/18-Related Genital Warts. By varying the approach to external genital inspection (an intensive genital inspection regimen or a more symptom-based approach), vaccine efficacy against HPV-related genital disease can be evaluated in settings of complete ascertainment or settings representing typical clinical practice.

2.1.3.2 Susceptible Populations

The median age of sexual debut is ~16 years in most countries [38; 39; 40]. By 5 years after sexual debut, ~50% of young women will have been infected with at least one of the 40 genital HPV types [1; 2]. Studies suggest a similar infection pattern in men [41]. This epidemiologic pattern can be observed on a population basis be examining the incidence of new genital warts by age categories (Figure 2). Genital warts are good markers for the timing of HPV infection, because they become apparent quickly after infection starts. As shown in Figure 2, the peak incidence of HPV infection occurs in young adults. Hence, the efficacy of GARDASIL® has been evaluated in 16- to 26-year-old subjects.

Figure 2

Rate of Reporting of New Cases of Genital Warts by Age and Gender Categories in a Large Private Insurance Database in the United States



[27]

To be representative of the general population, the efficacy trials of GARDASIL® and HPV 16 L1 VLP vaccine did not include a visit to screen out HPV-infected subjects. In 2001, VRBPAC recommended not screening for HPV infection/disease prior to enrollment because: (1) such a selected study population that did not include HPV-experienced subjects would not be generalizable; (2) type-specific HPV testing is not widely available; (3) safety in HPV-experienced subjects could not be assessed; and (4) clinicians would be likely to give the vaccine without screening. Thus, the clinical trials included primarily HPV naïve subjects, but they also included subjects who were already HPV-experienced at enrollment.

Because GARDASIL® is meant to be a prophylactic vaccine, adolescent girls and boys represent the key population for HPV vaccination programs. Immunogenicity and safety trials were conducted in boys and girls 9 to 15 years of age. Efficacy trials in these children were not conducted, because it is not feasible to collect genital samples and discuss sexual activity in children. In recognition of this difficulty, CBER has stated that a demonstration that anti-HPV responses to GARDASIL® in 9- to 15-year-old subjects (in whom efficacy was not evaluated) are non-inferior to anti-HPV responses in 16- to 26-year-old female subjects (the age range in which efficacy was shown) will allow for the inclusion of 9- to 15-year-old subjects within each of the indications for GARDASIL®.

Studies included evaluations of the vaccine in males, because men have a high incidence of genital warts, are at risk for HPV-related cancers, and transmit HPV to women [42; 43]. Also, gender-specific vaccination programs targeting infections in which the main pathologic consequence occurs in women only (e.g., rubella/congenital rubella syndrome) have been shown to be ineffective in eradicating disease [44; 45].

In the clinical program for GARDASIL® the populations studied and endpoints chosen were appropriate for the product circular sought in the BLA. The Phase III studies in 9- to 26-year-olds have continued after the principal study analyses contained in the BLA were conducted in order to obtain further safety, immunogenicity, and efficacy data. These analyses will be presented to regulatory agencies in subsequent supplemental BLAs.

2.2 Development of GARDASIL® (HPV [Types 6, 11, 16, 18] Recombinant Vaccine])

2.2.1 Chemical and Pharmacological Properties for GARDASIL®

All product manufacturing, filling, and packaging for GARDASIL® is performed at the Merck & Co., Inc. facility in West Point, Pennsylvania, U.S.A.

GARDASIL® is prepared from the highly purified virus-like particles (VLPs) of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The VLPs are adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant. Each 0.5-mL dose is formulated to contain 20 μg HPV 6 L1 protein, 40 μg HPV 11 L1 protein, 40 μg HPV 16 L1 protein, and 20 μg HPV 18 L1 protein. The quadrivalent final container product is a sterile suspension for injection in a single-dose vial or a prefilled syringe. For each image, the fill volume permits intramuscular injection of 0.5 mL of vaccine. GARDASIL® is not a live virus vaccine; it contains no viral DNA, and is incapable of causing infection.

2.2.2 Animal Model for Papillomavirus Disease

There are no animal models of HPV infection. Studies to select HPV vaccine candidates were conducted in animal models of species-specific papillomavirus (PV) disease. In these models, administration of species-specific L1 VLP vaccines induced robust serum anti-PV responses. Vaccinated animals were protected from species-specific PV infection and disease. This protective efficacy was associated with the development of

neutralizing antibodies. Unvaccinated animals that received transfusions of sera from vaccinated animals were also protected from infection and disease. Taken together, these data demonstrated that in animal PV models, the protective efficacy of L1 VLP vaccines is mediated by the development of serum anti-PV responses. These results also supported the hypothesis that induction of systemic anti-HPV responses by type-specific HPV L1 VLP vaccine will result in protection against type-specific HPV infection or disease [46; 47; 48].

2.3 Overview of the Clinical Development Plan for GARDASIL®

The clinical development program for GARDASIL® included girls and women 9 to 26 years of age and boys 9 to 15 years of age at the start of vaccination. This range covers the period just prior to sexual debut through the period of peak risk for HPV infection. Studies in men 16 to 26 years of age and women 26 to 45 years of age are in progress.

Five (5) Phase I/IIa studies with monovalent HPV 11, 16, and 18 L1 VLP vaccines were conducted. A total of 3160 16- to 25-year-old subjects received at least 1 dose of vaccine or placebo. Seven (7) Phase IIb/III studies evaluated formulations of quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine. A total of 21,480 subjects received at least 1 dose of vaccine or placebo. Key studies for the program are presented in Table 3.

The BLA for GARDASIL® was submitted at the time that the Phase III efficacy trials (Protocol 013, the CIN/Warts Efficacy Study; Protocol 015, the Cancer Efficacy Study), and an integrated analysis of Phase II/III efficacy trials had met prespecified success criteria (See Section 2.3.1.9).

Table 3

Summary of Key Studies Within the Clinical Program for GARDASIL®

Study	Phase	Test Vaccine	Study Population	Description
005† Proof-of-Concept Study	IIa	HPV 16 L1 VLP Vaccine	16- to 23-year-old women in the United States (N = 2391)	▪ HPV 16 infection/disease efficacy study ▪ 3.5 years of Postdose 3 follow-up to evaluate duration of efficacy and persistence of anti-HPV 16 responses
007† Quadrivalent Dose-Ranging and Efficacy Study	IIb	Formulations of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, including GARDASIL®	16- to 23-year-old women in the United States, Latin America, and Europe (N = 551- GARDASIL® and placebo only)	▪ Selection of formulation of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine for use in Phase III studies ▪ For the chosen dose, evaluation of efficacy and duration of anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses through 2.5 years of follow-up Postdose 3
011 (Substudy of 013) Hepatitis B Concomitant Use Study	III	GARDASIL®	16- to 23-year-old women in the United States, Latin America, and Europe (N = 1871)	▪ Evaluation of the immunogenicity and tolerability of GARDASIL® and hepatitis B vaccine when these vaccines are administered at the same visit.
012 (Substudy of 013) HPV 16 Bridging Study	III	GARDASIL® and HPV 16 L1 VLP Vaccine	16- to 23-year-old women in the United States, Latin America, Asia-Pacific, and Europe (N = 3875)	▪ Comparison of anti-HPV 16 responses to GARDASIL® to the responses observed with HPV 16 L1 VLP vaccine in Protocol 005 (to allow combining results from Protocol 005 in a combined efficacy analysis of Phase II/III efficacy studies)
013† CIN/Warts Efficacy Study	III	GARDASIL®	16- to 23-year-old women in the United States, Latin America, Asia-Pacific, and Europe (N = 5442)	▪ Pivotal Phase III efficacy study ▪ 2 Co-primary efficacy endpoints: o Combined incidence of HPV 6/11/16/18-related CIN, AIS, or cervical cancer o Combined incidence of HPV 6/11/16/18-related genital warts, VIN, VaIN, vulvar cancer, vaginal cancer ▪ evaluation of duration of anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses through up to 3.5 years of follow-up Postdose 3

Table 3 (Cont.)

Summary of Key Studies Within the Clinical Program for GARDASIL®

Study	Phase	Test Vaccine	Study Population	Description
015[†] Cancer Efficacy Study	III	GARDASIL®	16- to 26-year-old women in the United States, Latin America, Asia-Pacific, and Europe (N = 12,157)	▪ Pivotal Phase III efficacy study ▪ Primary endpoint: Combined incidence of HPV 16/18-related CIN 2/3, AIS, or cervical cancer
015CL (Substudy of 015) Consistency Lot Study	III	GARDASIL®	16- to 26-year-old women in the United States, Latin America, Asia-Pacific, and Europe (N = 1512)	▪ Evaluation of the consistency of manufacture of GARDASIL® and the duration of anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18 responses for up to 3.5 years Postdose 3
016 Adolescent/Adult Bridging and End-Expiry Study	III	Formulations of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, including GARDASIL®	10- to 23-year-old girls and women and 10- to 15-year-old boys in the United States, Latin America, Asia-Pacific, and Europe (N = 3049)	▪ Adolescent/adult bridge substudy: formal bridging of efficacy results from 16- to 26-year-old women to male and female adolescents 10 to 15 years of age using immunogenicity results ▪ Release potency substudy: to provide clinical information in support of manufacturing release specifications
018 Adolescent Immunogenicity and Safety Study	III	GARDASIL®	9- to 15-year-old boys and girls in the United States, Latin America, Asia-Pacific, and Europe (N = 1775)	▪ Study to compare anti-HPV responses induced by GARDASIL® in boys to those in girls ▪ Study to evaluate the safety of GARDASIL® in pre-adolescents

[†] Studies that comprised the Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 Vaccine of N = 20,541 women 13 to 26 years of age who were randomized and vaccinated in the United States, Latin America, Asia-Pacific, and Europe. This data set was used for the prespecified analysis of the 4 efficacy studies in the clinical program for GARDASIL® to increase the precision of efficacy estimate for the combined incidence of HPV 16/18-related CIN 2/3, AIS, or cervical cancer.

N = Number of subjects randomized in each study who received at least 1 injection of vaccine or placebo; HPV = Human papillomavirus; CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; VIN = Vulvar intraepithelial neoplasia; VaIN = Vaginal intraepithelial neoplasia; VLP = Virus-like particles.

2.3.1 Standard Research Procedures in Clinical Studies of GARDASIL®

The study methodology, subject selection, selection of endpoints, immunologic assays, and assessment of safety were in accordance with the established practices for conducting vaccine clinical studies. Key facets of the protocols are described herein.

2.3.1.1 Selection of Target Populations for Efficacy Studies

The efficacy trials enrolled 16- to 26-year-old adolescent and young adult women, as peak exposure to HPV occurs over this age range. To ensure that subjects were mostly HPV naïve but were at risk for HPV infection, the studies prohibited enrollment of women with more than 5 (Phase II studies) or more than 4 (Phase III studies) lifetime sexual partners. The Phase II and Phase III studies did not have screening phases; women were enrolled regardless of their baseline HPV status and Pap test result. Thus, the HPV vaccines were tested in the manner in which their post-licensure use was envisioned.

The clinical program enrolled 9- to 15-year-old preadolescents and adolescents. This age range represents the period immediately prior to the period in which the population is at highest risk for acquisition of HPV infection. Because GARDASIL® is intended primarily as a prophylactic vaccine, vaccination programs in 9- to 15-year-old subjects will have the greatest long-term impact on the burden of HPV disease, including anogenital cancer.

The clinical program has enrolled boys and men. Boys and men are at risk for RRP, anal cancer, penile cancer, HPV-related head/neck cancer, and genital warts. Men are also the main vector for transmission of HPV to women. A fundamental requirement for successful eradication or control of infectious diseases using vaccines is to maximize coverage in the susceptible population to prevent transmission (herd immunity). Gender-specific vaccination programs against infections in which the main pathologic consequence occurs in women only (e.g., rubella/congenital rubella syndrome) were not fully effective in eradicating disease.

The current BLA includes immunogenicity and safety data in 9- to 15-year-old boys. Ongoing studies are evaluating the efficacy of GARDASIL® in 16- to 26-year-old adolescent and young adult men.

2.3.1.2 Pap Test Triage Algorithms for Ascertainment of Cervical Lesions

The Phase II/III studies for GARDASIL® included Pap screening programs that were consistent with the standard of care in the United States or in some cases, more rigorous than the standard of care.

Subjects in the efficacy trials were referred to colposcopy based on Pap test triage algorithms.

The Pap test triage algorithm used in Protocol 007 (Quadrivalent Dose-Ranging and Efficacy Study) and Protocol 013 (CIN/Warts Efficacy Study) was more rigorous than the standard of care in the United States. Subjects underwent Pap testing every 6 months. Any Pap test result that suggested the presence of CIN (i.e., atypical squamous cells of

undetermined significance [ASC-US] with positive Hybrid Capture II HPV probe or worse) resulted in colposcopy. The intent of this approach was to capture all HPV 6-, HPV 11-, HPV 16-, and/or HPV 18-related cervical lesions.

The Pap test triage algorithm used in Protocol 015 (Cancer Efficacy Study) was consistent with the standard of care in the United States. Subjects underwent mandated Pap testing annually. High-grade abnormalities resulted in colposcopy. Low-grade cytology results (ASC-US and low grade squamous intraepithelial lesion [LSIL]) resulted in colposcopy only if they were recurrent. This strategy mirrored the standard of care also recommended in many countries. The triage algorithm in Protocol 005 (Proof-of-Concept Study) was similar to that in Protocol 015.

Protocol 005 and Protocol 007 included a mandatory end-of-study colposcopy to evaluate the performance of the cervical cancer screening program in studies of GARDASIL®. The results of this evaluation demonstrated that the Pap triage algorithm implemented in the clinical program for GARDASIL® was successful in ascertaining incident cervical disease and administration of HPV L1 VLP vaccines do not affect the ability of standard-of-care Pap screening to detect cervical disease.

2.3.1.3 Ascertainment of HPV-Related External Genital Lesions

Complementary methods to detect external genital and vaginal lesions were employed: (1) active inspection to ensure complete ascertainment of lesions (Protocol 013); and (2) a setting that represented typical clinical practice including a genital inspection as part of a yearly Pap test and inspection prompted by symptoms (Protocol 007 and Protocol 015). In all 3 trials, lesions that were possibly, probably, or definitely HPV related, or whose clinical diagnosis was unknown were biopsied. Further biopsies were obtained if new lesions of differing morphology or differing location appeared. Recurring lesions were not biopsied.

The standard of care in most countries is to perform colposcopy in women found to have HPV-related genital lesions, because HPV infection tends to be multifocal and not to respect anatomic boundaries. This approach was used in the clinical trials program for GARDASIL®.

Genital lesions are often treated on the basis of clinical impression. The primary study endpoint required a histologic diagnosis, because the reliability of clinical impressions of an international group of investigators was unknown, while the performance characteristics of the Pathology Panel that provided final histologic diagnosis for study purposes had been defined (see Section 2.3.1.5). The use of biopsies for the purpose of study endpoint determination also allowed for an evaluation of the causal HPV type in the suspect lesion.

2.3.1.4 Centralized Cytology/Pathology Management

A central laboratory processed and provided diagnoses for all ThinPrep® Pap Test (Cytyc, Boxborough MA, U.S.A.) specimens and all tissue specimens (biopsies, endocervical curettage [ECC], definitive therapy specimens) for the purposes of medical

management. It performed HPV testing on residual ThinPrep® material (Hybrid Capture II®, Digene, Gaithersburg MD, U.S.A.) for subjects with a Pap test result of ASC-US. Starting with Protocol 007, all of these functions were centralized at Diagnostic Cytology Laboratory, Indianapolis IN, U.S.A. (referred to as the Program Central Laboratory).

2.3.1.5 Pathology Panel

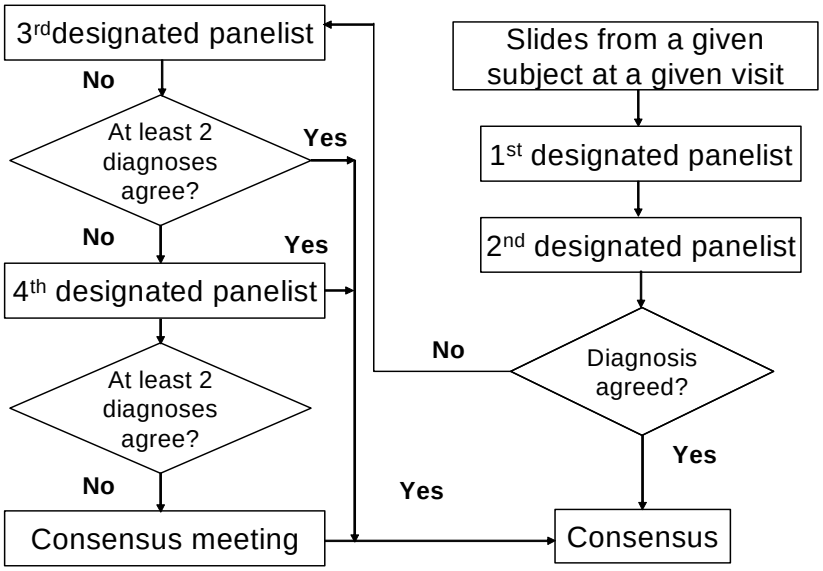
All biopsy specimens were reviewed by a Pathology Panel which consisted of 4 experts in the area of gynecologic pathology. After Protocol 005, all ECC and definitive therapy specimens were also reviewed by the Pathology Panel. Merck Research Laboratories (MRL) and the Pathology Panel followed established guidelines for histology review. The consensus diagnoses of the Pathology Panel were used in the definition of study endpoints only. The performance of the Pathology Panel was monitored using a prespecified quality control program: readings were reproducible, consistent over the course of the program, and correlated appropriately with presence of specific HPV types.

Panelists reviewed the specimen slides independently, blinded to the HPV status, central laboratory's diagnosis, other panelist's diagnosis, and other demographic and clinical data of the study subjects. If the diagnoses of the lesion made by the initial 2 panelists agreed, that diagnosis was considered the final consensus diagnosis with regard to the endpoint of the clinical trials. If the 2 diagnoses were discrepant, the third pathologist was called upon for the adjudication of the diagnosis, although the third panelist was not aware that he/she was a "tie-breaker". On the rare occasion that all 3 diagnoses disagreed, a fourth pathologist reviewed the slides. The final diagnosis was the one rendered by 2 pathologists. If the 4 pathologists provided 4 different diagnoses for a given biopsy, a panel meeting consisting of all 4 pathologists took place to reach the final consensus (shown in Figure 3). Overall, among the 12,428 biopsies in the program, 76.1% achieved consensus after review by 2 pathologists, 19.3% achieved consensus after review by 3 pathologists, 4.0% achieved consensus after review by 4 pathologists, and 0.6% required a consensus meeting.

The diagnosis of the central laboratory was used for the purposes of medical management. However, if a Pathology Panel consensus diagnosis for a given specimen was deemed more severe than the diagnosis of the central laboratory for the same specimen, a written notification was sent to the study site informing them of the discrepancy. Study site investigators could then use this information in determining the course of patient care.

Figure 3

Algorithm for Pathology Panel Review



2.3.1.6 Detection of Vaccine HPV Types in Biopsy Specimens

Tissue specimens were sent to MRL for HPV testing. Each specimen was tested by polymerase chain reaction (PCR) for HPV, regardless of whether an HPV-related histologic diagnosis was made, for the purpose of determining the causal HPV type in the lesion. Testing was performed on frozen biopsy tissue, a swab collected from the biopsy site, or thinsection microtomy specimens prepared by the Program Central Laboratory, depending on the study. All laboratory staff were blinded to vaccination allocation. After the primary results of Protocol 005 became available, the identification of all specimens provided to the PCR laboratory were masked so that personnel tested specimens without knowledge of subject identity, visit interval, or histologic diagnosis rendered by the Program Central Laboratory or the Pathology Panel.

2.3.1.7 Immunogenicity Assays

The clinical trials program for GARDASIL® evaluated vaccine-induced immune responses. Evaluation was conducted at the completion of the vaccination regimen and for up to 3.5 years thereafter in 16- to 26-year-old adolescent and young adult women and 1.5 years thereafter in 9- to 15-year-old boys and girls. Immunogenicity endpoints for clinical trials were: (1) anti-HPV geometric mean titers (GMTs), which is a standard summary measure of immunogenicity; and (2) the proportions of subjects who seroconverted to each HPV type 4 weeks Postdose 3 (levels for seroconversion for each

vaccine HPV type were: ≥20 milli-Merck Units per milliliter [mMU/mL] for HPV 6, ≥16 mMU/mL for HPV 11, ≥20 mMU/mL for HPV 16, and ≥24 mMU/mL for HPV 18). The minimum anti-HPV levels required to protect against acquisition of HPV infection has not been defined.

The immunogenicity of HPV L1 VLP vaccines was measured using one of 3 assay types: (1) a competitive radioimmunoassay (cRIA) format; (2) a competitive Luminex-based immunoassay (cLIA) format; and (3) a xenograft-based HPV 11 neutralization assay used only in the initial Phase I Immunogenicity and Safety Study, Protocol 001. During the course of Protocol 007 (Quadrivalent Dose-Ranging and Efficacy Study), the cRIA was transitioned to the cLIA that is currently in use.

cRIAs to Measure Serum Anti-HPV 6, Anti-HPV 11, Anti-HPV 16, and Anti-HPV 18 Responses. Vaccine-induced immune responses were measured in a radioimmunoassay format in Phase I and II studies up to and including Protocol 007. A fixed lower cutoff was derived for each vaccine type HPV cRIA by repeatedly testing a panel of positive and negative samples against a standard curve. Samples with values less than the cutoff were considered serostatus negative. Samples with values equal to or greater than the cutoff were considered serostatus positive, were corrected for dilution, and reported in mMU/mL.

cLIAs to Measure Serum Anti-HPV 6, Anti-HPV 11, Anti-HPV 16, and Anti-HPV 18 Responses. Vaccine-induced immune responses were measured in a Luminex-based format in Protocol 007 and all Phase III studies. Results for the assay were reported as concentration of antibody in mMU/mL. To define the serostatus cutoff, the positivity rates for ~500 samples were assessed at 11 different cutoffs. Prior to testing, sera were classified into panels according to their potential for being a true positive based on clinical history and PCR test results. The serostatus cutoff was selected as the lowest titer such that all or nearly all of the known PCR-negative samples and likely negative samples yielded negative results.

2.3.1.8 Evaluations of Vaccine Safety

GARDASIL® was evaluated for: (1) injection-site and systemic tolerability; (2) impact on long-term health status; and (3) interaction with pregnancy and lactation, events that are likely to occur in the target population for which GARDASIL® will be indicated.

In all trials of GARDASIL®, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of study vaccine. In Protocol 015 (Cancer Efficacy Study), a subset of subjects was followed using VRC-aided surveillance and the remainder of the subjects used a general surveillance method.

Temperature values and injection-site adverse experiences (pain, redness and swelling) were recorded for 5 days (Days 1 through 5 postvaccination), and systemic adverse experiences and any other medications administered were recorded for 15 days (Days 1 through 15 postvaccination) on the VRC by study subjects. The investigator determined seriousness, action taken, and relationship to study vaccine for any VRC-recorded adverse experience.

With the general surveillance method in Protocol 015, subjects were asked at each visit if they had any adverse experiences that qualified as serious based on the protocol definition. In general, subjects were not queried for nonserious adverse experiences.

In all clinical trials of GARDASIL®, investigators were instructed to report any serious adverse experience occurring in any subject from the time the consent form was signed through 14 days following the first vaccination and from the time of any subsequent vaccination through 14 days thereafter, whether or not the serious adverse experience was vaccine related. In addition, at any time during the study, if the event was considered by the investigator to be possibly, probably, or definitely vaccine related or related to a study procedure, it was to be immediately reported. Death due to any cause and discontinuation due to an adverse experience was reported at any time during the study.

In all trials, subjects were evaluated for new medical conditions for the duration of the study.

A study of HPV L1 VLPs in pregnant women had not been conducted. Thus, the clinical program for GARDASIL® prohibited vaccination of pregnant subjects. To avoid exposure of such women to the study vaccines, subjects were required to use effective contraception during the vaccination period. A pregnancy test was performed immediately prior to each vaccination. Subjects with positive pregnancy test results were not vaccinated. In early trials, such subjects were discontinued. In later trials, vaccination was resumed once the pregnancy resolved. Despite these precautions, a considerable number of pregnancies occurred during the study. All pregnancies were followed for outcome. In Phase II trials, this follow-up was limited to pregnancies with onset that occurred during the vaccination period. In Phase III trials, follow-up included all pregnancies, regardless of time of onset. Information regarding the health of infants was also collected.

Breast-feeding was not a contraindication to enrollment or vaccination. All cases of vaccination of lactating women in the Phase III trials were followed for outcome. Protocol-defined serious adverse experiences were collected in both the mother and her infant(s) from the time of the possible exposure of the infant to the vaccine via breast milk until the infant was weaned (if completely weaned prior to the Month 7 study visit) or until breast milk made up less than 50% of the infant's diet or until the Month 7 visit had occurred.

2.3.1.9 Statistical Analysis

Statistical analyses for each clinical study were prespecified in Data Analysis Plans (DAPs). All analyses were performed according to standardized and validated methods.

The Phase III trials followed fixed-case study designs whereby statistical analyses were to be performed when prespecified numbers of cases had been observed. For Protocol 013 (CIN/Warts Efficacy Study), analyses were to be performed after 38 cases of each primary endpoint (HPV 6/11/16/18-related CIN and HPV 6/11/16/18-related EGL) had occurred in the per-protocol population. For the interim analyses of HPV 16/18-related

CIN 2/3 or AIS, which were conducted both within Protocol 015 (Cancer Efficacy Study) alone and across the combined Protocols 005/007/013/015, analyses were to be conducted after 19 cases were observed in the per-protocol population of Protocol 015 and 33 cases were observed in the per-protocol population of the combined protocols. All efficacy estimates were to account for person-time at risk.

As of the cut-off dates in mid-2005, 21 subjects in Protocol 015 and 53 subjects in the 4 efficacy studies met the definition of a case of HPV 16- or HPV 18-related CIN 2/3 or AIS. Cases of vaccine HPV type-related EGL were observed in 40 subjects and cases of vaccine HPV type-related CIN, AIS, or cervical cancer were observed in 37 subjects in Protocol 013 based on visits through 15-Jul-2005. Given that: (1) the most important endpoint in the program was the combined incidence of HPV 16- or HPV 18-related CIN 2/3 or AIS and the number of subjects who developed an endpoint in the combined efficacy data set was much greater than the number prespecified for analysis; (2) the number of subjects who developed an EGL endpoint in Protocol 013 had exceeded the target number; and (3) the number of subjects who developed a CIN case in Protocol 013 was very close to its target and there was no loss in power to perform the analysis with 37 cases as opposed to 38 cases, the analyses of Protocol 013 were performed using data from visits that occurred on or prior to 15-Jul-2005.

Follow-up is continuing in both Phase III trials to obtain greater precision in the estimation of the primary study endpoints and addressing additional exploratory endpoints.

3. Clinical Efficacy

Efficacy was assessed in 4 randomized, double-blind, placebo-controlled studies (Table 3). Protocol 005 (Proof-of-Concept Study) (N=2391) evaluated the HPV 16 component of GARDASIL®. Protocol 007 (Dose-Ranging and Efficacy Study) (N=551) evaluated GARDASIL® (2 other quadrivalent HPV [Types 6, 11, 16, 18] L1 VLP vaccine formulations were also evaluated). Two (2) Phase III studies, Protocol 013 (CIN/Warts Efficacy Study) (N=5442 subjects who received GARDASIL® or placebo; N=304 subjects who received monovalent HPV 16 L1 VLP vaccine) and Protocol 015 (Cancer Efficacy Study) (N=12,157) evaluated GARDASIL®. Together, the 4 studies randomized 20,887 16- to 26-year-old adolescent and young adult women of whom 20,845 received at least 1 dose of study vaccine (GARDASIL®, HPV 16 L1 VLP vaccine component of GARDASIL®, or placebo).

3.1 Efficacy Endpoints

3.1.1 Measurements of Efficacy

GARDASIL® is a prophylactic vaccine. The primary goal of the efficacy evaluations was to evaluate **prophylactic efficacy**, defined as the impact of administration of GARDASIL® on the incidence of HPV 6-, 11-, 16-, and 18-related clinical HPV disease, compared with placebo, in women who are naïve to the relevant vaccine HPV types at baseline.

The public health utility of GARDASIL® can also be measured as the impact of the vaccine on the incidence of clinical HPV disease (due to vaccine and non-vaccine HPV types) in the general population of girls and women who are HPV-naïve (e.g., adolescents prior to sexual debut), and in the general population of young adult women (most of whom are sexually active; some of whom are already infected with vaccine or non-vaccine HPV types). These 2 measurements of utility are termed **prophylactic population impact and overall population impact,** respectively.

Of the various measures of prophylactic efficacy, the efficacy of the vaccine with respect to HPV 16- and HPV 18-related cervical intraepithelial neoplasia grade 2/3 (CIN 2/3) and adenocarcinoma in situ (AIS) is the most important. On the advice of the VRBPAC, FDA required a demonstration of the vaccine's prophylactic efficacy with respect to CIN 2/3 as the basis of licensure. Further discussions with FDA led to an agreement that the prophylactic population impact and overall population impact of GARDASIL® with respect to the overall risk for CIN 2/3 and AIS would be evaluated postlicensure at the end of the Phase III studies because key data for the evaluation are pending.

A measurement of the **therapeutic efficacy** of GARDASIL® was conducted to determine whether, among subjects who showed evidence of infection with a vaccine HPV type at Day 1, administration of GARDASIL® reduced the proportion of subjects who were found to have clinical disease due to that type, compared with placebo.

Thus, the BLA for GARDASIL® contained demonstrations of definitive prophylactic efficacy with respect to HPV 16- and HPV 18-related CIN 2/3 or AIS.

Estimates of prophylactic population impact and overall population impact were also provided, with the caveat that such estimates were preliminary because they do not include critical data which is still unavailable.

3.1.2 Prophylactic Efficacy Endpoints

The primary hypotheses for the efficacy studies of GARDASIL® tested the impact of prophylactic vaccination with GARDASIL® on infection or disease caused by HPV 6, HPV 11, HPV 16, and HPV 18 (Table 4).

Table 4

Endpoints Used to Evaluate the Prophylactic Efficacy of GARDASIL® or the HPV 16 L1 VLP Vaccine Component of GARDASIL®

Endpoint	Use	Purpose
HPV 16- or HPV 18-related CIN 2/3 or AIS	– Primary endpoint of Protocol 015 – Primary endpoint of Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 Vaccine for Protocols 005, 007, 013, 015	Evaluate impact of GARDASIL® on risk for development of HPV 16- or HPV 18-related invasive cervical cancer
HPV 16- or HPV 18-related condyloma acuminata, VIN 1, VaIN 1, VIN 2/3, VaIN 2/3	– Analyses of the Efficacy Data Set of Protocols 007, 013, 015 (defined prior to unblinding)	Evaluate impact of GARDASIL® on risk for development of HPV 16- or HPV 18-related vulvar and vaginal cancer
HPV 6-, 11-, 16-, or 18-related CIN or AIS	– Co-primary endpoint of Protocol 013 – Endpoint of the Efficacy Data Set of Protocols 007, 013, 015 (defined prior to unblinding)	Evaluate impact of GARDASIL® on the overall risk for development of CIN caused by vaccine HPV types
HPV 6-, 11-, 16-, or 18-related condyloma acuminata, VIN 1, VaIN 1, VIN 2/3, VaIN 2/3	– Co-primary endpoint of Protocol 013 – Endpoint of the Efficacy Data Set of Protocols 007, 013, 015 (defined prior to unblinding)	Evaluate impact of GARDASIL® on the overall risk for development of external genital lesions caused by vaccine HPV types
Persistent HPV 6, HPV 11, HPV 16, or HPV 18 Infection	– Primary endpoint of Protocol 005 (HPV 16 only) – Efficacy endpoint of Protocol 007	Evaluate impact of GARDASIL® on early markers of cervical cancer

HPV = Human papillomavirus; CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; VIN = Vulvar intraepithelial neoplasia; VaIN = Vaginal intraepithelial neoplasia; VLP = Virus-like particles.

3.1.2.1 HPV Infection Endpoints

Protocol 005 (Proof-of-Concept Study) and Protocol 007 (Quadrivalent Dose-Ranging and Efficacy Study) evaluated vaccine efficacy with regard to persistent HPV infection. Persistent HPV 16 infection (detection of HPV on at least 2 consecutive visits) has been shown to be a stronger predictor for progression to CIN 2/3 compared with single HPV detection [49; 50; 51]. In Protocol 005 and Protocol 007, the definition of persistent infection encompassed:

- Persistent vaccine-type HPV infection without confirmed HPV disease – defined as detection of the same vaccine-type HPV by PCR in cervicovaginal specimens collected on at least 2 consecutive visits spaced at least 4 months apart;
- Vaccine-type HPV infection with confirmed HPV disease – defined as a consensus Pathology Panel diagnosis of cervical of external genital HPV disease, plus detection of vaccine-type HPV in the same lesion in which HPV pathology was diagnosed and in a specimen collected at the routine visit immediately prior to or immediately following the colposcopy visit in which the biopsy showing HPV pathology was obtained; and

– Detection of vaccine-type HPV in cervicovaginal specimens on the last visit on record without the opportunity to evaluate persistence.

3.1.2.2 Disease Endpoints

Table 5 lists the endpoints, tissue specimens, and assays used for endpoint measurement in the efficacy trials in the clinical program for GARDASIL®. Cervical HPV disease endpoints were included in all efficacy studies. Protocol 005 (Proof-of-Concept Study) focused on cervical disease only and the study's endpoints were limited to those caused by HPV 16. Vulvar and vaginal HPV disease endpoints were included in Protocol 007 (Quadrivalent Dose-Ranging and Efficacy Study), Protocol 013 (CIN/Warts Efficacy Study), and Protocol 015 (Cancer Efficacy Study).

The method used to assess the causal HPV type within a lesion evolved over time. In Protocol 005 and the early phase of Protocol 007, frozen biopsy PCR and biopsy swab PCR (Protocol 007 only) was used. In this technique, each area of abnormality was biopsied. If the biopsy was large enough, the biopsy was divided into 2 portions. One portion was sent to for HPV typing. The other portion was sent for histology. If the biopsy sample was not large enough, a sample adjacent to the biopsied lesion was obtained for HPV typing by PCR.

Thinsection PCR was used in the later phases of Protocol 007 and all of the Phase III studies. Figure 4 provides a schematic of endpoint assessment using this technique. For this assay, each area of abnormality was biopsied using separate forceps and placed into an individual container. Individual biopsies underwent embedding and sectioning under ultraclean conditions (to minimize PCR contamination). A total of 13 sections were generated for each biopsy. The first 2 and last 2 sections were used for histologic analysis. Each of the remaining 9 sections was placed into an individual tube for PCR testing. This procedure allowed for precise co-localization of the histopathologic finding with the causal HPV type. This method ensured highly accurate assessment of causal HPV type, as the section in which HPV testing occurred was a section adjacent to the section in which histopathology was read.

Table 5

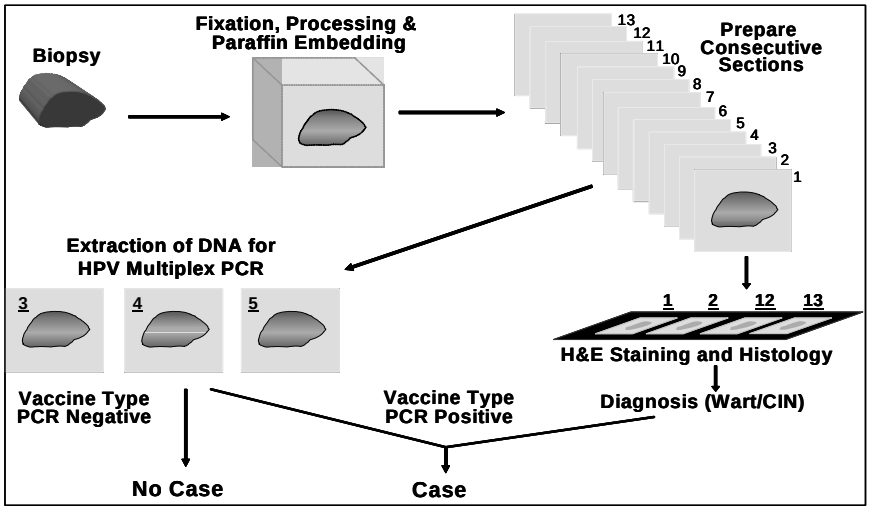
Endpoints, Tissue Specimens, and Assays Used for Endpoint Measurement in the Efficacy Trials in the Clinical Program for GARDASIL®

	Protocol 005	Protocol 007	Protocol 013	Protocol 015
Endpoint – HPV type				
HPV 6-related		X	X	X
HPV 11-related		X	X	X
HPV 16-related	X	X	X	X
HPV 18-related		X	X	X
Endpoint - Pathology				
CIN 1	X	X	X	X
CIN 2/3, AIS, or Cervical Cancer	X	X	X	X
VIN or Vulvar Cancer		X	X	X
VaIN or Vaginal Cancer		X	X	X
Genital Warts		X	X	X
Biopsy Specimen Eligible for Endpoint				
Cervical Biopsy (Colposcopic or Definitive Therapy)	X	X	X	X
LEEP/Conization Specimen		X	X	X
Endocervical Curettage		X	X	X
Vulvar Biopsy or Definitive Therapy Specimen		X	X	X
Vaginal Biopsy or Definitive Therapy Specimen		X	X	X
HPV Detection Method				
Frozen Biopsy PCR	X	X		
Thin Section PCR		X	X	X
Biopsy Swab PCR		X		

HPV = Human papillomavirus; CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; VIN = Vulvar intraepithelial neoplasia; VaIN = Vaginal intraepithelial neoplasia; LEEP = Loop electroexcision procedure; PCR = Polymerase chain reaction.

Figure 4

Detection of Study Endpoints in Biopsy Specimens in Clinical Trials of GARDASIL®



PCR = Polymerase chain reaction; CIN = Cervical intraepithelial neoplasia; H&E = Hematoxylin and eosin; HPV = Human papillomavirus; DNA = Deoxyribonucleic acid.

3.1.3 Population Impact Endpoints

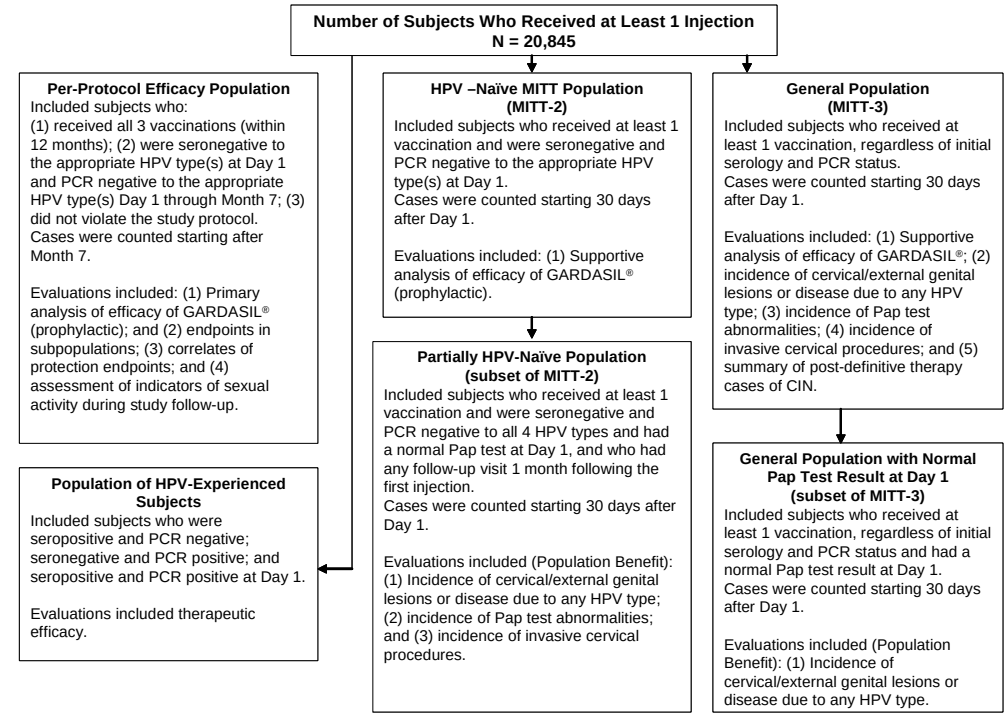
At the completion of the Phase III studies, prespecified analyses will evaluate the impact of GARDASIL® on the rates of cervical and genital disease related to any HPV type. In the interim, preliminary estimates of the efficacy of GARDASIL® with respect to these general parameters of disease burden were generated, including the proportion of subjects who developed a CIN, VIN, VaIN, or genital wart lesion regardless of causal HPV type.

3.2 Analysis Populations

A description of efficacy analysis populations can be found in Figure 5.

Figure 5

Description of the Populations Contributing to the Efficacy Analysis for GARDASIL®



Note: Protocol 005 contributed HPV 16-related cervical endpoints only.

MITT = Modified intention-to-treat; PCR = Polymerase chain reaction; Pap = Papanicolaou's test; HPV = Human papillomavirus.

In addition, a Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 L1 VLP Vaccine, comprised of 20,541 randomized and vaccinated subjects in the 4 efficacy studies in the clinical program for GARDASIL® (Protocol 005, Protocol 007, Protocol 013, and Protocol 015), was used in a prespecified analysis to increase the precision of the efficacy estimate for the combined incidence of HPV 16/18-related CIN 2/3, AIS, or cervical cancer. An Efficacy Data Set for GARDASIL®, which included randomized and vaccinated subjects in Protocol 007, Protocol 013, and Protocol 015, was used in a prespecified analysis to increase the precision of the efficacy estimate for the combined incidence of HPV 6/11/16/18-related CIN, VIN, VaIN, vulvar or vaginal cancer and genital warts.

The primary analysis population was conducted in a per-protocol efficacy (PPE) population; p-values are provided for this population in support of the planned hypothesis tests. Supplemental analyses were performed in the HPV-Naïve Modified Intention-to-Treat (HN-MITT) population and the General population and include 95% confidence intervals.

3.2.1 Analysis Populations for Prophylactic Efficacy

GARDASIL® was designed primarily as a prophylactic HPV vaccine. However, the trials enrolled subjects regardless of baseline HPV status or baseline Pap test result, because it is anticipated that vaccine recipients will not be screened for presence of HPV infection or disease prior to vaccination. At Day 1, serum and cervicovaginal swabs were obtained for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 serology and for HPV 6, HPV 11, HPV 16, and HPV 18 DNA testing by PCR, respectively. At Month 7 (1 Month Postdose 3), all subjects underwent cervicovaginal sampling for HPV 6, HPV 11, HPV 16, and HPV 18 DNA testing by PCR. Also, all specimens collected at any time during the vaccination period were similarly tested for HPV 6, HPV 11, HPV 16, and HPV 18 DNA.

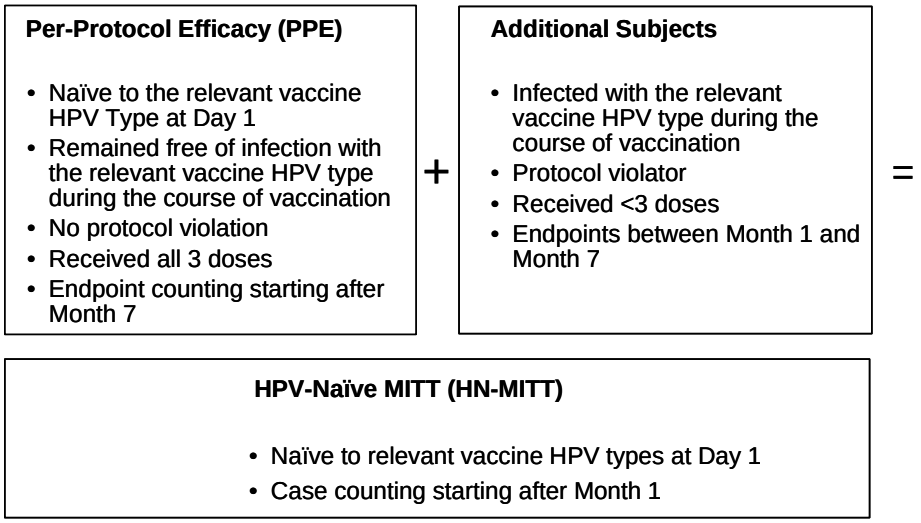
Because GARDASIL® is intended to be primarily a prophylactic vaccine, the main efficacy analyses were conducted in subjects who were naïve to the relevant vaccine HPV type at baseline **(prophylactic efficacy)**. Prophylactic efficacy was evaluated in the PPE population and the HPV-Naïve MITT population (Figure 6). These populations approximated adolescent and young adult women prior to sexual debut.

The primary analysis of efficacy was conducted in the PPE population. Analyses in this population approximated the impact of a 3-dose regimen of GARDASIL® with respect to cervical and genital disease caused by HPV 6, HPV 11, HPV 16, and HPV 18 in adolescent and young adult women who remain sexually-naïve until after completion of the 3-dose vaccination regimen.

Supplemental analyses were conducted in the HPV-Naïve MITT population. Analyses in this population approximated the impact of a 3-dose regimen of GARDASIL® with respect to cervical and genital disease caused by HPV 6, HPV 11, HPV 16, and HPV 18 in adolescent and young adult women who are sexually-naïve at the start of the vaccination regimen. The HPV-Naïve MITT analysis differed from the PPE analysis in that it included subjects with major protocol violations and subjects who became infected with a vaccine HPV type during the vaccination period. In the HPV-Naïve MITT population, efficacy evaluation started 30 days Postdose 1, compared with Post-Month 7 for the PPE population.

Figure 6

Prespecified Analysis Populations to Evaluate the Prophylactic Efficacy of GARDASIL®



MITT = Modified intention-to-treat; HPV = Human Papillomavirus

Prophylactic efficacy analyses represented a composite evaluation of the impact of GARDASIL® on the incidence of vaccine-type-specific HPV disease among subjects who were naïve to the relevant vaccine HPV type at baseline. In the great majority of cases, subjects were naïve to all 4 HPV types. However, in some cases, subjects were infected with one HPV type, but were naïve to the remaining vaccine HPV types. These subjects were included in the overall assessments of the prophylactic efficacy of GARDASIL®, but only with respect to the types for which they were naïve (Table 6). For example, if a subject had evidence of infection with HPV 18 at baseline (but was naïve to HPV 6, 11, or 16), she was eligible to be included in the overall analyses of prophylactic efficacy for HPV 6, HPV 11, HPV 16 infection or related disease. If she developed a case of HPV 6-related CIN, this case was counted within all relevant endpoints within the prophylactic efficacy analyses. If she developed HPV 18-related CIN, this case was not counted in the prophylactic efficacy analyses, as the subject had been already infected at baseline. HPV 6 and HPV 11 are counted as a single HPV type for the purposes of assignment to the relevant analysis population because the L1 proteins for HPV 6 and HPV 11 are 92% homologous at the amino acid level.

Table 6

Role of Baseline HPV Status With Respect to Endpoint Counting for Prophylactic Efficacy Analyses

Baseline HPV Status	Clinical Endpoint (Pathology Panel Confirmed CIN, AIS, VIN, VaIN, Genital Warts)			
	HPV 6-Related	HPV 11-Related	HPV 16-Related	HPV 18-Related
Naïve to all 4 vaccine HPV types	YES	YES	YES	YES
Positive to HPV 6 or HPV 11 Naïve to HPV 16 and HPV 18	NO	NO	YES	YES
Positive to HPV 16 Naïve to HPV 6, 11, and 18	YES	YES	NO	YES
Positive to HPV 18 Naïve to HPV 6, 11, and 16	YES	YES	YES	NO

HPV = Human papillomavirus; CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; VIN = Vulvar intraepithelial neoplasia; VaIN = Vaginal intraepithelial neoplasia.

3.2.2 Analysis Populations for Population Impact Efficacy

Analyses to evaluate whether administration of GARDASIL® benefits women who are already infected with vaccine HPV types (**therapeutic efficacy**) are presented in Section 3.5.

At the completion of the Phase III studies, prespecified analyses will evaluate the impact of GARDASIL® on the overall rates of cervical and genital disease caused by any HPV type. In the interim, estimates of the efficacy of GARDASIL® with respect to these general parameters of disease burden were generated. These analyses, termed **population impact analyses**, are presented in Section 3.6.

3.3 Baseline Characteristics of Subjects Enrolled in Efficacy Trials of GARDASIL®

Table 7 summarizes baseline demographic characteristics for the population enrolled in the efficacy trials in the development program for GARDASIL®. Of the 20,887 subjects enrolled in these studies, 19,321 subjects (92.5%) continued in the study from the time of enrollment through the date at which each study's database was closed. The low attrition rate strengthens the program's efficacy conclusions. The subjects were enrolled in 22 countries, providing diversity that justifies the application of study findings to the general population of 9- to 26-year-old subjects worldwide.

Overall, 12.0% of the combined study population had a Pap test result suggestive of CIN at Day 1, and 27.0% of the combined study population was either seropositive (suggestive of prior infection) or PCR positive (suggestive of ongoing infection) to a given vaccine HPV type. The inclusion of subjects with evidence of prior or ongoing

HPV infection allowed for an evaluation of GARDASIL® with respect to the given vaccine HPV type with which the subject was experienced (through prior or ongoing infection) as well as to the remaining vaccine HPV types to which the subject was naïve. For a substantial proportion of subjects enrolled in the clinical trials for GARDASIL®, the first Pap test conducted in the study represented their very first Pap test. Given that the population was sexually active, the incidence of CIN at baseline was high due to this lack of previous screening.

Table 7

Selected Day 1 Demographic Characteristics of Subjects Enrolled in the Phase II/III Efficacy Trials for GARDASIL® by Geographic Region of Origin of the Study Population

Day 1 Parameter	Total (N=20887)	Asia Pacific (N=748)	Europe (N=9181)	Latin America (N = 5666)	North America (N=5292)
Percent of total	100%	4%	44%	27%	25%
Mean Age (years)	20	21	20	21	20
Non-virgin	94%	96%	92%	99%	93%
Chlamydia (+)	4%	3%	3%	7%	3%
Abnormal Pap (ASC-US or worse)	12%	7%	11%	12%	14%
HPV 6, 11, 16, or 18 (+)	27%	16%	25%	32%	25%
Naïve to all 4 HPV types	73%	84%	75%	68%	75%

N = Number of subjects randomized in each geographic region. ASC-US = Atypical squamous cells of undetermined significance; HPV = Human papillomavirus.

3.4 Prophylactic Efficacy

The median durations of follow-up (enrollment to final study visit) were 4.0, 3.0, 2.4, 2.0, and 2.0 years for Protocol 005 (Proof-of-Concept Study), Protocol 007 (Quadrivalent Dose- Ranging and Efficacy Study), Protocol 013 (CIN/Warts Efficacy Study), Protocol 015 (Cancer Efficacy Study), and the combined efficacy datasets, respectively. This section presents the analyses of prophylactic efficacy in the PPE and HPV-Naïve MITT populations.

3.4.1 Prophylactic Efficacy Against HPV 16- and HPV 18-Related Cervical Cancer

Efficacy of prophylactic administration of GARDASIL® with respect to HPV 16- or HPV 18-related cervical cancer was evaluated by assessing the impact of GARDASIL® on the incidence of HPV 16- or HPV 18-related CIN 2/3 or AIS. This endpoint was defined as histologically confirmed CIN 2/3 or AIS lesions in which HPV 16 or HPV 18 was detected.

The efficacy analyses of GARDASIL® with respect to this endpoint were performed in Protocol 015 (Cancer Efficacy Study), and in the Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 L1 VLP Vaccine. The evaluation in the combined data set was intended to increase the precision of the efficacy estimate.

Success in Protocol 015 required that the lower bound of the confidence interval for efficacy in the PPE population exceed 0%. In the Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 L1 VLP Vaccine, success required that the lower bound of the confidence interval for efficacy in the PPE population exceed 25%. Success in both analyses was required to meet overall success criteria and trigger application for licensure.

Pre-specified analyses were also conducted in the broader HPV-naïve population of both Protocol 015 and the Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 L1 VLP Vaccine. These analyses estimated efficacy against HPV 16/18-related CIN 2/3 and AIS, as well as HPV 16/18-related CIN 3 and AIS.

The efficacy of GARDASIL® with respect to HPV 16- or HPV 18-related CIN 2/3 or AIS in Protocol 015 is displayed in Table 8. Efficacy was 100% in the PPE population.

The efficacy of HPV L1 VLP vaccine with respect to HPV 16- or HPV 18-related CIN 2/3 or AIS in the Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 L1 VLP Vaccine is displayed in Table 9. Efficacy was 100% in the PPE population.

Table 8

Prophylactic Efficacy Against HPV 16/18-Related Cervical Cancer (via CIN 2/3 or AIS) in Protocol 015

Population	Endpoint	GARDASIL® Cases	Placebo Cases	Efficacy	CI	p-Value
Per-Protocol Efficacy	HPV 16/18-related CIN 2/3 or AIS	0	21	100%	76%, 100%	<0.001
	HPV 16-related CIN 2/3 or AIS	0	16	100%	75%, 100%	
	HPV 18-related CIN 2/3 or AIS	0	8	100%	42%, 100%	
HPV-Naïve MITT	HPV 16/18-related CIN 2/3 or AIS	1	36	97%	83%, 100%	

Subjects are counted once per applicable row.
A 97.96% Confidence Interval (CI) is provided for the primary analysis of HPV 16/18-related CIN 2/3 or AIS in the PPE population to adjust for multiplicity for the interim analyses and the end-of-study analyses at the 0.025 (1-sided) level. A 95% CI is presented for the remaining rows representing supplemental summaries.

CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; HPV = Human papillomavirus.

Table 9

Prophylactic Efficacy Against HPV 16/18-Related Cervical Cancer (via CIN 2/3 or AIS) in the Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 L1 VLP Vaccine – Protocols 005, 007, 013, and 015

Population	Endpoint	HPV Vaccine Cases	Placebo Cases	Efficacy	95% CI	p-Value
Per-Protocol Efficacy	HPV16/18-related CIN 2/3 or AIS	0	53	100%	93%,100%	<0.0001
	HPV16-related CIN 2/3 or AIS	0	44	100%	92%,100%	
	HPV 18-related CIN 2/3 or AIS	0	14	100%	70%,100%	
HPV – Naïve MITT	HPV 16/18-related CIN 2/3 or AIS	1	81	99%	93%, 100%	
Subjects are counted once per applicable row.						

CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ;
HPV = Human papillomavirus.

Among all HPV-related cervical pathological states, CIN 3 and AIS are the closest in pathological and temporal sequence to invasive cervical cancer. A display of the efficacy of GARDASIL® with respect to these endpoints is in Table 10. Efficacy was 100%.

Table 10

Prophylactic Efficacy Against HPV 16/18-Related Cervical Cancer (via CIN 3 or AIS) in the Combined Efficacy Data Set for GARDASIL® and Monovalent HPV 16 L1 VLP Vaccine – Protocols 005, 007, 013, and 015
(HPV-Naïve MITT Population)

Endpoint	HPV Vaccine Cases	Placebo Cases	Efficacy	95% CI
HPV 16/18-related CIN 3 or AIS	0	52	100%	93%,100%
HPV 16/18-related CIN 3	0	47	100%	92%, 100%
HPV 16/18-related AIS	0	9	100%	49%, 100%

CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ;
HPV = Human papillomavirus.

These data demonstrate that prophylactic administration of GARDASIL® to 16- to 26-year-old women prevents development of high-grade cervical dysplasia and *in situ* cervical cancer caused by HPV 16 and HPV 18. Based on these findings, it can be stated that prophylactic administration of GARDASIL® prevents development of HPV 16- and HPV 18-related cervical cancer.

3.4.2 Prophylactic Efficacy Against HPV 16- and HPV 18-Related Vulvar and Vaginal Cancer

As is the case for cervical cancer, HPV-related vulvar and vaginal cancer arise from a field of high-grade precancerous dysplasia (VIN 2/3 and VaIN 2/3, respectively).

Vulvar and vaginal precancers are uncommon. Efficacy of prophylactic administration of GARDASIL® with respect to HPV 16- or HPV 18-related vulvar and vaginal cancers was evaluated by determining the impact of GARDASIL® on the incidence of HPV 16- or HPV 18-related VIN 2/3 or VaIN 2/3.

To have sufficient sample size to detect differences between vaccination groups, pre-specified analyses of efficacy were conducted in the HPV-Naïve MITT population in the Efficacy Data Set for GARDASIL® (Protocols 007, 013, and 015). Protocol 005 was not included as it did not include a systematic evaluation of external genital lesions. The results are in Table 11. Efficacy was 100%.

Table 11

Prophylactic Efficacy Against HPV 16/18-Related Vulvar and Vaginal Cancer (via VIN 2/3 or VaIN 2/3) in the Efficacy Data Set for GARDASIL® – Protocols 007, 013, and 015 (HPV-Naïve MITT Population)

Endpoint	GARDASIL®	Placebo	Efficacy	95% CI
HPV 16/18-related VIN 2/3 or VaIN 2/3	0	24	100%	83%, 100%

MITT = Modified intention-to-treat; VIN = Vulvar intraepithelial neoplasia; VaIN = Vaginal intraepithelial neoplasia; HPV = Human papillomavirus; CI = Confidence interval.

These data demonstrate that prophylactic administration of GARDASIL® to 16- to 26-year-old women prevents development of high-grade vulvar and vaginal pre-cancers caused by HPV 16 and HPV 18. On the basis of these findings and the pathologic association of VIN 2/3 and VaIN 2/3 with vulvar and vaginal cancer, respectively, it can be stated that prophylactic administration of GARDASIL® prevents development of HPV 16- and HPV 18-related vulvar and vaginal cancer.

3.4.3 Prophylactic Efficacy Against HPV 6-, HPV 11-, HPV 16-, and HPV 18-Related CIN or AIS

CIN 1 represents the most common manifestation of cervical HPV disease. While CIN 1 lesions often resolve spontaneously, the management of these lesions represents a significant physical and psychological burden to women and a substantial health economic burden to health care systems. It is estimated that about 700,000 HPV 6-, 11-, 16-, and 18-related CIN lesions are detected in American women annually.

CIN 1 lesions caused by HPV 6, HPV 11, HPV 16, and HPV 18 are visually (at colposcopy) and morphologically (at histology) indistinguishable. Thus, from the perspective of the patient and her physician, these 4 types of lesions are accompanied by similar morbidity.

The primary evaluation of efficacy for this endpoint was prespecified to occur in Protocol 013, the CIN/Warts Efficacy study. This study was designed with an intensive screening program so as to ascertain all incident CIN lesions, including CIN 1, which tend to be relatively short lived lesions. The primary analysis was designated to occur in the Per-Protocol Efficacy population of Protocol 013. Success required that the lower bound of the confidence interval for efficacy exceed 20%. Prespecified supplemental analyses were conducted in HPV-Naïve MITT population of Protocol 013 and in the PPE and HPV-Naïve MITT populations of the Efficacy Data Set for GARDASIL® (Protocol 007, 013, and 015). The HPV 16 vaccine study (Protocol 005) was not designed to address this endpoint as it could not address CIN due to HPV 6, 11, or 18.

The efficacy of prophylactic administration of GARDASIL® with respect to the overall burden of HPV 6-, HPV 11-, HPV 16- or HPV 18-related CIN or AIS was evaluated in the PPE population and HPV-Naïve MITT population of Protocol 013 (Table 12). Efficacy was 100% in the PPE population. In the HPV-Naïve MITT population, 2 cases of vaccine-HPV type-related CIN 1 were observed in the group that received GARDASIL®. One of the 2 cases occurred in a woman who was randomized to GARDASIL® but received 3 doses of placebo in error. Since the analysis was specified to occur in populations "as randomized", rather than "as treated", she was counted in the group that received GARDASIL®.

A display of the efficacy of GARDASIL® with respect to HPV 6-, HPV 11-, HPV 16- or HPV 18-related CIN or AIS in the PPE population and HPV-Naïve MITT population for the Efficacy Data Set for GARDASIL® (Protocol 007, Protocol 013, and Protocol 015) is presented in Table 13. All cases observed in the group that received GARDASIL® in the PPE population were CIN 1 cases that occurred very early in the follow-up period. Of the 9 cases of HPV 6/11/16/18-related CIN or AIS observed in the HPV-Naïve MITT population in the group that received GARDASIL® (Table 13), 8 of these cases were CIN 1 and 1 case was CIN 2. As noted above, one case occurred in a woman who was randomized to GARDASIL® (and is, therefore, included in the group that received GARDASIL®) but received 3 doses of placebo in error. Of the remaining 8 cases, 4 occurred as a consequence of infection with vaccine HPV type prior to completion of the 3-dose vaccination regimen. The remaining 4 cases occurred shortly after completion of the 3-dose vaccination regimen. Robust anti-HPV levels were detected in 3 of the 4 cases; 1 case did not undergo serology testing. Thus, none of the cases of HPV 6-, HPV 11-, HPV 16-, or HPV 18-related CIN observed in the group that received GARDASIL® was a consequence of waning immunity.

Table 12

Prophylactic Efficacy Against HPV 6-, HPV 11-, HPV 16-, and HPV 18-Related CIN or AIS in Protocol 013

Population	Endpoint	GARDASIL® Cases	Placebo Cases	Efficacy	CI	p-Value
Per-Protocol Efficacy	HPV 6/11/16/18-related CIN or AIS	0	37	100%	87%,100%	<0.001
	HPV 6-related CIN or AIS	0	7	100%	30%, 100%	
	HPV 11-related CIN or AIS	0	3	100%	<0%, 100%	
	HPV 16-related CIN or AIS	0	22	100%	82%, 100%	
	HPV 18-related CIN or AIS	0	8	100%	41%, 100%	
HPV – Naïve MITT	HPV 6/11/16/18-related CIN or AIS	2	57	97%	87%, 100%	

Subjects are counted once per applicable row.
A 97.5% Confidence Interval (CI) is provided for the HPV 6/11/16/18-related CIN or AIS endpoint in the PPE population to correspond with the multiplicity adjusted primary hypothesis test. A 95% CI is presented for the remaining rows representing supplemental summaries.

PPE = Per-protocol efficacy population; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; AIS = Adenocarcinoma in situ.

Table 13

Prophylactic Efficacy Against HPV 6-, HPV 11-, HPV 16-, and HPV 18-Related CIN or AIS in the Efficacy Data Set for GARDASIL®– Protocols 007, 013, and 015

Population	Endpoint	GARDASIL® Cases	Placebo Cases	Efficacy	95% CI
Pre-Protocol Efficacy	HPV 6/11/16/18-related CIN or AIS	4	83	95%	87%, 99%
	HPV 6/11-related CIN or AIS	0	23	100%	83%, 100%
	HPV 16-related CIN or AIS	4	49	92%	78%, 98%
	HPV 18-related CIN or AIS	0	20	100%	80%, 100%
HPV-Naïve MITT	HPV 6/11/16/18-related CIN or AIS	9	143	94%	88%, 97%
Subjects are counted once per applicable row. Cases in PPE subjects who received GARDASIL® were CIN 1 detected early in the follow-up period.					

CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; HPV = Human papillomavirus; CI = Confidence interval.

Overall, prophylactic administration of GARDASIL® was highly effective in preventing HPV 6-, HPV 11-, HPV 16-, and HPV 18-related CIN or AIS lesions. This benefit is expected to translate into a substantial reduction in the burden of cervical HPV disease (Pap test abnormalities, colposcopies, and biopsies) in the general population.

3.4.4 Prophylactic Efficacy Against HPV 6-, HPV 11-, HPV 16-, and HPV 18-Related External Genital Lesions (EGL)

Vaginal and vulvar condyloma acuminata and flat warts (so-called VIN 1 and VaIN 1) are generally not malignant. However, these lesions are difficult to treat, and they cause great damage to the affected individual's body self-image and ability to maintain relationships.

The primary evaluation of prophylactic efficacy of GARDASIL® with respect to the overall burden of HPV 6-, HPV 11-, HPV 16- or HPV 18-related genital warts, VIN, and VaIN was designed to occur in Protocol 013, the Phase III CIN/Warts Efficacy study. This study was designed to focus on detection of external genital lesions. The protocol called for detailed genital examinations every 6 months, with biopsy of all suspicious lesions. Supplemental analyses were to be conducted in the Efficacy Data Set for GARDASIL®. Because Protocol 005 did not systematically evaluate genital lesions, it was not included in this analysis.

The efficacy of prophylactic administration of GARDASIL® with respect to the overall burden of HPV 6-, HPV 11-, HPV 16- or HPV 18-related EGL in Protocol 013 is presented in Table 14. Efficacy was 100% in the PPE population. A large majority of the lesions were classic genital warts cases. Efficacy in the HPV-Naïve MITT population was also high.

Table 15 presents the efficacy of prophylactic administration of GARDASIL® with respect to the overall burden of HPV 6-, HPV 11-, HPV 16- or HPV 18-related EGL in the PPE population and HPV-Naïve MITT population of the Efficacy Data Set for GARDASIL® (Protocols 007, 013, 015). The single case in the vaccine group in the PPE population was an HPV-6-related lesion that occurred early in the follow-up period. Of the 9 cases of HPV 6/11/16/18-related EGL observed in the HPV-Naïve MITT population in the group that received GARDASIL®, all cases were low grade (condyloma, VIN 1, VaIN 1). Seven (7) of the cases occurred as a consequence of infection with vaccine HPV type prior to completion of the 3-dose vaccination regimen. One case occurred in a subject with incomplete Month 7 PCR data (thus, it was not possible to determine whether this subject became infected during the course of the vaccination or thereafter). One case occurred in a subject shortly after completion of the vaccination regimen. This subject had robust anti-HPV 6 levels at the completion of the vaccination regimen.

Table 14

Prophylactic Efficacy Against HPV 6-, HPV 11-, HPV 16-, and HPV 18-Related EGL in Protocol 013

Population	Endpoint	GARDASIL® Cases	Placebo Cases	Efficacy	CI	p-Value
Per-Protocol Efficacy	HPV 6/11/16/18-related EGL	0	40	100%	88%, 100%	<0.001
	HPV 6-related EGL	0	23	100%	83%, 100%	
	HPV 11-related EGL	0	10	100%	55%, 100%	
	HPV 16-related EGL	0	10	100%	56%, 100%	
	HPV 18-realted EGL	0	3	100%	<0%, 100%	
HPV-Naïve MITT	HPV 6/11/16/18-related EGL	3	59	95%	84%, 99%	
Subjects are counted once per applicable row. A 97.5% Confidence Interval (CI) is provided for the HPV 6/11/16/18-related EGL endpoint in the PPE population to correspond with the multiplicity adjusted primary hypothesis test. A 95% CI is presented for the remaining rows representing supplemental summaries.						

EGL = External genital lesion; PPE = Per-protocol efficacy population; HPV = Human papillomavirus; CI = Confidence interval.

Table 15

Prophylactic Efficacy Against HPV 6-, HPV 11-, HPV 16-, and HPV 18-Related EGL in the Efficacy Data Set for GARDASIL® - Protocols 007, 013, 015
(Per-Protocol Efficacy Population and HPV-Naïve MITT Population)

Population	Endpoint	GARDASIL® Cases	Placebo Cases	Efficacy	95% CI
Per-Protocol Efficacy	HPV 6/11/16/18-related EGL	1	113	99%	95%, 100%
	HPV 6/11-related EGL	1	97	99%	94%, 100%
	HPV 16-related EGL	0	26	100%	85%, 100%
	HPV 18-related EGL	0	9	100%	50%, 100%
HPV-Naïve MITT	HPV 6/11/16/18-related EGL	9	174	95%	90%, 98%
Subjects are counted once per applicable row. The case in the PPE subject who received GARDASIL® was a genital wart detected early in the follow-up period.					

EGL = External genital lesion; CI = Confidence interval; HPV = Human papillomavirus.

Overall, prophylactic administration of GARDASIL® was highly effective in preventing HPV 6-, HPV 11-, HPV 16-, and HPV 18-related external genital lesions. This benefit is expected to translate into a substantial reduction in the burden of genital warts and vulvar and vaginal pre-cancers and cancers.

3.4.5 Prophylactic Efficacy Against Persistent HPV 6, HPV 11, HPV 16, and HPV 18 Infection

Protocol 005 and Protocol 007 evaluated vaccine efficacy with regard to persistent HPV infection. Persistent infection was defined as: (1) persistent vaccine-type HPV infection with or without clinically-documented HPV disease; and (2) detection of vaccine-type HPV at the last visit on record (without the opportunity to evaluate persistence). Estimates of vaccine efficacy in Protocol 005 (HPV 16 only) and Protocol 007 (HPV 6, 11, 16, 18) were 94.3% and 89.5%, respectively, when including cases as defined above. Estimates of vaccine efficacy in Protocol 005 and Protocol 007 were 100% and 96.4%, respectively, when the endpoint was restricted to confirmed persistent infection with vaccine HPV types.

3.4.6 Other Prophylactic Efficacy Analyses

Prophylactic efficacy in women infected with a vaccine HPV type at Day 1. As noted in Section 3.2.1, a small proportion of subjects in the prophylactic efficacy populations were infected with one HPV type, but were naïve to the remaining vaccine HPV types. These subjects were included in the overall assessments of the prophylactic efficacy of GARDASIL® discussed above, but only with respect to the types for which they were

naïve at Day 1. For example, if a subject had evidence of infection with HPV 18 at Day 1 but was naïve to HPV 6, 11, or 16, then she was eligible to be included in the overall analyses of prophylactic efficacy for HPV 6-, HPV 11-, HPV 16-related endpoints, but not HPV 18-related endpoints. The analysis was conducted in the HPV-Naïve MITT population.

Women who are infected with one vaccine HPV type are at higher risk for acquiring infection with additional HPV types compared with HPV-naïve women. Analyses focusing on subjects who were already infected with one or more vaccine-related HPV types prior to vaccination were conducted to evaluate whether these subjects derived benefit with respect to clinical disease caused by the remaining vaccine HPV types (example: efficacy against disease caused by HPV 6, HPV 11, and HPV 16 in a woman with evidence of HPV 18 infection at Day 1). In this population, efficacy with respect to HPV 6-, HPV 11-, HPV 16-, or HPV 18-related CIN or AIS was 89% (95% confidence interval [CI]: 64%, 98%). Efficacy for HPV 6-, HPV 11-, HPV 16-, or HPV 18-related EGL was 91% (95% CI: 64%, 99%).

Impact of baseline covariates on prophylactic efficacy. No interaction was observed between the efficacy of GARDASIL® and age, ethnicity, or region of origin.

Impact of postvaccination events on prophylactic efficacy. The prophylactic efficacy of GARDASIL® was not impacted by:

- variations in dosing schedule (the sole requirement with respect to dosing schedule for inclusion in the PPE population was receipt of 3 doses of vaccine or placebo within a 1-year period).
- the magnitude of peak anti-HPV levels (as represented by Month 7 anti-HPV levels).
- pregnancy, use (or lack-of-use) of hormonal contraceptives during the study follow-up period, acquisition of new sexual partners, or acquisition of genital infections.

3.4.7 Summary- Prophylactic Efficacy

GARDASIL® is intended to be primarily a prophylactic vaccine. Thus, prophylactic efficacy analyses represented the most important evaluations of efficacy for the vaccine. In these analyses, prophylactic administration of GARDASIL® to older adolescent and young adult women was shown to be highly efficacious in preventing

- HPV 16- and HPV 18-related cervical cancer (via CIN2/3 and AIS),
- HPV 16- and HPV 18-related vulvar and vaginal cancer (via VIN 2/3 and VaIN 2/3);
- HPV 6-, HPV 11-, HPV 16, and HPV 18-related CIN (any grade) or AIS;
- HPV 6-, HPV 11-, HPV 16-, and HPV 18-related external genital lesions; and
- Persistent HPV 6, HPV 11, HPV 16, and HPV 18 infection.

With respect to the primary efficacy hypotheses of each efficacy study, vaccine efficacy was 100%. In the broadest prophylactic efficacy population (HPV-Naïve MITT population), vaccine efficacy exceeded 94% for all endpoints. In this broad population, vaccine efficacy with respect to CIN 3/AIS, representing high-grade cervical pre-cancer, squamous cell cervical carcinoma *in situ*, and cervical adenocarcinoma *in situ*, vaccine efficacy was 100%. Similarly, vaccine efficacy with respect to VIN 2/3 and VaIN 2/3, the immediate and obligate precursors to HPV-related vulvar and vaginal cancer, respectively, was 100%. Based on the contribution of HPV 16 and HPV 18 to HPV-related anogenital and aerodigestive tract cancers, universal vaccination will eventually result in the prevention of ~25,000 cancer cases in the United States annually.

The efficacy trials also demonstrated that administration of GARDASIL® will substantially reduce the burden of cervical pre-cancers. HPV 6, 11, 16, and 18 cause ~40% of the overall burden of low and high grade cervical pre-cancerous lesions. Based on this contribution, universal vaccination will eventually result in the prevention of ~700,000 cases of cervical pre-cancer in the United States annually.

Finally, efficacy trials also demonstrated that administration of GARDASIL® will substantially reduce the burden of genital warts. HPV 6 and HPV 11 cause ~90% of these lesions. Based on this contribution, universal vaccination will eventually result in the prevention of nearly 900,000 cases of genital warts in the United States annually. It is possible that up to 5400 cases of RRP will be prevented in the United States annually.

3.5 Therapeutic Efficacy

Therapeutic efficacy was defined as the ability of GARDASIL® to prevent development of clinical disease caused by a vaccine HPV type in women who were infected with that particular vaccine HPV type at the start of vaccination.

These analyses considered only the vaccine's impact on development of disease caused by the types for which there was evidence of previous exposure or current infection at baseline. For example, if a subject had HPV 18 infection at baseline (i.e., was HPV 18 PCR positive in cervicovaginal samples collected at Day 1), but was naïve to HPV 6, HPV 11, or HPV 16, then these analyses considered only the development of cases of HPV 18-related disease. Thus, if the subject developed HPV 18-related CIN, then this event was counted as a case, whereas if she became infected with HPV 16 and developed a case of HPV 16-related CIN, then this event was not counted for these therapeutic analyses (see Table 16), but were counted for the prophylactic efficacy analyses displayed in Section 3.4 of this document.

Table 16

Role of Baseline HPV Status With Respect to Endpoint Counting for Therapeutic Efficacy Analyses

Baseline HPV Status	Clinical Endpoint (Pathology Panel Confirmed CIN, AIS, VIN, VaIN, Genital Warts)			
	HPV 6-Related	HPV 11-Related	HPV 16-Related	HPV 18-Related
Naïve to all 4 vaccine HPV types	NO	NO	NO	NO
Positive to HPV 6 Naïve to HPV 11, 16 and 18	YES	NO	NO	NO
Positive to HPV 11 Naïve to HPV 6, 16 and 18	NO	YES	NO	NO
Positive to HPV 16 Naïve to HPV 6, 11, and 18	NO	NO	YES	NO
Positive to HPV 18 Naïve to HPV 6, 11, and 16	NO	NO	NO	YES

HPV = Human papillomavirus; CIN = Cervical intraepithelial neoplasia; AIS = Adenocarinoma in situ;
VIN = Vulvar intraepithelial neoplasia; VaIN = Vaginal intraepithelial neoplasia.

The efficacy studies of GARDASIL® did not include a screening phase; 27% of study subjects were positive either by PCR or serology to at least one vaccine HPV type at Day 1. The impact of GARDASIL® in this population was evaluated in a set of supplemental analyses (the studies were not powered to provide statistical significance for these analyses). For each of the 4 vaccine HPV types, the study population of the efficacy trials can be divided into 4 groups, based on the results of anti-HPV serology and cervicovaginal HPV DNA testing (by PCR) conducted on Day 1. These 4 groups are presented diagrammatically in Table 17. The relative proportions of the study population within each of the 4 subgroups depend on the baseline prevalence of the vaccine HPV types. The baseline prevalence (PCR and/or serology positivity) for HPV 16 was highest (16.9%), followed by HPV 6, HPV 18, and HPV 11 (11.5%, 7.3%, and 3.5%, respectively).

Table 17

Efficacy Sub-Populations Defined by HPV Testing at Day 1

	Seronegative to a Given HPV Type	Seropositive to a Given HPV Type
PCR (-)	Naïve	Previously infected, then cleared infection prior to Day 1 (potentially immune to reacquisition of infection)
PCR (+)	Infected, but has not mounted an immune response (early Infection)	Failed to clear infection despite the presence of a humoral immune response (chronic infection)

PCR = Polymerase chain reaction; HPV = Human papillomavirus.

The seronegative/PCR-negative groups represented the largest group for each HPV type. These subjects were naïve to the relevant vaccine HPV type at Day 1. Efficacy of GARDASIL® in these groups is in Section 3.4 (Prophylactic Efficacy).

The seropositive/PCR-negative groups were the next-largest sub-populations of the overall study population (1.8%, 2.7%, 6.4% and 6.9% of the total population for HPV 11, HPV 18, HPV 6 and HPV 16, respectively). These subjects had acquired infection with a vaccine HPV type after sexual debut, but then had mounted an immune response that resulted in clearance of infection prior to Day 1. The presence of detectable anti-HPV is a marker of this immune response. Studies have suggested that such anti-HPV levels remain stable over long periods of time, and that these anti-HPV responses confer a degree of protection against recurrence of infection with the same HPV type [51]. The clinical trials for GARDASIL® supported these observations. CIN caused by the relevant vaccine HPV type was rare. Administration of GARDASIL® appeared to prevent development of CIN due to the relevant vaccine HPV type (efficacy = 100%; 95% CI: <0%, 100%).

The seronegative/PCR-positive groups included subjects who had evidence of infection with HPV 6, HPV 11, HPV 16, and/or HPV 18, but no evidence of an immune response to that infection. Studies have shown that anti-HPV responses are detected in only 50 to 70% of subjects who acquire HPV infection, and that these responses typically develop several months after initial infection [52]. Thus, subjects in this population were either early in their infection, or were unable to mount an immune response to that infection.

A prespecified analysis was conducted in this population to determine whether administration of GARDASIL® reduced the incidence of subjects who were found to have clinical disease due to that type, compared with placebo. This group of HPV-infected subjects was of interest because it was possible that vaccination could compensate for an absence of an immune response to clear the infection or reduce its clinical impact.

Among subjects who were PCR positive and seronegative to a particular HPV type, there was a trend towards a reduction in the incidence of CIN caused by that type in subjects who received GARDASIL® compared with placebo subjects. Vaccine efficacy was 28%, but the lower bound of the 95% CI included 0%. No efficacy against EGLs was observed.

The seropositive/PCR-positive groups represented the smallest of groups of the overall study populations defined by baseline HPV status. Subjects who were both seropositive and PCR positive at Day 1 were likely to represent a subset of the general population whose infection persisted despite a humoral response. Such chronically-infected subjects would be unlikely to benefit from additional boosting of anti-HPV levels. In post-hoc analyses in subjects with a chronic infection with a vaccine HPV type (PCR positive and seropositive to a given HPV type at Day 1); the incidence of CIN (all grades) caused by the relevant HPV type was similar in both vaccination groups.

Table 18 displays the sizes, event rates, and impact of GARDASIL® in the subpopulations described above. In the first row, the General Population represents all subjects who were enrolled in the studies and received at least one dose of vaccine and placebo. Thus, this population included all subjects regardless of their baseline HPV status. The baseline PCR positive populations were small, but subjects had a high incidence of CIN 2/3 or AIS because they were already infected with a high-risk HPV type (compared to the naïve population), and because their infection was likely to have been persistent.

Table 18

Size of Subpopulations Defined by Day 1 HPV 16 and 18 Status, Along With Event Rates for CIN 2/3 and AIS (Protocols 005†, 007, 013‡, and 015 Combined)

			HPV L1 VLP Vaccine			Placebo				
Population Based on Day 1 Status	Population Definition	Event	N§	Number of Cases	Incidence per 100 Subject-Years at Risk	N§	Number of Cases	Incidence per 100 Subject-Years at Risk	Observed Efficacy (%)	95% CI
General Population	All Subjects	HPV 16/18-CIN 2/3 or AIS	9381	122	0.6	9896	201	0.9	39.0%	23.3, 51.7
PCR(-)/Sero(-)	Naive	HPV 16/18-CIN 2/3 or AIS	9342	1	0.0	9400	81	0.4	98.8%	92.9, 100.0
PCR(-)/Sero(+)	Cleared Infection	CIN 2/3 or AIS caused by the type with which the subject was infected	853	0	0.0	910	4	0.2	100.0%	<0.0, 100.0
PCR(+)/Sero(-)	Early Infection	CIN 2/3 or AIS caused by the type with which the subject was infected	661	42	3.2	626	57	4.6	31.2%	<0.0, 54.9
PCR(+)/Sero(+)	Chronic Infection	CIN 2/3 or AIS caused by the type with which the subject was infected	473	79	9.1	499	69	7.3	<0.0%	<0.0, 10.1

† Protocol 005 cases only include HPV 16-related CIN 2/3 or AIS.
‡ Protocol 013 excludes the monovalent HPV 16 vaccination group.
§ Subjects may be counted in more than one row. Subjects are counted once within each row.
CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ; HPV = Human papillomavirus; PCR = Polymerase chain reaction; VLP = Virus-like particles.

3.6 Population Impact

3.6.1 Overview

The public health utility of GARDASIL® can be measured as the impact of the vaccine on the incidence of clinical HPV disease (due to vaccine and non-vaccine HPV types) in the general population of adolescents who are HPV-naïve (e.g., prior to sexual debut), and in the general population of women (most of whom are sexually active; some of whom are already HPV-infected). These 2 measurements of utility are termed **prophylactic population impact** and **overall population impact,** respectively.

At the start of the Phase III program, Merck and Co., Inc. and CBER agreed that the primary evaluation of population impact will be conducted **at the end of the Phase III trials in 2007**. Early estimates of population impact were provided with the original BLA.

3.6.2 Early Estimation of Prophylactic Population Impact

A preliminary analysis of **prophylactic population impact** with respect to CIN 2/3 and AIS is presented herein. Prophylactic population impact measures the impact of GARDASIL® on the incidence of CIN 2/3 and AIS (due to vaccine and non-vaccine HPV types) in the general population of girls and women who are HPV-naïve (e.g., adolescents prior to sexual debut).

3.6.2.1 Approach to Analysis

To measure **prophylactic population impact**, it would be necessary to evaluate the vaccine in sexually-naïve adolescents. Such a trial is not feasible due to constraints surrounding evaluations of sexuality and genital sampling in pre-adolescents.

The alternative is to model the impact of GARDASIL® in sexually-naïve adolescents by measuring the impact of GARDASIL® in **an adult population that is completely HPV-naïve at Day 1**. Logistically, such a population would be negative at Day 1 to vaccine HPV types (HPV 6, 11, 16, 18) as well as 8 other types responsible for >90% of cervical cancers.

At present, only assay results to define Day 1 HPV 6, HPV 11, HPV 16, and HPV 18 status are available. Assay results to define Day 1 status for the 8 other HPV types will be available in 2007. Current estimates of **prophylactic population impact** are provided in a **partially HPV-naïve population**, defined as:

- negative to HPV 6, HPV 11, HPV 16, and HPV 18 at Day 1;
- status with respect to the other 8 high-risk HPV types unknown; and
- negative Pap test at Day 1 (in lieu of testing for non-vaccine HPV types at Day 1).

Although the prophylactic population impact analysis is intended to evaluate the impact of GARDASIL® on the incidence of CIN 2/3 and AIS caused by HPV infection occurring after Day 1, the **partially HPV naïve population** includes CIN 2/3 and AIS cases that are caused by infections with non-vaccine HPV types present at Day 1 (Table 19). Thus, analyses in this population provide **imperfect estimates** of prophylactic population impact.

Table 19

Comparison of the Ideal Prophylactic Population Impact Population and the Currently Available "Partially HPV-Naïve Population"

Requirement	Disease Excluded
Ideal Population for Analysis of Prophylactic Population Impact – Available 2007	
Negative to HPV 6/11/16/18 at Day 1	Disease caused by infections with vaccine HPV types present at Day 1
Negative to non-vaccine HPV types at Day 1	Disease caused by infections with non-vaccine HPV types present at Day 1
Partially HPV-Naïve Population – Imperfect Model of Prophylactic Population Impact – Available Now	
Negative to HPV 6/11/16/18 at Day 1	Disease caused by infections with vaccine HPV types present at Day 1
Negative to non-vaccine HPV types at Day 1	**(Test results are not available)**
Negative Pap Test at Day 1 (In lieu of testing for non-vaccine HPV types)	▪ Partially effective (~65%) in excluding CIN 2/3 and AIS caused by non-vaccine HPV types that is present at Day 1 ▪ Unable to exclude CIN 2/3 and AIS that develops after Day 1 in subjects who are infected with non-vaccine HPV types at Day 1
HPV = Human papillomavirus; CIN = Cervical intraepithelial neoplasia; AIS = Adenocarcinoma in situ	

A schematic representation of the CIN 2/3 and AIS endpoints that contribute to the analyses in the partially HPV-naïve population, and the timing of the detection of such endpoints within the study follow-up period, are displayed in Figure 7.

Types of cases that contribute to the analyses in the partially HPV-naïve population. Three types of CIN 2/3 and AIS cases contribute the cumulative incidence of CIN 2/3 and AIS in the partially HPV-naïve population:

- CIN 2/3 or AIS caused by HPV 16 and HPV 18 infection acquired **after** Day 1
- CIN 2/3 or AIS caused by infection with non-vaccine HPV types acquired **after** Day 1
- CIN 2/3 or AIS caused by infection with non-vaccine HPV types present at Day 1.

The endpoint cases of interest for prophylactic population impact analyses are CIN 2/3 and AIS cases caused by infection with HPV 16, HPV 18, and non-vaccine HPV types acquired **after** Day 1. These cases are represented by the solid objects in the figure.

Inclusion of subjects who are infected with non-vaccine HPV types at Day 1 adds "noise" to the analysis of prophylactic population impact in the form of cases that should not be counted in this analysis (hatched triangle in Figure 7).

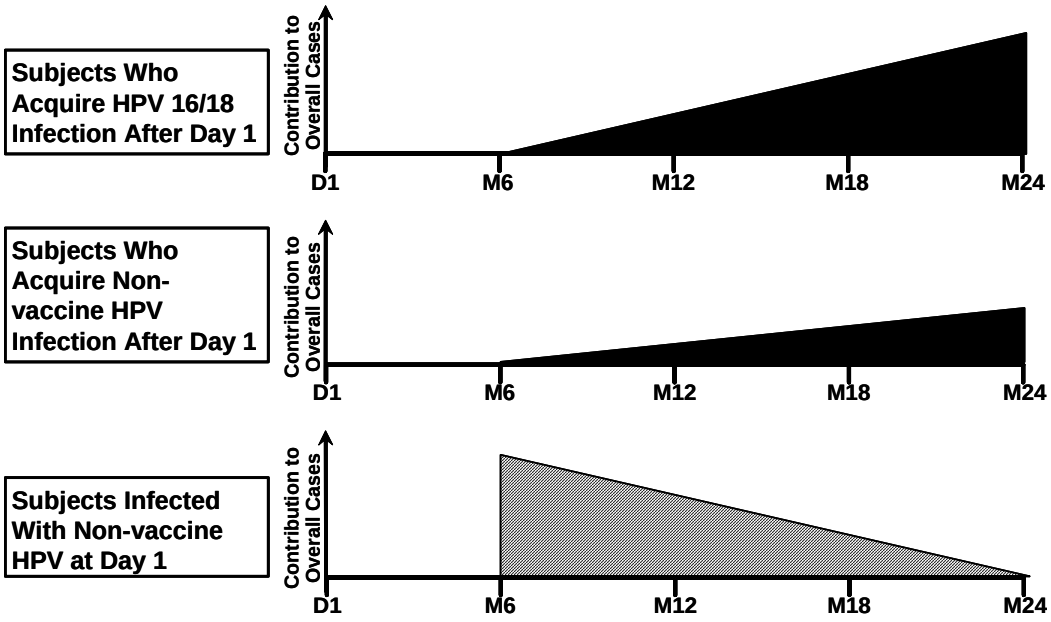
Timing of Detection of the 3 Types of CIN 2/3 and AIS Cases That Contribute to the Cumulative Incidence of CIN 2/3 and AIS in the Partially HPV-Naïve Population. The contribution of each of the 3 categories of CIN 2/3 and AIS to the cumulative incidence of CIN 2/3 and AIS is also presented in Figure 6. The X-axes define time from Day 1 of the study. To be included in the partially HPV-naïve population, subjects were required to have a negative Pap test at Day 1. Thus, none of the subjects was referred to colposcopy until the next Pap test (at Month 6). The accumulation of CIN 2/3 and AIS cases occurs as follows:

- Over time, HPV-naïve subjects may acquire HPV 16/18 infections, some of which result in CIN 2/3 or AIS. Such cases become the dominant contributor to the cumulative incidence of CIN 2/3 and AIS. These endpoints should occur only in placebo subjects.
- Over time, HPV-naïve subjects may acquire new infections with non-vaccine HPV types, some of which result in CIN 2/3 or AIS. GARDASIL® may reduce the incidence of these infections (i.e., "cross-protection").
- CIN 2/3 and AIS cases in subjects infected with non-vaccine HPV types at Day 1 represent the dominant cause of CIN 2/3 and AIS detected early in the study:
    - Some of these subjects may have CIN 2/3 or AIS at Day 1 that was not detected by the Day 1 Pap test. Because the cumulative sensitivity of multiple Pap tests is higher than that of a single Pap test, these lesions are detected by Pap tests conducted at Month 7 and Month 12. The incidences of such cases should be comparable between vaccination groups.
    - Some of these subjects may be free of CIN 2/3 or AIS at Day 1, but they develop lesions over time. Natural history studies have shown that CIN 2/3 and AIS lesions generally occur within 1 year of infection. Given that infection was already present at Day 1, these lesions should develop rapidly, with detection occurring shortly after detection (given the frequency of Pap testing in the study). The incidences of such cases should be comparable between vaccination groups.
    - Over time, the contribution of CIN 2/3 and AIS caused by infection present at Day 1 diminishes: lesions are detected, or infection resolves (no CIN 2/3 develops).

Overall, because of the inclusion of: (1) subjects who were infected with non-vaccine HPV types in the analysis of prophylactic population impact; and (2) the lower early incidence of HPV 16/18 related disease in baseline HPV-naive women, it is expected that the population impact of GARDASIL® appears lower early on in the study, but will increase over time.

Figure 7

Schematic of the Expected Contributions Over Time of Types of Disease Endpoints Counted in the Prophylactic Population Impact Analysis in Partially HPV-Naïve Subjects in the Efficacy Dataset for GARDASIL® (Protocols 007, 013, 015)



3.6.2.2 Early Estimates of Prophylactic Population Impact of GARDASIL® in a Partially HPV-Naïve Population

With the introduction provided in Section 3.6.2.1 in mind, Table 20 displays the results of the analyses of efficacy in the Partially HPV-Naïve population.

The expected prophylactic population efficacy of GARDASIL® should equal the proportion of CIN 2/3 and AIS cases that is caused by vaccine HPV types. In the clinical trials program, women who developed CIN 2/3 or AIS caused by HPV 16 or HPV 18 represented 55% of the overall population of women with CIN 2/3 or AIS. Prophylactic efficacy of GARDASIL® against HPV 16- and HPV 18-related CIN 2/3 in the HPV-Naïve MITT population was 99% (See Table). Assuming no cross-protective efficacy against non-vaccine HPV types, the expected prophylactic population impact of GARDASIL® is expected to be:

(99% efficacy) X (55% contribution of HPV 16/18 CIN 2/3 or AIS to overall CIN 2/3 or AIS) = 54.5%

The actual estimate of prophylactic population impact in the partially HPV-naïve population is 37.9% (95% CI 13.2%, 55.9%). The reason for this somewhat lower estimate of efficacy is the presence of CIN 2/3 and AIS cases in subjects infected with

non-vaccine HPV types at Day 1. This impact is shown in Figure 8, which displays a graph of time to detection of CIN 2 or AIS (regardless of causal HPV type) in the partially HPV-Naïve population (an imperfect model of prophylactic population impact). The X-axis displays time from the start of the follow-up period. The Y-axis displays the cumulative incidence of CIN 2/3 or AIS. The cumulative incidence lines for the 2 vaccination groups start at 6 Months of follow-up because in this population, only subjects with a negative Pap test at Day 1 are included.

Cases of CIN 2/3 or AIS among HPV-infected women at Day 1 represented most of the events observed early in the study. GARDASIL® is a prophylactic vaccine that should have little impact on these cases. Over time, the efficacy of the vaccine became more apparent, as placebo subjects, but not subjects in the group that received GARDASIL®, acquired HPV 16- or 18-related CIN 2/3 or AIS.

Table 20

Impact of GARDASIL® on the Incidence of CIN 2/3 or AIS† by Severity of Disease
Partially HPV-Naïve Population‡
(Protocols 007, 013, and 015 Combined)

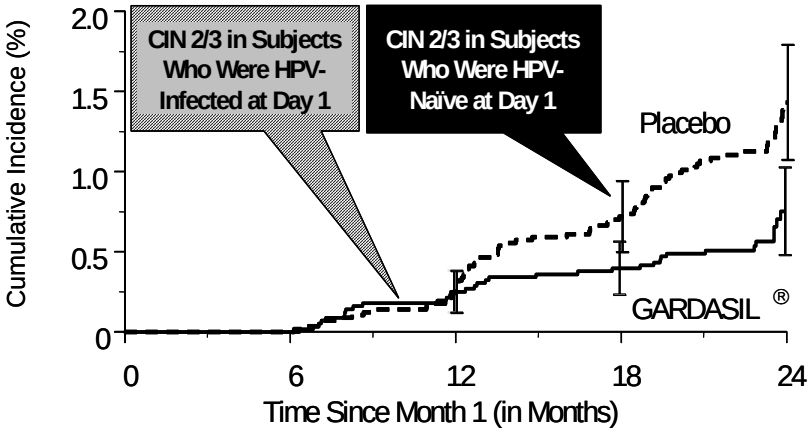
Endpoint	GARDASIL® Cases	Placebo Cases	Efficacy	95% CI
CIN 2/3 or AIS	59	96	37.9%	13.2%, 55.9%
CIN 2	42	74	42.6%	15.1%, 61.7%
CIN 3	28	50	43.4%	8.3%, 65.7%
AIS	0	5	100.0%	<0.0%, 100.0%

† CIN 2/3 or AIS due to any HPV type is defined as a tissue sample diagnosed by the Pathology Panel as CIN 2/3 or AIS. In Protocols 013 and 015, cervical biopsies that were performed in the absence of an abnormal Pap test result at the antecedent visit were excluded

‡ Includes all subjects who received =1 vaccination. Subjects were required to be seronegative and PCR negative for all vaccine HPV types and have a Pap test diagnosis of "Negative for SIL" at Day 1. Cases were counted starting 30 days after Day 1.

Figure 8

Time to Detection of CIN 2/3 or AIS in the Partially HPV-Naïve Population (Imperfect Model of Prophylactic Population Impact) in the Efficacy Data Set for GARDASIL® – Protocols 007, 013, and 015



	Number of Subjects at Risk				
GARDASIL ®	5638	5623	5474	5405	1873
Placebo	5701	5682	5537	5446	1958

CIN = Cervical intraepithelial neoplasia; CI = Confidence interval.

3.6.2.3 Summary - Prophylactic Population Impact of GARDASIL® in a Partially HPV-Naïve Population

- The primary analysis of the prophylactic (and general) population impact of GARDASIL® on the overall incidence of CIN 2/3 and AIS (regardless of causal HPV type) will be available at the end of the Phase III studies in 2007.
- Preliminary estimates of prophylactic population impact were provided in the original BLA. Because Day 1 status for non-vaccine HPV types could not be ascertained, these estimates are partially confounded by presence of CIN 2/3 occurring in subjects who were already infected at Day 1 with non-vaccine HPV types
- Despite this limitation, the preliminary estimations of prophylactic population impact demonstrate that mass vaccination campaigns in pre-sexually active adolescents using GARDASIL® will reduce the overall population risk for cervical cancer.

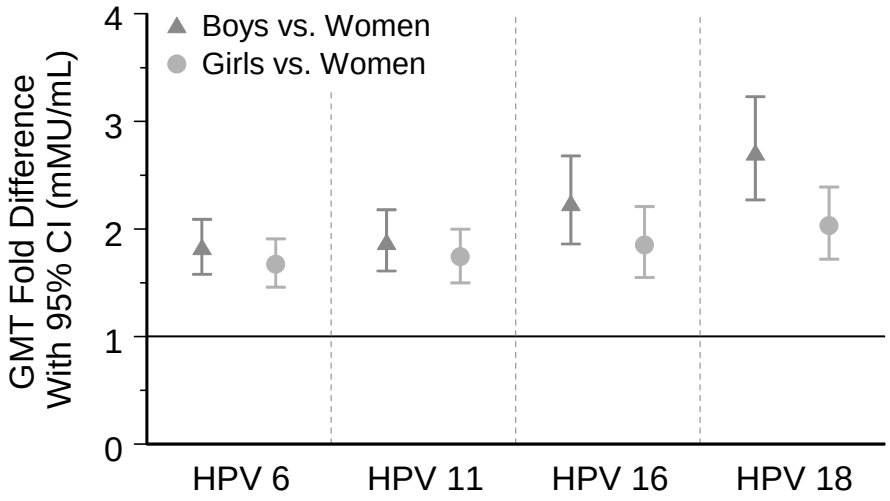
3.7 Bridging Prophylactic Efficacy Findings From 16- to 26-Year-Old Women to 9- to 15-Year-Old Adolescents

As noted in Section 2.1.3.2, CBER has stated that a demonstration that anti-HPV responses to GARDASIL® in 9- to 15-year-old subjects (in whom efficacy was not evaluated) are non-inferior to anti-HPV responses in 16- to 26-year-old female subjects (the age range in which efficacy was demonstrated) will allow for the inclusion of 9- to 15-year-old subjects within each of the indications for GARDASIL®.

The Adolescent Immunogenicity substudy of Protocol 016 was a safety and immunogenicity bridging study in 10- to 15-year-old girls, 10- to 15-year-old boys, and 16- to 23-year-old adolescent and young adult women. A comparison of the fold difference in the Month 7 anti-HPV geometric mean titers (GMTs) for boys versus women and girls versus women is shown in Figure 9. A ratio of adolescent GMT/adult GMT of 1.0 is denoted by the solid line in the figure). The study showed that: (1) administration of GARDASIL® to baseline HPV 6-, HPV 11-, HPV 16-, and/or HPV 18-naïve 10- to 15-year-old girls results in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3 that are higher than those in baseline HPV 6-, HPV 11-, HPV 16-, and/or HPV 18-naïve 16- to 23-year-old female subjects. These results justify the bridging of efficacy findings in 16- to 23-year-old female subjects to 10- to 15-year-old girls; (2) Administration of GARDASIL® to baseline HPV 6-, HPV 11-, HPV 16-, and/or HPV 18-naïve 10- to 15-year-old boys results in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3 that are higher than those in baseline HPV 6-, HPV 11-, HPV 16-, and/or HPV 18-naïve 16- to 23-year-old female subjects. These data indicate that GARDASIL® is highly likely to induce protective efficacy in boys.

Figure 9

Fold Difference in Month 7 Anti-HPV Geometric Mean Titers - Adolescents Versus Adults in Protocol 016



Note: each anti-HPV assay uses arbitrary mMU/mL to report anti-HPV levels. The read-out scale for each anti-HPV assay is set independently. Thus, comparisons of GMTs across assays (e.g., between anti-HPV 6 levels and anti-HPV 16 levels) are not valid.
GMT = Geometric mean titer; mMU/mL = Milli-Merck units per milliliter; HPV = Human papillomavirus; CI = Confidence interval.

3.8 Duration of Efficacy – Clinical Findings, Ongoing Studies

Individuals remain at risk for acquisition of HPV infection and associated diseases as long as they remain sexually active. A prophylactic HPV vaccine must confer long-term protective efficacy in order to meaningfully protect women against HPV infection and disease.

The clinical program for GARDASIL® was designed so that the long-term protective efficacy of the vaccine would be evaluated in a timely and thorough manner. The following items are discussed below:

- a minimum circulating anti-HPV level that protects against acquisition of HPV infection and/or disease (minimum protective level);
- currently available information on the duration of efficacy of GARDASIL®;
- implementation of a program to evaluate the longer-term efficacy of GARDASIL®;
- evaluation of the protective efficacy through the period of highest risk for acquisition of HPV infection in pre-adolescents vaccinated with GARDASIL®.

3.8.1 Minimum Protective Level of Antibody

It was not possible to find a minimum protective level of antibody for GARDASIL® due to the high prophylactic efficacy of the vaccine in clinical trials. Furthermore, natural history studies have not been able to find a minimum protective anti-HPV response (generated in the setting of HPV infection) that protects against re-acquisition/recurrence of infection.

Thus, the duration of efficacy of GARDASIL® will be defined by monitoring study subjects for breakthrough infections over longer-term periods of postvaccination follow-up.

3.8.2 Available Information on the Duration of Efficacy of GARDASIL®

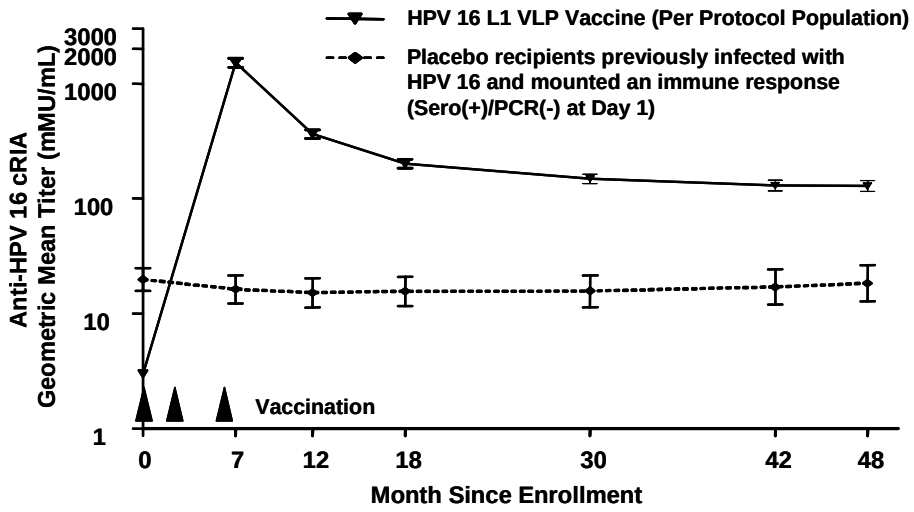
The longest duration of follow-up currently available for any component of GARDASIL® occurred in Protocol 005 (Proof-of-Concept Study). In this study, prophylactic administration of the HPV 16 L1 VLP vaccine component of GARDASIL® was highly effective in preventing development of persistent HPV 16 infection or related CIN through 3.5 years Postdose 3. At the end-of-study, prophylactic efficacy against HPV 16-related CIN was 100% (95% CI: 96.3%, 100%).

Figure 10 summarizes anti-HPV 16 levels in the per-protocol population of Protocol 005. As a comparison, anti-HPV 16 levels in women in the placebo group who were seropositive and PCR negative at Day 1 are provided. Such subjects were likely to have been infected with HPV 16 after sexual debut, and then mounted an immune response associated successful clearance of HPV 16 infection prior to Day 1. Anti-HPV 16 GMTs generated in response to HPV 16 infection remain stable for at least 4 years. Such natural

anti-HPV responses are thought to be generally protective against recurrent infection. Vaccine-induced anti-HPV 16 GMTs declined in the year following vaccination. Thereafter, anti-HPV 16 GMTs reached a plateau at levels higher than those likely induced by HPV 16 infection, consistent with extended durability of efficacy.

Figure 10

Anti-HPV 16 Geometric Mean Titers in Subjects Who Received HPV 16 L1 VLP Vaccine in the Per-Protocol Population and in Subjects in the Placebo Group Who Were Anti-HPV 16 Seropositive and HPV 16 PCR-Negative at Day 1 in Protocol 005



mMU/mL = Milli-Merck units per milliliter; cRIA = Competitive radioimmunoassay; PCR = Polymerase chain reaction; HPV = Human papillomavirus; VLP = Virus-like particles.

3.8.3 Ongoing Studies to Evaluate the Long-Term Effectiveness of GARDASIL®

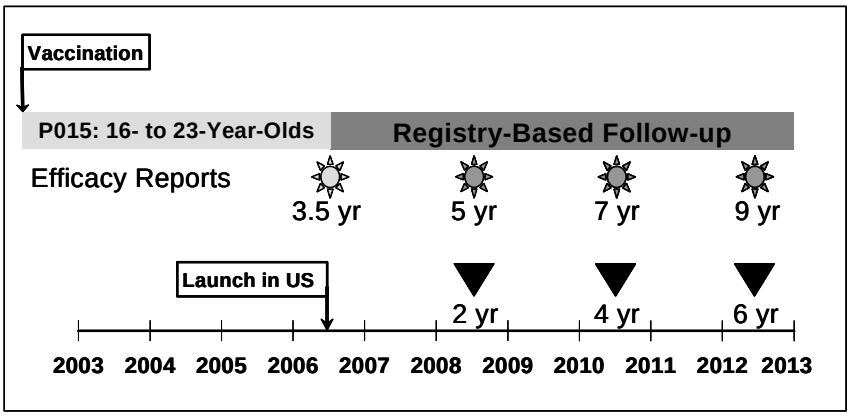
The long-term effectiveness of GARDASIL® will be evaluated through longer-term extensions of the Phase II and Phase III program. The Nordic Cancer Registry program is the most important study within these trials. Of the 12,167 subjects enrolled in Protocol 015 (Cancer Efficacy Study), 5800 subjects were enrolled in the Nordic Region (Denmark, Iceland, Norway, Sweden). In this region, the cervical cancer screening apparatus is centralized. To monitor compliance, compulsory reporting of Pap test results and results of all cervical biopsy and definitive therapy procedures to a central cancer registry by subject national identification number is mandated. Legislation allows for the use of registry data for research. Compliance with screening and with reporting approaches 100%.

The Nordic population within Protocol 015 will serve as a sentinel cohort to monitor the duration of protection induced by GARDASIL® (Figure 11). At defined intervals, the national cancer registry databases will be scanned. Cervical biopsy specimens will be retrieved and subjected to HPV testing and centralized histopathology reading. At any

given time, the Sentinel Cohort will be at least 3 years ahead of the first subject who will have received GARDASIL® post-licensure with respect to efficacy follow-up. If breakthrough cases are detected, then implementation of a booster vaccination policy can be considered and implemented well in advance of the actual time in which such boosters would be required.

Figure 11

Nordic Cancer Registry Program (N ~5800) to Evaluate the Long-Term Effectiveness of GARDASIL®



3.8.4 Long-Term Evaluation of GARDASIL® in Adolescents

Because GARDASIL® is most effective as a prophylactic vaccine, the population impact of the vaccine will be greatest when it is administered to adolescents and young adults prior to sexual debut. However, mass vaccination campaigns using GARDASIL® may be instituted in these populations several years prior sexual debut, so the high-level protective efficacy induced by GARDASIL® would have to persist for several years.

An evaluation of the duration of anti-HPV levels induced by GARDASIL® in 9- to 15-year-old boys and girls is ongoing. To date, the following observations have been made:

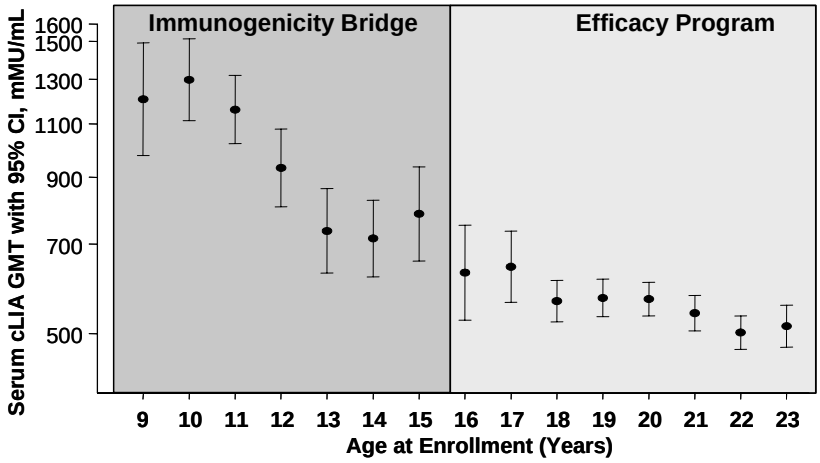
- Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs measured 4 weeks following administration of a 3-dose regimen of GARDASIL® are comparable between 9- to 15-year-old boys and 9- to 15-year-old girls;
- Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs measured 4 weeks following administration of a 3-dose regimen of GARDASIL® are higher in young adolescent boys and girls compared with older adolescent and young adult women (the age range in which the efficacy of GARDASIL® was demonstrated) (See Figure 12 for an example of this effect).

These data suggest that administration of GARDASIL® to pre-adolescents induces higher anti-HPV levels at peak, and likely for several years thereafter, compared with adults in whom robust efficacy through at least 2.5 years of Postdose 3 follow-up has been shown.

Long term immunogenicity studies in adolescents are ongoing.

Figure 12

Month 7 Anti-HPV 6 Geometric Mean Titers (GMTs) by Age at First Vaccination in the Per-Protocol Immunogenicity Population of the Phase III Integrated Immunogenicity Data Set for 9- to 15-Year-Old Boys, 9- to 17-Year-Old Girls, and 18- to 26-Year-Old Women (Protocols 011, 012, 015, 016, and 018)



	Number of Subjects Evaluable (n)														
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	68	129	166	141	166	148	109	85	137	440	511	624	576	564	400

HPV = Human papillomavirus; mMU/mL = Milli-Merck units per milliliter; CI = Confidence interval.

3.9 Conclusions Regarding the Efficacy of GARDASIL®

Based on the data from the clinical development program for GARDASIL® submitted in the BLA, administration of GARDASIL® is highly efficacious in preventing vaccine HPV type 6-, 11-, 16-, and 18-related cervical, vulvar, and vaginal cancers and pre-cancers, and benign genital lesions as follows:

1. Prophylactic administration of a 3-dose regimen of GARDASIL® to 16- to 26-year-old women is highly effective in preventing the development of:

   - CIN 2/3 and AIS caused by HPV 16 and HPV 18, thereby preventing the development of HPV 16- and HPV 18-related cervical cancer;
   - HPV 6-, HPV 11-, HPV 16-, and HPV 18-related CIN and AIS;
   - VIN 2/3 and VaIN 2/3 caused by HPV 16 and HPV 18, thereby preventing the development of HPV-related vulvar and vaginal cancers caused by these types
   - HPV 6-, HPV 11-, HPV 16-, and HPV 18-related condyloma acuminata, VIN 1, and VaIN 1; and

- cervical and external genital infection caused by vaccine HPV types.

2. Prophylactic administration of GARDASIL® to older adolescent and young adult women prior to sexual debut reduces:
   - the overall incidence of CIN 2/3 and AIS, thereby reducing their overall risk for development of cervical cancer;
   - their overall risk for development of CIN;
   - the overall incidence of VIN 2/3 and VaIN 2/3, thereby reducing their overall risk for development of vulvar and vaginal cancer; and
   - their overall risk for development of HPV-related external genital lesions.
3. Administration of GARDASIL® to subjects who are infected with a vaccine HPV type but have no evidence of immune responses to that infection at the time of initiation of vaccination (early infection), suggests in a small reduction in the rate of progression to detectable cervical disease. Administration of GARDASIL® to subjects who have evidence of both infection and an immune response to this infection at the start of the vaccination regimen does not reduce the incidence of detectable cervical disease.
4. The protective efficacy induced by GARDASIL® is durable through at least 2.5 years postvaccination with respect to infection and disease caused by HPV 6, HPV 11, and HPV 18 and at least 3.5 years postvaccination with respect to infection and disease caused by HPV 16.
5. The prophylactic efficacy of GARDASIL® with respect to HPV 6-, HPV 11-, HPV 16-, or HPV 18-related cervical and external genital disease is not impacted by ethnic/national background, age (within the 16- to 26-year-old age range), sexual history, pregnancy history, hormonal contraceptive use, or presence of non-HPV cervicovaginal disease.

4. Immunogenicity

4.1 Overview of the Phase III Immunogenicity Studies

A total of 12,344 subjects (9- to 26-year-old girls and women; 9- to 15-year-old boys) in the immunogenicity trials were randomized to receive at least one dose of GARDASIL® or placebo. The key studies that provided immunogenicity data are presented in Table 3 (Section 2.3).

4.2 Immunogenicity of GARDASIL®

None of the Phase II or Phase III studies excluded subjects from enrollment who had been already exposed to vaccine HPV types, as it was anticipated that post-licensure, GARDASIL® will be given without prescreening. The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population, consisting of

individuals who were seronegative and PCR negative to the relevant HPV type(s) at Day 1, remained HPV PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7), received all 3 vaccinations within prespecified time intervals, did not deviate from the study protocol in ways that could interfere with vaccine effect, and met prespecified criteria for the time interval between the Month 6 and Month 7 visit.

In all age/gender cohorts within the PPI population, at least 99.5% of subjects seroconverted at 1 month following completion of a 3-dose regimen of GARDASIL®. For each vaccine HPV type, there was an inverse relationship between age and anti-HPV GMTs measured 1 month Postdose 3. In Protocol 016 (Adolescent/Adult Bridging and End-Expiry Study), Postdose 2 anti-HPV GMTs in 10- to 15-year-old subjects were already comparable to Postdose 3 anti-HPV responses in 16- to 23-year-old subjects. Anti-HPV GMTs were highest in 9- to 15-year-old boys, followed by 9- to 17-year-old girls, and 18- to 26-year-old women (see Figure 9 in Section 3.7).

Administration of a 3-dose regimen of GARDASIL® induced robust anti-HPV responses regardless of gender, ethnicity, national origin, BMI, smoking status, Day 1 Pap test result, lifetime number of sexual partners at enrollment, and method of contraception used prior to vaccination.

4.3 Demonstration of the Consistency of the Manufacturing Process

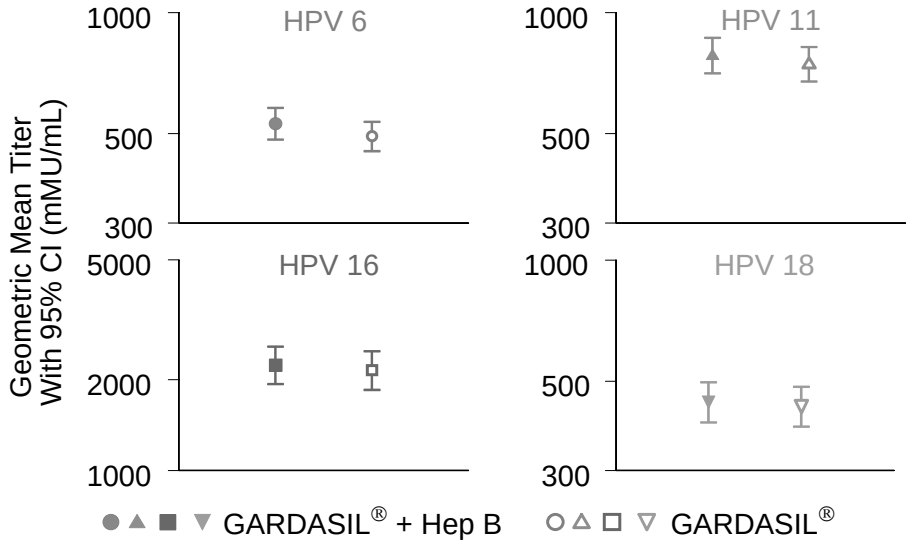
In a substudy of Protocol 015 (Consistency Lot Study), anti-HPV GMTs were compared 1 month following a 3-dose administration of 3 manufacturing lots of GARDASIL® in 16- to 26-year-old subjects. Each vaccine component was analyzed separately. The statistical criterion for consistency required that the upper bound of the confidence interval for the fold-difference in GMTs between any 2 lots exclude a fold-difference of 2 or greater for each HPV type. Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs at Month 7 met these equivalence criteria, confirming the consistency of manufacture of GARDASIL®.

4.4 Immunogenicity of Vaccines Administered Concomitantly With GARDASIL®

Hepatitis B vaccine is often given to adolescents. It is anticipated that GARDASIL® will be given to adolescents. Hepatitis B vaccine is given as a 2- or 3-dose regimen. GARDASIL® is given as a 3-dose regimen. To avoid the need for 5 or 6 separate visits to receive these vaccines, a trial of the concomitant administration of GARDASIL® with hepatitis B vaccine (recombinant) at separate injection sites was conducted (Protocol 011, Hepatitis B Concomitant Use Study). Concomitant administration of 3-dose regimens (0, 2, 6 months) of GARDASIL® and hepatitis B vaccine (recombinant): (1) resulted in no interference in the immune responses to either vaccine; and (2) generated robust anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks after the completion of the vaccination regimen (Figure 13).

Figure 13

Postdose 3 Anti-HPV Geometric Mean Titers for GARDASIL® When Given Concomitantly With Hepatitis B Vaccine (Protocol 011)



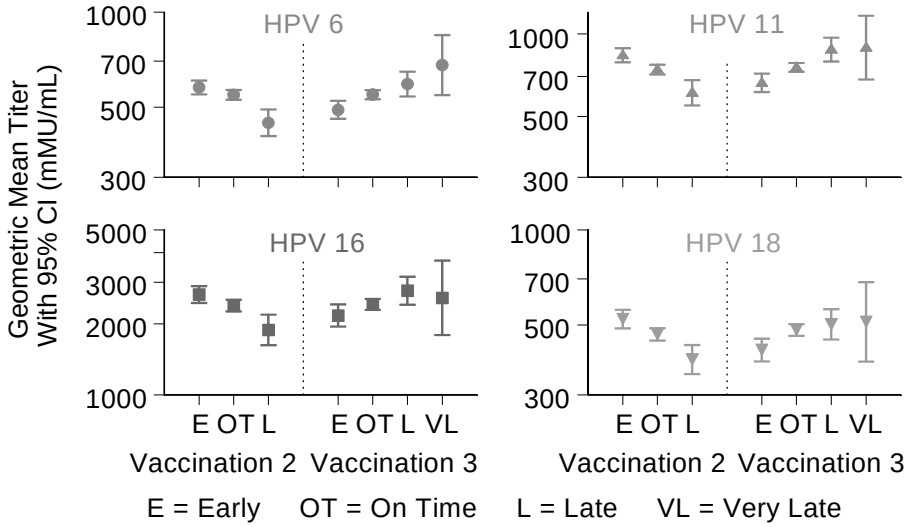
CI = Confidence interval; HPV = Human papillomavirus.

4.5 Variations in the Timing of Vaccine Administration

The interval between Vaccination 1 and Vaccination 2 was divided into 3 categories: early (36 to 50 days), on time (51 to 70 days), late (71 to 84 days). Likewise, the interval between Vaccination 2 and Vaccination 3 was divided into 4 categories: early (80 to 105 days), on time (106 to 137 days), late (138 to 160 days), and very late (161 to 200 days). Month 7 GMTs were modestly impacted by variations in the intervals between Vaccination 1 and Vaccination 2, and Vaccination 2 and Vaccination 3. Given the high prophylactic efficacy seen in the Phase III trials, and the inclusion of subjects who received the 3-dose study vaccine regimen within a 1-year period (regardless of dosing intervals) in the PPE population of these trials, such variations did not impact the efficacy of GARDASIL® (Figure 14).

Figure 14

Impact of Dosing Deviations on Anti-HPV Levels 4 Weeks Following a 3-Dose Regimen of GARDASIL®



4.6 Conclusions Regarding the Immunogenicity of GARDASIL®

Based on the data from the clinical development program for GARDASIL® submitted in the BLA, administration of GARDASIL® is highly immunogenic in all populations tested and can be administered concomitantly with hepatitis B vaccine with no interference in the immune responses to either vaccine; specifically:

1. A 3-dose regimen of GARDASIL® induces robust vaccine HPV type-specific immune responses at 1 month Postdose 3 in 9- to 26-year-old girls and young women, and 9- to 15-year-old boys.
2. Administration of a 3-dose regimen of GARDASIL® induces robust anti-HPV responses regardless of gender, ethnicity, national origin, BMI, smoking status, Day 1 Pap test result, lifetime number of sexual partners at enrollment, and method of contraception used prior to vaccination.
3. GARDASIL® induces robust anti-HPV 6, anti- HPV 11, anti-HPV 16, and anti-HPV 18 responses that persist for at least 2.5 years Postdose 3 and anti-HPV 16 responses that persist for at least 3.5 years Postdose 3.
4. Administration of a 3-dose regimen of GARDASIL® to 9- to 15-year-old boys and girls results in Month 7 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs that are higher than those seen in 16- to 23-year-old adolescent and young adult women.
5. Concomitant administration of 3-dose regimens of GARDASIL® with RECOMBIVAX HB® results in anti-HPV levels and anti-HBs levels that are comparable to those observed when these vaccines are administered nonconcomitantly.

6. Flexibility of ±1 month with respect to the administration of Dose 2 of GARDASIL™ (i.e., 1 to 3 months after the initiation of vaccination) and flexibility of ±2 months with respect to the administration of Dose 3 of GARDASIL® (i.e., 4 to 8 months after initiation of vaccination) results in acceptable Postdose 3 immune responses.
7. The final manufacturing process for GARDASIL® produces materials that generate consistent Month 7 anti-HPV cLIA responses.

5. Clinical Safety

This section summarizes safety data for GARDASIL® from 12 randomized, controlled clinical trials with GARDASIL® and its monovalent precursors conducted in support of licensure. These studies demonstrated that GARDASIL® is generally well tolerated.

5.1 Overview of Safety in Phase III Studies Including Populations Studied and Extent of Exposure

The safety of GARDASIL® and its monovalent precursors was assessed in 12 clinical trials. Figure 15 displays the populations that contributed to the safety evaluation in the clinical development program for GARDASIL®. Seven (7) trials evaluated the safety of GARDASIL®. Two (2) general populations were considered for evaluations of safety:

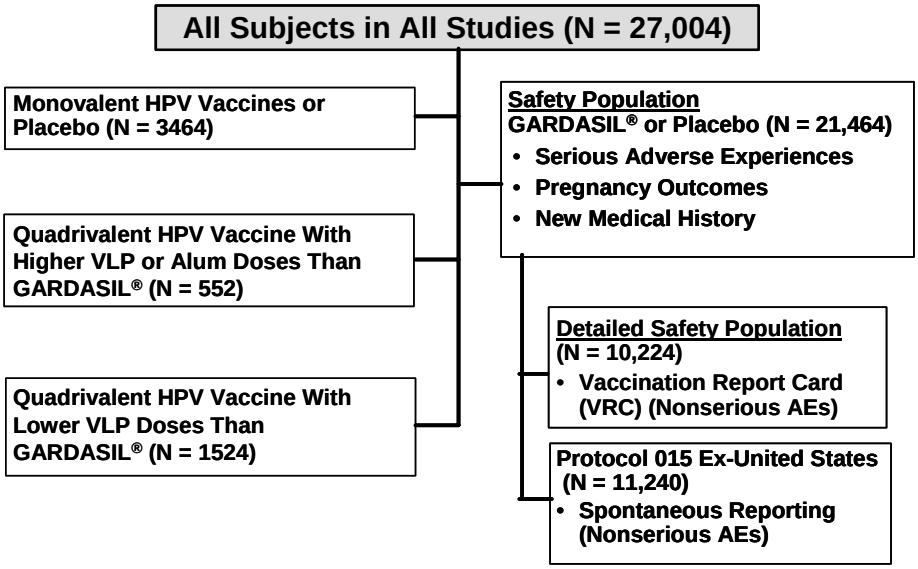
(1) Safety Population, defined as all subjects who were enrolled in Protocol 007 (Quadrivalent Dose-Ranging and Efficacy Study), Protocol 011 (Hepatitis B Concomitant Use Study), Protocol 012 (HPV 16 Bridging Study), Protocol 013 (CIN/Warts Efficacy Study), Protocol 015 (Cancer Efficacy Study), Protocol 016 (Adolescent/Adult Bridging and End-Expiry Study), and Protocol 018 (Adolescent Immunogenicity and Safety Study) and who received only GARDASIL® or only placebo (aluminum or non-aluminum), regardless of method of surveillance. The evaluation included all serious adverse experiences Day 1 through Day 15 postvaccination. In addition, serious adverse experiences determined by the investigator to be vaccine related or related to a study procedure or resulting in death at any time during the study were also reported.

(2) Detailed Safety Population, defined as all subjects who were enrolled in Protocol 007, Protocol 011, Protocol 012, Protocol 013, Protocol 015, Protocol 016, and Protocol 018, who received only GARDASIL® or only placebo (aluminum or non-aluminum), and who were followed using the VRC-aided surveillance method. The evaluation included all adverse experiences (serious or nonserious) from Day 1 through Day 15 postvaccination. Serious adverse experiences determined by the investigator to be vaccine related, related to a study procedure, or resulting in death at any time during the study were also reported.

Subjects who received monovalent HPV vaccines or formulations of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine containing total VLP doses that were different from GARDASIL® are not included in either population.

Figure 15

Populations Contributing to the Safety Evaluation
in the Clinical Development Program for GARDASIL®



N = Number of subjects who received 1, 2, or 3 doses of study vaccine or placebo.
AE = Adverse experience; HPV = Human papillomavirus.

5.2 Adverse Experiences

Safety surveillance methods can be found in Sec. 2.3.1.8. Investigators were instructed to report any serious adverse experience occurring in any subject from the time the consent form was signed through 14 days following the first vaccination and from the time of any subsequent vaccination through 14 days thereafter, whether or not the serious adverse experience was vaccine related. In addition, at any time during the study, if the event was considered by the investigator to be possibly, probably, or definitely vaccine related or related to a study procedure, it was to be immediately reported. Death due to any cause and discontinuation due to an adverse experience was reported at any time during the study.

5.2.1 Serious Adverse Experiences (SAEs), Deaths, and Discontinuations

The proportions of subjects reporting a serious adverse experience were comparable between the vaccination groups within the Safety Population (Table 21). The vaccination groups were also comparable with respect to the types of serious adverse experiences reported at any time during the course of the clinical studies (Table 22). Aside from overdoses (defined by the protocols as ≥0.75 mL/dose or more than 3 doses of study vaccine) caused by inadvertent administration of the full content of the study vaccine vial, the most common serious adverse experiences in both vaccination groups were infections and pregnancy complications.

In the Safety Population there were 7 subjects with serious, vaccine-related clinical adverse experiences (5 in the group that received GARDASIL® and 2 in the placebo group) (Table 21). The serious, vaccine-related clinical adverse experiences in the group that received GARDASIL® were: 1 case each of bronchospasm (possibly related), gastroenteritis (possibly related), headache and hypertension (definitely related), injection-site pain with injection-site joint movement impairment (probably related), and vaginal hemorrhage (probably related). In the placebo group, there was 1 case of hypersensitivity and 1 case of chills with headache and pyrexia.

In the Safety Population, 10 subjects in the group that received GARDASIL® and 7 subjects in the placebo group died at any time during the clinical studies (Table 23). None of the deaths was considered by the investigator to be vaccine or procedure related. In the group that received GARDASIL®, there were 4 cases of trauma, 2 cases of infection, 1 case each of overdose (non-study medication), cancer, pulmonary embolism (associated with oral contraceptive use) and arrhythmia (in the context of a strong family history of arrhythmias). In the placebo group, there were 3 cases of trauma, 2 cases of suicide, and 1 case each of pulmonary embolism (associated with oral contraceptive use) and complication of Caesarean section.

Table 21

Summary of Serious Adverse Experiences, Deaths, and Discontinuations – Safety Population
(Days 1 to 15 Following any Vaccination)

	GARDASIL® (N=11778)		Placebo (N=9686)	
	n	(%)	n	(%)
Subjects with follow-up	11,641		9578	
Number (%) of subjects:				
with serious AEs	59	(0.5)	43	(0.4)
with serious vaccine-related AEs†	5	(0.0)	2	(0.0)
who died‡	3	(0.0)	1	(0.0)
Discontinued§ due to an AE	15	(0.1)	10	(0.1)
Discontinued due to a serious AE	4	(0.0)	3	(0.0)
Discontinued due to a serious vaccine-related AE	0	(0.0)	1	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine. One subject who received GARDASIL® reported a serious vaccine-related AE beyond Day 15 after a vaccination.

‡ Seven subjects who received GARDASIL® and 6 subjects in the placebo group died beyond Day 15 after a vaccination.

§ Discontinued = Subject discontinued from therapy.

AE = Adverse experience.

N = Number of subjects who received 1, 2, or 3 doses of only the clinical material in the given column.

Table 22

Listing of Serious Clinical Adverse Experiences by System Organ Class and Vaccination Group (Entire Study Period) – Safety Population

	GARDASIL®	Placebo
Total Number of Serious Clinical Adverse Experiences	102	97
Blood and Lymphatic System Disorders	2	0
Cardiac Disorders	2	1
Endocrine Disorders	1	0
Gastrointestinal Disorders	8	3
General Disorders and Administrative Site Conditions	3	3
Hepatobility Disorders	3	0
Immune System Disorders	0	3
Infections and Infestations	17	11
Injury, Poisoning, and Procedural Complications	27	38
Neoplasms, Benign, Malignant, and Unspecified	4	1
Nervous System Disorders	5	5
Pregnancy, Puerperium, and Perinatal Conditions	36	46
Psychiatric Disorders	2	2
Renal and Urinary Disorders	5	4
Reproductive System and Breast Disorders	8	2
Respiratory, Thoracic, and Mediastinal Disorders	5	5
Skin and Subcutaneous Tissue Disorders	0	1
Surgical and Medical Procedures	1	0
Vascular Disorders	7	3

Table 23

Listing of Clinical Adverse Experiences Resulting in Death (Entire Study Period)
Safety Population

	GARDASIL®	Placebo
Total Number of Deaths	10	7
Arrhythmia	1	0
Asphyxia	0	1
Infection	2	0
Pancreatic Cancer	1	0
Thromboembolic Events	1	1
Trauma/Suicide	5	5
None of the deaths was determined to be vaccine/placebo related.		

A total of 41 subjects (23 and 18 in subjects who received GARDASIL® or placebo, respectively) in the Safety Population discontinued study participation due to an adverse experience. Of these 41 subjects, 19 (10 and 9 in subjects who received GARDASIL® or placebo, respectively) discontinued due to a serious adverse experience. Serious adverse experiences resulting in discontinuation in the group that received GARDASIL® included 4 cases of trauma, 2 cases of infection, and 1 case each of acute renal failure, arrhythmia, pulmonary embolism, and overdose. In the placebo group, the following serious adverse experiences resulted in discontinuation: 3 cases of trauma, 2 cases of suicide, and 1 case each of pulmonary embolism, syncope, hypersensitivity, and asphyxia. A total of 17 subjects (10 and 7 in subjects who received GARDASIL® or placebo, respectively) discontinued due to an adverse experience determined by the investigator to be vaccine/placebo related. In the group that received GARDASIL® vaccine-related adverse experiences resulting in discontinuation included: 2 cases each of rash and injection-site pain; 1 case of injection-site swelling; 1 case of injection-site swelling and erythema with dizziness; and 1 case each of urticaria, bronchial irritation, polyarthritis, and rheumatoid arthritis. In the placebo group, there was 1 case of each of the following: hypoesthesia, injection-site pain, herpes zoster, allergic edema, eczema, injection-site reaction, and hypersensitivity.

5.2.2 Systemic and Injection-Site Adverse Experiences

Table 24 presents a summary of clinical adverse experiences reported Day 1 to Day 15 following any study vaccination for the Detailed Safety Population. Overall, the proportions of subjects reporting adverse experiences were comparable between the 2 vaccination groups, In the group that received GARDASIL®, 83% of subjects reported

injection-site adverse experiences compared with 73.4% of placebo recipients. Few subjects reported a serious adverse experience. The proportions of subjects who reported serious adverse experiences were comparable between the 2 vaccination groups. Few subjects (0.2% in each vaccination group) discontinued due to an adverse experience.

Table 24

Clinical Adverse Experience (AE) Summary – Detailed Safety Population
(Days 1 to 15 Following Any Vaccination)

	GARDASIL® (N=6160)		Placebo (N=4064)	
	n	(%)	n	(%)
Subjects with follow-up	6069		3994	
Number (%) of subjects:				
with one or more AEs	5455	(89.9)	3416	(85.5)
injection-site AEs	5035	(83.0)	2932	(73.4)
systemic AEs	3591	(59.2)	2413	(60.4)
with serious AEs	37	(0.6)	26	(0.7)
with serious vaccine-related AEs†	1	(0.0)	0	(0.0)
who died	1	(0.0)	1	(0.0)
Discontinued‡ due to an AE	11	(0.2)	6	(0.2)
Discontinued due to a serious AE	2	(0.0)	2	(0.1)
Discontinued due to a serious vaccine-related AE	0	(0.0)	0	(0.0)

†Determined by the investigator to be possibly, probably or definitely related to the vaccine.
‡Discontinued = Subject discontinued from therapy.

N = Number of subjects who received 1, 2, or 3 doses of only the clinical material in the given column.

Injection-Site Adverse Experiences. The proportion of subjects reporting an injection-site adverse experience within 5 days after any vaccination was higher in subjects who received GARDASIL® compared with subjects who received placebo. The large majority of injection-site adverse experiences reported in recipients of GARDASIL® were mild to moderate in intensity. Subjects who received GARDASIL® were more likely to report injection-site adverse experiences of severe intensity compared with placebo subjects. The 3 most common injection-site adverse experiences reported by subjects in the Detailed Safety Population were erythema, pain, and swelling.

Systemic Adverse Experiences. The proportions of subjects who reported systemic adverse experiences were comparable between the vaccination groups. Most of these adverse experiences were judged to be mild or moderate in intensity. The most common systemic adverse experiences reported by subjects in the Detailed Safety Population were headache, pyrexia, and nausea. No specific trends/patterns of systemic adverse experiences were noted.

Fever. Overall, 11.4% of subjects who received GARDASIL® and 9.6% of placebo recipients reported a temperature ≥100°F (≥37.8°C), oral equivalent. A total of 1.5% of subjects who received GARDASIL® and 1.1% of placebo recipients reported a temperature of ≥102°F (≥38.9°C), oral equivalent.

5.3 Safety With Respect to Pregnancy

In the post-licensure period, it is likely that GARDASIL® will be administered to women of childbearing potential.

In developmental and reproductive toxicology studies in animal models, administration of GARDASIL® did not impact fertility or pregnancy outcomes. Because there were no data on the use of this vaccine in pregnant women, efforts were made to avoid administration of study vaccine to pregnant women during the clinical trials program. Subjects underwent urine beta human gonadotropin (β-HCG) testing prior to administration of each dose of study vaccine. In pregnant subjects, vaccination was deferred until the resolution of the pregnancy.

The Phase III trials of GARDASIL® included a detailed evaluation of pregnancy outcomes. All pregnancies were followed for outcome. Prenatal medical histories were collected. The reasons for elective termination, and information regarding the circumstances surrounding miscarriages were collected. The status of infants born to study subjects was followed for the duration of the trials.

During the Phase III trials of GARDASIL®, 2266 women experienced 2516 pregnancies. Of these pregnancies, outcomes were known for 2013 pregnancies (most pregnancies whose outcomes were not known were ongoing at the time of finalization of the study databases for the SUR). Overall, 10.7% of the subjects in the group that received GARDASIL® and 12.6% of the subjects in the group that received placebo became pregnant. The group that received GARDASIL® included more 9- to 15-year-old girls than the group that received placebo. Among 16- to 26-year-old adolescent girls and young women enrolled in the Phase III trials of GARDASIL®, the proportions of subjects who became pregnant were comparable between the vaccination groups. Thus, administration of GARDASIL® did not impact fertility.

The proportions of pregnancies that resulted in a live birth were comparable among subjects in the group that received GARDASIL® and the group that received placebo (Table 25).

Table 25

Summary of Pregnancies in the Phase III Program for GARDASIL®
(as of 11-Nov-2005)

	GARDASIL® (N=10,418)	Placebo (N=9120)
Subjects with Pregnancies	1115	1151
Number of Pregnancies	1244	1272
Pregnancies With Unknown Outcomes/Ongoing Pregnancies	258	263
Pregnancies With Known Outcomes	996	1018
Live Births (% of preg w/known outcomes)	621 (62%)	611 (60%)
Fetal Loss (% of preg w/known outcomes)	375 (38%)	407 (40%)
More 9- to 15-year-old subjects in group receiving GARDASIL®		

N = Number of subjects who received 1, 2, or 3 doses of only the clinical material in the given column.

Studies of pregnancy use the following standard metrics to describe pregnancy outcomes:

- Rate of spontaneous loss as a proportion of pregnancies that were not electively terminated. In studies in which pregnancy is monitored using β-HCG testing, the proportion of pregnancies (excluding elective termination) that result in spontaneous loss range from 28 to 33% [53; 54].
- Rate of congenital anomalies as a proportion of live births. In the United States, 3 to 4% of all liveborn children are found to have a congenital anomaly that requires intervention [55].

Table 26 provides outcomes in pregnancies with estimated onset within 30 days or beyond 30 days from administration of any dose of GARDASIL® or placebo (for 10 pregnancies, the estimated onset of pregnancy, or EOP, could not be determined with certainty).

Among subjects in the group that received GARDASIL®, pregnancies with an EOP within 30 days of a vaccination resulted in 112 fetuses/infants. Among placebo subjects, pregnancies with an EOP within 30 days of a vaccination resulted in 115 fetuses/infants.

Among subjects in the group that received GARDASIL®, pregnancies with an EOP beyond 30 days of a vaccination resulted in 879 fetuses/infants. Among placebo subjects, pregnancies with an EOP beyond 30 days of a vaccination resulted in 898 fetuses/infants.

The proportions of pregnancies that resulted in spontaneous loss, elective abortion, or live birth were generally comparable between the vaccination groups.

Table 26

Summary of Known Pregnancy Outcomes by Estimated Onset of Pregnancy Relative to Vaccination in the Phase III Program for GARDASIL®
(as of 11-Nov-2005)

	GARDASIL®	Placebo
Fetuses/Infants With Known Outcomes in Pregnancies with Estimated Onset Within 30 Days of a Vaccination	112	115
Spontaneous Loss	21 (18.8%)	26 (22.8%)
Elective Abortion	21 (18.8%)	23 (20.2%)
Live Birth	70 (62.5%)	66 (57.9%)
Fetuses/Infants With Known Outcomes in Pregnancies with Estimated Onset Beyond 30 Days of a Vaccination	879	898
Spontaneous Loss	236 (26.8%)	237 (26.4%)
Elective Abortion	93 (10.6%)	117 (13.0%)
Live Birth	549 (62.5%)	544 (60.6%)

Table 27 presents the summary of congenital anomalies in the Phase III Program for GARDASIL®. Overall, 31 pregnancies (15 in women who received GARDASIL®, and 16 in women who received placebo) were marked by detection of a congenital anomaly. Of these, 27 anomalies were detected among live-born children (14 cases in infants born to women who received GARDASIL® and 13 cases in infants born to women who received placebo). Thus, a total of 2.2% of live-born infants of women who received GARDASIL® and 2.1% of live-born infants of women who received placebo were found to have a congenital anomaly.

Although the overall proportions of pregnancies and live births that resulted in a congenital anomaly were comparable between the vaccination groups, there were differences in the distribution of congenital anomaly cases when considering the interval between vaccination and EOP. In pregnancies with an EOP within 30 days of a vaccination, 5 infants born to subjects who received GARDASIL® and no infants born to placebo subjects were found to have a congenital anomaly. The 5 cases were: ankyloglossia and pyloric stenosis, congenital hydronephrosis, congenital megacolon, club foot, and hip dysplasia.

In contrast, in pregnancies with an EOP beyond 30 days of a vaccination, fewer infants/fetuses in the group that received GARDASIL® (n = 10) had a congenital anomaly compared with infants/fetuses in the group that received placebo (n = 16).

Table 27

Summary of Congenital Anomalies in the Phase III Program for GARDASIL®
(as of 11-Nov-2005)

	GARDASIL®	Placebo
	n	n
Infant/Fetus Congenital Anomalies	**15**	**16**
EOP Within 30 Days of a Vaccination	5	0
Anomaly reported in Live-Born Infant	5	0
Anomaly reported in Fetal Loss	0	0
Intrauterine Observation	0	0
EOP Beyond 30 Days of a Vaccination	10	16
Anomaly reported in Live-Born Infant	9	13
Anomaly reported in Fetal Loss	0	2
Intrauterine Observation	1	1
Estimated Onset of Pregnancy (EOP) could not be precisely ascertained in 10 women. N = Number of live birth outcomes.		

The rates of spontaneous pregnancy loss observed in the clinical trials are comparable to those seen in studies in which pregnancy is detected through β-hCG screening (as was done in the clinical trials for GARDASIL®) [53; 54]. The incidence of congenital anomalies overall was consistent with that seen in population-based birth registries. The congenital anomalies observed in the studies of GARDASIL® were diverse in morphology and were either due to chromosomal abnormalities or were common defects of multifactorial origin with pathogenesis that occurs later in gestation relative to when exposure to GARDASIL® occurred. A review of these findings by an independent expert confirmed that the congenital anomalies observed in the clinical trials for GARDASIL®, including those that occurred in pregnancies with onset within 30 days of a dose of GARDASIL®, were highly unlikely to have been caused by study vaccination. Thus, there is no evidence to suggest that administration of GARDASIL® adversely affects fertility, pregnancy, or infant outcomes.

5.4 New Medical Conditions

The most commonly reported new medical conditions during the vaccination period (Day 1 through Month 7) were nasopharyngitis and headache. The percentages of subjects who developed new medical conditions during the vaccination period for each system organ class were generally comparable between the vaccination groups. No trends, patterns of new medical conditions, or safety signals were noted.

The most commonly reported new medical conditions during the follow-up period (Post-Month 7) were vaginal infections and discharge. The percentages of subjects who developed new medical conditions during the follow-up period were also generally comparable between the 2 vaccination groups. No trends, patterns of new medical conditions, or safety signals were identified during the follow-up period.

5.5 Conclusions Regarding the Safety of GARDASIL®

Based on the data submitted in the BLA, administration of GARDASIL® is generally well tolerated in a broad range of populations; specifically:

1. Administration of GARDASIL® is generally well tolerated in 18- to 26-year-old young women, 9- to 17-year-old girls, and 9- to 15-year-old boys.
2. Although administration of GARDASIL® is generally well tolerated among 9- to 26-year-old subjects, use of GARDASIL® is associated with an increase in injection-site adverse experiences, compared with placebo. However, most of these adverse experiences are mild in intensity.
3. Although administration of GARDASIL® is generally well-tolerated among 9- to 26-year-old subjects, use of GARDASIL® is associated with a modest increase in the incidence of transient low-grade fevers, compared with placebo.
4. Administration of GARDASIL® does not adversely affect fertility or pregnancy outcomes in older adolescents and young women; is generally well tolerated in nursing mothers; and does not appear to impact the health of breast-feeding infants of mothers who receive GARDASIL®.
5. Administration of GARDASIL® concomitantly with hepatitis B vaccine (recombinant) is generally well tolerated. However, concomitant administration of these vaccines is associated with more injection-site adverse experiences than when hepatitis B vaccine is administered alone.
6. The adverse experience profiles of GARDASIL® in 9- to 15-year-old boys and 9- to 17-year-old girls and older adolescents are generally comparable.
7. Administration of GARDASIL® is generally well tolerated in 9- to 26-year-old subjects who are seropositive to at least one vaccine HPV type at the start of vaccination.
8. Administration of GARDASIL® is generally well tolerated in 18- to 26-year-old young women who are infected with a vaccine HPV type at the start of vaccination.
9. Use of GARDASIL® does not have any adverse health impact through 2 years following the completion of the vaccination regimen.

6. Post-Licensure Surveillance

GARDASIL® has been shown in clinical trials to have a favorable safety profile. Because clinical trials do not always reveal rare adverse experiences associated with a vaccine, Merck & Co., Inc. will continue to monitor the safety of the vaccine after licensure and with increasing use. Monitoring will be accomplished by a combination of routine passive pharmacovigilance and post-licensure surveillance studies.

A postmarketing safety surveillance study in 35,000 subjects is planned in individuals who receive GARDASIL®. The results of pregnancy exposures that occur during the course of this study will be summarized.

The Nordic Cancer Registry Substudy (part of Protocol 015, the Cancer Efficacy Study), will ensure complete ascertainment of HPV-related disease and evaluate the long-term duration of safety and efficacy of GARDASIL® among 5800 subjects in Protocol 015 who were enrolled in eligible countries in the Nordic Region. Data collection on exposure to GARDASIL® during pregnancy will also be conducted within the context of this substudy. These subjects represent a sentinel population – they will have been given GARDASIL® at least 3 years in advance of the first person who will receive the vaccine post-licensure. If waning efficacy is observed in this population, there will be sufficient time to implement booster dose vaccination strategies.

GARDASIL® may reduce the incidence of disease caused by HPV types closely related to HPV 16 and HPV 18 (i.e., "cross-protection"). Analyses of the efficacy of GARDASIL® with respect to disease caused by HPV types related to HPV 16 and HPV 18 in the Phase III efficacy trials are forthcoming, and will be available in a subsequent Application.

The removal of common HPV types from their ecological niche after administration of GARDASIL® may result in an increase in disease caused by non-vaccine HPV types. Despite 100% prophylactic efficacy against persistent HPV 16 infection, administration of HPV 16 L1 VLP vaccine was not associated with an increase in the incidence of HPV 6, HPV 11, and HPV 18 infections through 3.5 years Postdose 3. Longer durations of follow-up will be required to confirm these findings.

7. Overall Summary and Conclusions: Benefits Versus Risks

HPV infection is the most common sexually transmitted infection worldwide. Most HPV infection occurs in the 10-year period after sexual debut (in most countries, age 16 years). Thus, the efficacy of GARDASIL® was evaluated in 16- to 26-year-old subjects.

The placebo arm of the Efficacy Data Set for GARDASIL® documents the burden of HPV infection. At Day 1, 27.0% had evidence for prior/ongoing HPV 6, HPV 11, HPV 16, or HPV 18 infection. There was also evidence of disease: 12% of subjects had Pap test results suggestive of CIN. Among placebo subjects in the Efficacy Data Set for GARDASIL®, over a median of 2.0 years of follow-up: (1) 31.8% experienced a Pap test result suggestive of CIN; (2) 21.3% underwent colposcopy in follow-up to a Pap test result suggestive of CIN; (3) 8.9% were diagnosed with a CIN lesion; (4) 4.4% underwent definitive therapy; and (5). 3.4% developed an HPV-related EGL. Much of this disease was caused by HPV 6, HPV 11, HPV 16, or HPV 18.

Taking these data together, a vaccine targeting common HPV types is urgently needed.

Benefit Assessment

Prophylactic administration of GARDASIL® was highly effective in preventing the development of HPV 16- and HPV 18-related CIN 3, AIS, VIN 2/3, and VaIN 2/3 lesions, thereby removing the risk of development of HPV 16- or HPV 18-related cervical, vulvar and vaginal cancers. Extrapolating these results to a global setting, universal prophylactic administration of GARDASIL® has the potential to reduce the

annual number of new cervical cancers from ~500,000 to ~150,000, and to reduce deaths from cervical cancer from ~290,000 to ~90,000 [5]. Similar reductions in the burden of HPV-related vulvar and vaginal cancer are possible.

With the primary (per-protocol) efficacy endpoints of each efficacy study, vaccine efficacy was 100%. In the broadest HPV-Naïve MITT population, vaccine efficacy exceeded 94% for all endpoints. In this broad population, vaccine efficacy with respect to CIN 3/AIS, representing high-grade cervical pre-cancer, squamous cell cervical carcinoma in situ, and cervical adenocarcinoma in situ, vaccine efficacy was 100%. Similarly, vaccine efficacy with respect to VIN 2/3 and VaIN 2/3, the immediate and obligate precursors to HPV-related vulvar and vaginal cancer, respectively, was 100%. Based on the contribution of HPV 16 and HPV 18 to HPV-related cancers, universal vaccination will eventually result in the prevention of nearly 25,000 anogenital and aerodigestive tract cancer cases in the United States annually.

Prophylactic administration of GARDASIL® is highly effective in preventing the development of HPV 16- and HPV 18-related CIN 3, AIS, VIN 2/3, and VaIN 2/3 lesions, and thereby removes the risk of development of HPV 16- or HPV 18-related cervical, vulvar and vaginal cancers. In a global setting, universal prophylactic administration of GARDASIL® has the potential to reduce the annual number of new cervical cancers from ~500,000 to ~150,000, and to reduce deaths from cervical cancer from ~290,000 to ~90,000 [5]. Similar reductions in the burden of HPV-related vulvar and vaginal cancer are possible.

With the primary (per-protocol) efficacy endpoints of each Phase III efficacy study, vaccine efficacy was 100%. In the broadest HPV-Naïve MITT population, vaccine efficacy exceeded 94% for all endpoints. In this broad population, vaccine efficacy with respect to CIN 3/AIS, representing high-grade cervical pre-cancer, squamous cell cervical carcinoma in situ, and cervical adenocarcinoma in situ, vaccine efficacy was 100%. Similarly, vaccine efficacy with respect to VIN 2/3 and VaIN 2/3, the immediate and obligate precursors to HPV-related vulvar and vaginal cancer, respectively, was 100%. Based on the contribution of HPV 16 and HPV 18 to HPV-related cancers, universal vaccination will eventually result in the prevention of nearly 25,000 anogenital and aerodigestive tract cancer cases in the United States annually.

Finally, efficacy trials also demonstrated that administration of GARDASIL® will substantially reduce the burden of genital warts. HPV 6 and HPV 11 cause ~90% of these lesions. Based on this contribution, universal vaccination will eventually result in the prevention of nearly 900,000 cases of genital warts in the United States annually. It is possible that up to 5400 cases of RRP will be prevented in the United States annually.

In subjects with evidence of ongoing or previous infection with a vaccine HPV type, administration of GARDASIL® was efficacious in preventing disease caused by the other 3 vaccine HPV types. Administration of GARDASIL® appeared to modestly reduce the incidence of CIN related to the relevant HPV type in subjects found to have an early infection with a vaccine HPV type at Day 1 (PCR positive but seronegative to a given

HPV type at Day 1). In subjects with evidence of a cleared HPV infection (seropositive/PCR negative at Day 1), disease caused by recurrent infection in placebo subjects was rare; there is evidence to suggest that GARDASIL® prevented such recurrences.

GARDASIL® induces protective efficacy through at least 2.5 years Postdose 3 (and at least 3.5 years Postdose 3 for the HPV 16 component of the vaccine).

GARDASIL® was highly immunogenic in all populations tested. Anti-HPV levels in 9- to 15-year-old subjects were much higher than those observed in older adolescents and young adults. Thus, administration of GARDASIL® to sexually-naïve 9- to 15-year-old girls will be highly efficacious in preventing cervical, vulvar, and vaginal cancer, pre-cancerous lesions, and genital warts caused by vaccine HPV types.

Programs designed to eradicate infection and disease caused by vaccine HPV types should be gender-neutral, because HPV infection is also common in men, causing genital warts, anal cancer, and penile cancer and men also transmit HPV to women. Evaluation of the efficacy of GARDASIL® in men is ongoing. However, the nearly 100% prophylactic efficacy of GARDASIL® with respect to EGLs in women, the fact that most HPV-related EGLs occur in keratinized vulvar skin, and the high immunogenicity of GARDASIL® in 9- to 15-year-old boys strongly suggest that administration of GARDASIL® to boys and men will reduce the incidence of infection and genital warts caused by vaccine HPV types. The efficacy of GARDASIL® with respect to CIN caused by vaccine HPV types suggests that the vaccine will also reduce the incidence of anal dysplasia caused by vaccine HPV types. These data support the value of gender-neutral vaccination programs for GARDASIL® in adolescents.

Risk Assessment

Administration of GARDASIL® was generally well tolerated in all groups tested. Vaccine-related serious adverse experiences occurred in <0.1% of subjects. There was no safety signal with respect to allergic reactions or other immune-mediated diseases. The proportion of subjects who reported injection-site adverse experiences and low-grade fevers in subjects who received GARDASIL® was higher than in placebo subjects, but few subjects discontinued vaccination due to an adverse experience. The proportions of subjects reporting new medical conditions through up to 2.5 years Postdose 3 were comparable between subjects who received GARDASIL® and placebo subjects. Baseline HPV status did not impact vaccine safety. Administration of GARDASIL® did not impact overall pregnancy outcomes. The long-term safety of GARDASIL® (>3 years from first vaccination) has not been evaluated. This evaluation will be conducted in the Nordic Cancer Registry Program.

Differences between vaccination groups in outcomes of pregnancies with onsets within 30 days of or greater than 30 days from administration of a dose of study vaccine were seen. A detailed evaluation of congenital anomalies in infants born to study subjects confirmed that the types of anomalies and the distribution of their occurrence relative to vaccination precluded a direct injury caused by GARDASIL®. Preclinical development

and reproductive toxicology studies did not show any teratogenic effect of GARDASIL®. Thus, there is no evidence to suggest that administration of GARDASIL® impacts pregnancy outcomes.

It will be important to assess whether universal administration of GARDASIL® will increase the incidence of infection with HPV types against which the vaccine offers no protection, thereby blunting the population benefit of the vaccine (although cross-protection for types related to vaccine HPV types is plausible). In clinical studies with monovalent HPV 16 L1 VLP vaccine, there was no evidence of an increase in the incidence of infection caused by HPV 6, HPV 11, or HPV 18. The long-term impact of GARDASIL® on cancer rates will be monitored in the Nordic Cancer Registry Program.

The long-term duration of efficacy remains to be evaluated. The Phase III trials will continue to accrue follow-up. Scandinavian subjects in Protocol 015 will be followed for >10 years through Nordic Cancer Registry Program. These subjects will be a sentinel cohort with observed follow-up that is at least 3 years in advance of the first person who will receive GARDASIL® post-licensure. If waning immunity is observed in this cohort, implementation of booster vaccination as public health policy can be implemented well in advance of the period of lower protection in the general population.

Summary The clinical development program for GARDASIL® was well designed, executed, and analyzed; and it supports licensure of GARDASIL®. There was strong evidence of efficacy in a population that was representative of the population for which GARDASIL® is intended, with little safety risk. GARDASIL® has clearly demonstrated a favorable benefit/risk ratio. On the basis of the data from this clinical program, GARDASIL® should be indicated for the prevention of HPV 16- and HPV 18-related cervical, vulvar, and vaginal cancers, and the high-grade pre-cancers that immediately precede them; GARDASIL® should be indicated for the prevention of HPV 6-, HPV 11-, HPV 16-, and HPV 18-related CIN, VIN, VaIN, and genital warts; and GARDASIL® should be indicated for the prevention of HPV 6, HPV 11, HPV 16, and HPV 18 infection.

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