Application Type	BLA Original
STN	125508/0
CBER Received Date	December 10, 2013
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Division / Office	DB/OBE
Clinical Reviewer(s)	Sixun Yang, M.D
Project Manager	Bharat Khurana, Ph.D.; Laura Montague
Priority Review	No
Reviewer Name(s)	Lihan Yan, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin, Ph.D. Team Leader, DB/VEB A. Dale Horne, Dr. P.H. Chief, DB/VEB Estelle Russek-Cohen, Ph.D. Director, DB
Applicant	Merck Sharp & Dohme Corp.
Established Name	Human Papillomavirus 9-valent Vaccine, Recombinant
(Proposed) Trade Name	GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant)
Pharmacologic Class	9-valent Human Papillomavirus (HPV) (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) recombinant vaccine
Formulation(s), including Adjuvants, etc	Human Papillomavirus Recombinant L1 Nine-valent (Types 6, 11, 16, 18, 31, 33, 45, 52 and 58; Saccharomyces cerevisiae) Virus-Like Particle Vaccine with Alum Adjuvant
Dosage Form(s) and Route(s) of Administration	0.5-mL suspension for intramuscular injection

Dosing Regimen	0, 2 months, 6 months
Indication(s) and Intended Population(s)	GARDASIL 9 is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine: • Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58. • Genital warts (condyloma acuminata) caused by HPV types 6 and 11. And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: • Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS). • Cervical intraepithelial neoplasia (CIN) grade 1. • Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3. • Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3. • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. GARDASIL 9 is indicated in boys 9 through 15 years of age for the prevention of the following diseases caused by HPV types included in the vaccine: • Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58. • Genital warts (condyloma acuminata) caused by HPV types 6 and 11. And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

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GLOSSARY

Abbreviation/Term	Definition
9vHPV vaccine	Nine-valent Human Papillomavirus vaccine
AEs	Adverse experiences
AHN or All-HN	All-HPV Naive
AIN	Anal intraepithelial neoplasia
AIS	Adenocarcinoma in situ
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ANSS	All (HPV Type-specific) Naïve Subjects with
ASaT	All-Subjects-as-Treated
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
cLIA	Competitive Luminex Immunoassay
CRF	Case report form
CSS	Clinical study summary
CSR	Clinical study report
CV	Coefficient of variation
DSMB	Data and Safety Monitoring Board
ECC	Endocervical curettage
ELISA	Enzyme-linked immunosorbent assay
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMR	Geometric mean ratio
GMTs	Geometric Mean Titers
HIV	Human immunodeficiency virus
HN-TS	HPV-Naïve Type-Specific
HPV	Human Papillomavirus
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug
LLOQ	Lower Limit of quantitation
LOQ	Limit of quantitation
LOD	Limit of detection
LS means	Least-squares means
LSIL	Low-Grade Squamous Intraepithelial Lesion
Pap	Papanicolaou
PBNA	Pseudovirion-based neutralization assay
PCR	Polymerase Chain Reaction
PPE	Per Protocol Efficacy
PPI	Per Protocol Immunogenicity
qHPV vaccine	Quadrivalent Human Papillomavirus vaccine

RR	Risk reduction
S0P0	Seronegative and PCR Negative
S0P1	Seronegative and PCR Positive
S1P0	Seropositive and PCR Negative
S1P1	Seropositive and PCR Positive
SAEs	Serious Adverse Experiences
SAP	Statistical analysis plan
SUBJID	Subject identification number (a.k.a., AN)
VaIN	Vaginal Intraepithelial Neoplasia
VE	Vaccine efficacy
VIN	Vulvar Intraepithelial Neoplasia

1. Executive Summary

The applicant,Merck Sharp & Dohme Corporation, submitted the initial biologic license application (BLA 125508) to seek licensure for GARDASIL®9 (9vHPV vaccine), a recombinant vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This vaccine, if approved, will be indicated in girls and women 9 through 26 years of age, and boys 9 through 15 years of age for the reduction of the incidence of HPV 6/11/16/18/31/33/45/52/58-related cervical, vulvar, vaginal, and anal cancers, and condyloma acuminate. A 3-dose regimen at 0, 2, and 6 months is proposed.

Six Phase III GARDASIL®9 clinical studies (V503-001, V503-002, V503-005, V503-006, V503-007, and V503-009/GDS01C) in female subjects 9 to 26 years of age and male subjects 9 to 15 years of age are included in this submission.

Efficacy
In the efficacy study (Study V503-001), the primary population was 16- 26 year-old adolescent and young adult women who were seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type. An efficacy of 96.7% (with the lower bound of the two-sided 95% confidence interval (CI) being 80.9%) was observed with regard to the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer, compared with GARDASIL™ (Table 12). The vaccine was also found to be efficacious (efficacy of 96%) against HPV 31-, 33-, 45-, 52-, and 58-related persistent infection of $\geq$ 6 or 12 months (Table 16).

Immunogenicity

The primary immunogenicity endpoint to evaluate responses to 9vHPV vaccine was Month 7 HPV Competitive Luminex Immunoassay (cLIA) Geometric Mean Titers (GMT) against HPV-types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Non-inferiority comparisons were made between age groups (boys or girls 9-15 years of age vs. women 16-26 years of age) or between vaccine groups (9vHPV vs. qHPV) using the margin of 0.67.

Among adolescent and young women 16 through 26 years of age, the non-inferiority criteria with regard to responses to anti-HPV 6, 11, 16, and 18 were met for the 9vHPV when compared with the qHPV group (Table 15).

The non-inferiority criteria were met with regard to responses to anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 when comparing girls or boys 9 through 15 years of age with young women 16-26 years of age (Table 43).

It also appears that no interference was observed when GARDASIL®9 was co-administered with Menactra™ and Adacel™.

Safety

Across all studies, 88% of the subjects reported at least one injection-site reactions and about 53% reported at least one systemic reaction within 15 days of vaccination. There were 2% of the 9vHPV recipients who reported one or more serious adverse events, the majority of the serious adverse events (SAEs) were related to pregnancy. Five of the SAEs (pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis) were determined to be related to 9vHPV vaccine by the investigators. There were 7 deaths reported, all in the 9vHPV vaccine group. None of these deaths were considered to be related to the 9vHPV vaccine by the investigators.

On a separate note, in a post hoc analysis, an imbalance was observed in spontaneous abortion rates between subjects who received 9vHPV and subjects who received qHPV when pregnancies (28.4% vs. 12.7%) were restricted to those where the estimated conception dates were within 30 days of any vaccination.

Please refer to the clinical review for more safety details and assessment of clinical significance of some of the observed differences.

Conclusion and Recommendations:

In conclusion, there were no major statistical issues related to the submission. Primary results were confirmed by the reviewer's independent analyses. The efficacy and immunogenicity objectives pre-specified in the studies were met and supported the approval of the vaccine. The reviewer defers to the medical officers and epidemiologists on the review committee with respect to regulatory decisions regarding the imbalance in spontaneous abortion rates noted in the above summary.

2. Clinical and Regulatory Background

Pursuant to the approval in 2006 of Gardasil, a quadrivalent human papillomavirus (qHPV) Types 6, 11, 16, 18 recombinant vaccine, the applicant developed the 9-valent HPV vaccine (9vHPV) which targets HPV Types 6, 11, 16, and 18 (the "original types") as well as HPV types 31, 33, 45, 52, and 58 (the "new types").

As of September 2013, the quadrivalent HPV vaccine has been approved and marketed under the name GARDASIL/SILGARD in over 130 countries including the US.

2.1 Disease or Health-Related Condition(s) Studied

Please refer to the clinical review.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The 9vHPV vaccine program was designed so that the proposed indications would include all the current qHPV vaccine indications plus the indications related to the new HPV types. The data presented in this Application support that the 9vHPV vaccine could offer significant benefit for the reduction in the incidence of HPV 6/11/16/18/31/33/45/52/58-related cervical, vulvar, vaginal, and anal cancers and condyloma acuminata in all individuals regardless of gender, with safety and tolerability comparable to existing licensed HPV vaccines.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

This product has not been licensed for use in any country.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

Please refer to the clinical and bioresearch and monitoring (BIMO) reviews.

3.1 Submission Quality and Completeness

Submission quality is acceptable. The applicant has responded to all information requests sent by the agency.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the clinical and bioresearch and monitoring (BIMO) reviews.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to the reviews of the corresponding discipline reviewers.

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review

4.2 Assay Validation

Please refer to the CMC/bioassay reviews

4.3 Nonclinical Pharmacology/Toxicology

N/A

4.4 Clinical Pharmacology

N/A

4.5 Clinical

Please refer to the clinical review

4.6 Pharmacovigilance

Please refer to the pharmacovigilance review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Reviews for individual Studies 001, 002, 009, 006, and 005 will be presented in Section 6. Integrated summary of safety results will be presented in Section 8.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review is based on the applicant's BLA submission (STN 125508/0) dated December 10, 2013 and subsequent amendments to the original submission, primarily Modules 2 and 5 in the following location in the Electronic Document Room (EDR):
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5.3 Table of Studies/Clinical Trials

There are six clinical studies included in the submission to support the proposed indication. A description of the clinical studies is provided in Table 1.

Protocol V503-001: This is a double-blinded (with in-house blinding), controlled with qHPV vaccine, dose-ranging, efficacy, immunogenicity, and safety study of the 9vHPV vaccine. The study used a seamless Phase II/III adaptive design, which allowed prompt progression from Phase II dose selection to Phase III efficacy evaluation. To this end, subjects were enrolled in 2 parts (Part A and Part B). The V503-001 Part B was designed to demonstrate that compared with qHPV vaccine, the 9vHPV vaccine is highly efficacious in reducing the incidence of: (1) A composite endpoint of HPV 31/33/45/52/58-related high-grade cervical, vulvar, and vaginal disease (primary efficacy endpoint); (2) HPV 31/33/45/52/58-related persistent infection (secondary efficacy endpoint); and (3) HPV 31/33/45/52/58-related cervical, vulvar and vaginal disease (any grade) (secondary efficacy endpoint).

Protocol V503-002: No efficacy study was conducted in adolescents due to the ethical constraints in collecting samples and performing examinations with children and low exposure to HPV in this age group. The 9vHPV vaccine efficacy findings in females 16-26 years of age were bridged to females and males 9 to 15 years of age based on the demonstration of non-inferior immunogenicity. This study was also conducted to demonstrate clinical consistency of manufactured material through immunogenicity assessment of three different final manufacturing process lots of the 9vHPV vaccine.

Protocol V503-009/GDS01C: This supportive non-IND study, requested by the European Medicines Agency (EMA), was conducted to demonstrate that 9vHPV vaccine

and qHPV vaccine have similar immunogenicity with respect to HPV 6, 11, 16, and 18 in females 9 to 15 years of age.

Protocol V503-006: It is possible that some girls and women previously vaccinated with qHPV vaccine may want to receive the 9vHPV vaccine in order to benefit from broader protection against HPV diseases after this vaccine is approved for use. In anticipation of this need, the 9vHPV vaccine was assessed for safety and immunogenicity in prior qHPV vaccine recipients in Protocol V503-006.

Protocols V503-005 and V503-007: Both studies were conducted to document the immunogenicity and safety profile of the 9vHPV vaccine administered concomitantly with vaccines recommended for routine vaccination of adolescents. Protocol V503-005 addressed concomitant administration of 9vHPV vaccine with Menactra™ and Adacel™. Protocol V503-007 addressed concomitant administration of 9vHPV vaccine with Repevax™ (diphtheria, tetanus, pertussis [acellular component] and poliomyelitis [inactivated] vaccine [adsorbed, reduced antigen(s) content]. Repevax™ is available in the European Union and some other countries.

Table 1: List of Clinical Studies

Prot-ocol	Key objectives	Treatment Groups (years of age)	Duration	Country(ies)
001	• Safety/tolerability assessment of the 9vHPV in females 16-26 years of age • Non-inferiority of immunogenicity of 9vHPV compared to GARDASIL® in females 16-26 years of age with respect to the original types (6,11, 16, 18) • Superior efficacy of 9vHPV compared to qHPV in females 16 to 16 years of age with respect to the new types (31, 33, 45, 52, 58) • Supportive efficacy assessment relative to historic placebo with respect to the original types (6, 11, 16, 18)/demonstration of no negative trend in efficacy relative to qHPV with respect to oncogenic types 16 and 18	Efficacy study: 9vHPV : females (16-26) (N=7106) qHPV : females (16-26) (N=7109)	Sep 2007 – Oct 2011 (last subject last vaccination)	28 centers in US; 77 centers Ex-US
002	• Safety/tolerability assessment of 9vHPV in preadolescent and adolescent boys and girls • Non-inferiority of 9vHPV immunogenicity (all 9 vaccine types) in males and females 9 to 15 years of age versus females 9 to 15 years of age • Demonstration of lot consistency	9vHPV : females (9-15) (N=646) 9vHPV : males (9-15) (N=666) 9vHPV : females (16-26) (N=468)	Aug 2009 – Mar 2011	21 centers in US; 51 centers Ex-US
005	• Non-inferiority of 9vHPV immunogenicity in concomitant vs. non concomitant cohort • Non-inferiority of Adacel® immunogenicity in concomitant vs. non concomitant cohort	9vHPV administered concomitantly (N=621) or non-concomitantly (N=620) with Adacel® and Menactra® Males and Females: (11-15)	Oct 2009 – Jan 2011	34 centers in US; 7 centers in Latin America
006	• Safety and immunogenicity of 9vHPV in prior qHPV recipients	9vHPV: females (12-26) (prior qHPV recipients) (N=618) Placebo: females (12-26) (prior qHPV recipients) (N=306)	Feb 2011-May 2011	32 centers in US
007	• Non-inferiority of 9vHPV immunogenicity in concomitant vs. non-concomitant cohort • Non-inferiority of Repevax® immunogenicity in concomitant vs. non concomitant cohort (Ex-US label only)	9vHPV administered concomitantly (N=526) or non-concomitantly with Repevax® (N=528) Males and Females: (11-15)	Apr 2010 – May 2011	22 centers in Europe
009	• Non-inferiority of 9vHPV immunogenicity with regard to HPV-16 and HPV-18 compared to qHPV in preadolescent and adolescent girls (9- to 15-year-olds)	9vHPV: Females: (9-15) (N=300) qHPV: Females: (9-15) (N=300)	Feb 2011-Dec 2011	24 centers in Europe

Source: Constructed by the reviewer based on individual study synopses provided in the application.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Protocols 001, 002, 009, 006, 005, and 007 (in order) are discussed in the following subsections.

6.1 Trial #1: Protocol 001

This protocol is entitled "*A Randomized, International, Double-Blinded (With In-House Blinding), Controlled With GARDASIL™ , Dose-Ranging, Tolerability, Immunogenicity, and Efficacy Study of a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine Administered to 16- to 26-Year-Old Women.*"

6.1.1 Objectives

The studies were divided into two parts – Part A and Part B.

The objectives in Part A were:
1) To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine when administered to 16-26 year-old women.
2) To evaluate a formulation of 9-valent HPV L1 VLP vaccine for use in the efficacy evaluation in Part B.

The primary objectives for Part B were:
1) To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine when administered to 16-26 year-old women.
2) To demonstrate that administration of 9-valent HPV L1 VLP vaccine will reduce the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer, compared with GARDASIL™ in 16-26 year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.
3) To demonstrate that the 9-valent HPV L1 VLP vaccine induces non-inferior GMTs for anti-HPV 6, 11, 16, and 18 compared to GARDASIL™ .

The secondary objectives in Part B were:
1) To demonstrate that administration of 9-valent HPV L1 VLP vaccine will reduce the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related persistent infection detected in samples from two or more consecutive visits ($\pm$1 month visit windows) 6 months or longer apart compared with GARDASIL™ in 16-26 year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.
2) To demonstrate that 9-valent HPV L1 VLP vaccine is immunogenic with respect to HPV types 31, 33, 45, 52, and 58.

3) To demonstrate that the 9-valent HPV L1 VLP vaccine induces non-inferior immune responses with respect to seroconversion percentages for HPV 6, 11, 16, and 18 compared to GARDASIL™ .
4) To quantify the amount by which the administration of 9-valent HPV L1 VLP vaccine reduces the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar, and vaginal disease compared with GARDASIL™ in 16-26 year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type(s).
5) To evaluate the persistence of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 immune responses generated by 9-valent HPV L1 VLP vaccine.
6) To evaluate the impact of administration of 9-valent HPV L1 VLP vaccine on the incidence of Pap test abnormalities (ASC-US [Positive for High Risk HPV] or worse).

In addition, there were 10 exploratory objectives:

1) To demonstrate that administration of 9-valent HPV L1 VLP vaccine reduces the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related persistent infection detected in samples from two or more consecutive visits (±1 month visit windows) 12 months or longer apart compared with GARDASIL™ in 16-26 year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type(s).
2) To evaluate whether the administration of 9-valent HPV L1 VLP vaccine reduces the combined incidence of persistent HPV 16 and 18 infection detected in samples from two or more consecutive visits (±1 month visit windows) 6 months or longer apart and HPV 16- and 18-related cervical, vulvar, and vaginal disease.
3) To evaluate whether the administration of 9-valent HPV L1 VLP vaccine results in a combined incidence of HPV 6- and 11-related cervical, vulvar, and vaginal disease that is comparable to the combined incidence observed with Gardasil.
4) To evaluate the impact of administration of 9-valent HPV L1 VLP vaccine on the combined incidence of CIN, AIS, and cervical cancer caused by any HPV type.
5) To evaluate the impact of administration of 9-valent HPV L1 VLP vaccine on the combined incidence of vulvar and vaginal disease caused by any HPV type.
6) To characterize the titers of anti-HPV type 6/11 in both peripartum maternal blood and in cord blood of infants born to subjects for evaluating the potential impact of 9-valent HPV L1 VLP vaccine on recurrent respiratory papillomatosis.
7) To evaluate the efficacy of the selected formulation of 9-valent HPV L1 vaccine against persistent HPV 35-, 39-, 51-, 56-, and 59-related infection detected in samples from two or more consecutive visits (±1 month visit windows) 6 months or longer apart and HPV 35-, 39-, 51-, 56-, and 59-related cervical, vulvar, and vaginal disease.
8) To evaluate the impact of administration of 9-valent HPV L1 VLP vaccine on the incidence of Pap test abnormalities (ASC-US [Positive for High Risk HPV] or worse) related to HPV Types 31, 33, 45, 52, & 58.
9) To evaluate the impact of administration of 9-valent HPV L1 VLP vaccine on the incidence of cervical biopsy and cervical definitive therapy treatments.

10) To assess humoral immune responses to HPV type 6, 11, 16, 18, 31, 33, 45, 52, and 58 using a 9-valent HPV total IgG Luminex immunoassay upon availability of a validated assay.

6.1.2 Design Overview

This was a randomized, double-blind (operating under in-house blinding procedures), controlled with qHPV vaccine, multicenter, multinational, dose-ranging, safety, immunogenicity, and efficacy study with a target enrollment of 14,620 subjects. The study was enrolled in 2 parts. Approximately 1240 subjects were to be enrolled in Part A and equally randomized to 3 dose formulations of 9vHPV vaccine or qHPV vaccine. One dose formulation was selected based on interim immunogenicity results. Approximately 13,380 subjects were to be enrolled in Part B and equally randomized to the selected dose formulation of 9vHPV vaccine or qHPV vaccine.

Three substudies were conducted:

1) A dose-ranging substudy including all subjects enrolled in Part A with an evaluation of immunogenicity and safety from Day 1 through Month 7
2) An efficacy substudy including all subjects who received the selected dose formulation of 9vHPV vaccine or qHPV vaccine with an efficacy and safety evaluation from Day 1 through at least Month 42
3) An immunogenicity substudy including all subjects enrolled in Part B with an immunogenicity evaluation from Day 1 through Month 42.

To assess efficacy, Papanicolaou (Pap) testing was to be done at Day 1, Month 7, Month 12, Month 18, Month 24, Month 30, Month 36, Month 42, Month 48, and Month 54 and Pap test abnormalities were followed up according to a pre-defined mandatory triage algorithm. All subjects were to be followed for efficacy at least up to Month 42. Efficacy analyses were to be conducted after 30 primary efficacy cases had accrued. To evaluate immunogenicity, sera were to be obtained at Day 1, Month 3, Month 7, Month 12, Month 24, Month 36, and Month 42. All subjects were to be followed for safety for the duration of the study.

6.1.3 Population

All subjects in this study were healthy females 16 through 26 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

A summary of the study treatments is presented in Table 2. In Part A of the study, three 9vHPV vaccine dose formulations (low, mid, high) and qHPV vaccine were used. In Part B, mid-dose 9vHPV vaccine and qHPV were used. These vaccines were administered as a 0.5 mL intramuscular injection in a three-dose regimen (Day 1, Month 2, and Month 6).

Table 2: Description of Study Vaccines: 9vHPV Vaccine and qHPV Vaccine

Vaccine	Enrollment Period	Dosage
Low-Dose 9vHPV Vaccine	Part A	20/40/40/20/20/20/20/20/20 μg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 μg aluminum adjuvant/0.5 mL
Mid-Dose 9vHPV Vaccine	Part A, Part B	30/40/60/40/20/20/20/20/20 μg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 μg aluminum adjuvant/0.5 mL
High-Dose 9vHPV Vaccine	Part A	30/40/80/55/30/30/30/30/30 μg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 μg aluminum adjuvant/0.5 mL
qHPV Vaccine	Part A, Part B	20/40/40/20 ug HPV 6/11/16/18 VLP with 225 ug aluminum adjuvant/0.5 mL

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 9-4

6.1.6 Sites and Centers

One hundred five centers located in Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Mexico, New Zealand, Norway, Peru, Republic of Korea, Sweden, Taiwan, Thailand, and the U.S. enrolled subjects into the study.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoints

The primary efficacy endpoint was the combined incidence of HPV 31/33/45/52/58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer (starting after Month 7).

The key secondary endpoints included the combined incidence of HPV 31/33/45/52/58-related persistent infection for a duration of 6 months (within 1 month windows) or longer; HPV 31/33/45/52/58-related cervical, vulvar, and vaginal disease; and incidence of Pap test abnormalities.

The primary immunogenicity endpoint was Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs at Month 7.

The primary safety endpoints were:

- Incidence of injection-site adverse experiences (Day 1 to Day 5 after any vaccination visit). (Part A and Part B)
- Incidence of elevated temperatures (≥100°F, oral equivalent) (Day 1 to Day 5 after any vaccination visit) (Part B only)
- Incidence of serious adverse experiences (Day 1 to Day 15 following any vaccination visit) (Part A and Part B)

- Incidence of severe systemic adverse experiences (Day 1 to Day 15 following any vaccination visit) (Part B only)
- Incidence of serious vaccine related adverse experiences occurring at any time during the study (Part B only)

Declaration of study success requires demonstration of success on both the primary efficacy hypothesis and the primary Part B immunogenicity hypothesis.

Statistical Evaluation Criteria

Efficacy

The primary efficacy objective was addressed by testing (at a 1-sided α =0.025 level of significance) the hypothesis that the incidence of the composite endpoint HPV 31-, 33-, 45-, 52-, and 58-related CIN 2/3, AIS, invasive cervical carcinoma, VIN 2/3, VaIN 2/3, and vulvar or vaginal cancer among subjects vaccinated with the qHPV vaccine would be reduced by more than 25% among subjects vaccinated with the 9vHPV vaccine). The statistical criterion for success required that the lower bound of the two-sided 95% confidence interval for vaccine efficacy be greater than 25%.

The secondary efficacy objective (1) was addressed by testing (at a 1-sided α=0.025 level of significance) the hypothesis that the incidence of the composite endpoint HPV 31-, 33-, 45-, 52-, and 58-related persistent infection detected on two or more consecutive study visits at least 6 months ($\pm$1 month) apart among subjects vaccinated with the qHPV vaccine would be reduced by more than 25% among subjects vaccinated with the 9vHPV vaccine. The statistical criterion for success required that the lower bound of the two-sided 95% confidence interval for vaccine efficacy be greater than 25%.

There were no pre-specified hypotheses to be tested corresponding to secondary efficacy objectives (2) and (3). For these two secondary efficacy objectives, point and 95% interval estimates of VE against the endpoints associated with each objective were computed and descriptive summaries were provided.

The exploratory efficacy objective (1) was addressed by testing (at a 1-sided α=0.025 level of significance) the hypothesis that the incidence of the composite endpoint HPV 31-, 33-, 45-, 52-, and 58-related persistent infection detected on two or more consecutive study visits at least 12 months ($\pm$1 month) apart among subjects vaccinated with the HPV vaccine would be reduced by more than 0% among subjects vaccinated with the 9vHPV vaccine. The statistical criterion for success required that the lower bound of the two-sided 95% confidence interval for vaccine efficacy be greater than 0%.

Immunogenicity

The primary Part A objective with regard to immunogenicity was to evaluate a formulation of the 9vHPV vaccine for use in the efficacy evaluation in Part B. An interim analysis of immunogenicity was conducted when ~100% of all serology data were available through Week 4 post-dose 2 for subjects in Part A. Although no formal hypothesis testing was done during this interim analysis and although the interim analysis was based on post-dose 2 data and the final Part A immunogenicity hypothesis testing

was based on post-dose 3 data, a nominal 1-sided alpha level of 0.0247 was used to test the hypothesis relating to non-inferiority of GMTs at Month 7 for each of HPV types 6, 11, 16, and 18. This adjustment of alpha level at the final test of hypothesis is similar to having used part of the alpha level (i.e., a nominal $\leq$0.001) during the interim analysis using an extreme alpha-spending method, such as the Haybittle-Peto rule.

The primary Part B objective with regard to immunogenicity was addressed by testing (at 1-sided α=0.025 level) the hypothesis that the 9vHPV vaccine generates anti-HPV 6, 11, 16, and 18 GMTs 4 weeks post-dose 3 that are non-inferior to those generated by the qHPV vaccine. Non-inferiority is demonstrated if the lower bound of the 95% confidence interval of the 9vHPV vaccine group versus the qHPV vaccine group GMR is greater than 0.67.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size and Power

The study sample size was determined to provide sufficient statistical power to demonstrate success against the primary efficacy hypothesis if the 9vHPV vaccine is truly efficacious. A total sample size of 14,000 subjects (Part A = 620; Part B = 13,380) randomized to either the 9v HPV vaccine or the qHPV vaccine on a 1:1 allocation ratio provides the study a > 90% power to demonstrate success on the primary efficacy hypothesis based on a test with one-sided α=0.025 level of significance. The power and sample size were determined based on the following assumptions:

- Efficacy of the 9vHPV vaccine relative to placebo is 88%;
- Efficacy of the 9vHPV vaccine relative to the qHPV vaccine against HPV types 31, 33, 45, 52, and 58 is 83% under the assumption that the qHPV vaccine has cross-protection efficacy of 30% relative to placebo against these HPV types;

With these assumptions, 30 cases of the primary efficacy endpoint needed to be accrued to have > 90% power to succeed on the test of the primary efficacy hypothesis at α =0.025 level of significance based on a fixed-event design.

Phase IIb/III seamless design

A seamless Phase IIb/III design was implemented for Protocol V503-001. Three (3) dose formulations were assessed for immunogenicity and safety under Part A. Following dose selection, development promptly proceeded with the initiation of Part B enrollment, to a global Phase III safety, efficacy, and immunogenicity study.

Neither the unblinded safety and efficacy data nor the treatment allocation of Part A subjects were viewed by Merck personnel involved in the conduct of the study during the dose selection process. Thus, participants enrolled under Part A and vaccinated with the selected 9vHPV dose formulation or qHPV vaccine control continued into the Phase III efficacy study without compromising the blinding.

Vaccine Efficacy Estimation Method

Table 3 provides a listing of the primary and secondary efficacy endpoints analyzed along with the efficacy analysis populations for each and the analysis methods used.

Vaccine efficacy is defined as: $VE = 100\%*\{1-(r_N/r_G)\}$,

where r_N, the incidence rate among 9-valent HPV L1 VLP vaccine recipients, is defined as $r_N = C_N/\tau_N$. C_N = number of primary efficacy cases among 9vHPV vaccine recipients and τ_N = total person-years of follow-up among 9vHPV vaccine recipients. Similarly, $r_G = C_G/\tau_G$ is the incidence rate among qHPV recipients, where C_G is the number of primary efficacy cases among qHPV recipients and τ_G is the total person-years of follow-up among qHPV recipients.

Under the assumption that r_N and r_G are the means of independent Poisson processes, and given that there are a total of $n = C_N + C_G$ primary efficacy cases observed on all subjects, the number of primary efficacy cases C_N among 9vHPV vaccine recipients is distributed as *Binomial* (n,p), where the binomial probability p is defined as $p= \tau_N r_N/(\tau_N r_N+\tau_G r_G)$. The probability p is a person-years-adjusted estimate of the probability that a given primary efficacy case is a 9vHPV vaccine recipient. The lower bound of the $100*(1-\alpha)\%$ exact confidence interval for the probability p is obtained by searching for the proportion p_L such that the probability of observing C_N or more primary efficacy cases out of n total primary efficacy cases is $\leqslant \alpha/2$. Similarly, the upper bound of the $100*(1-\alpha)\%$ exact confidence interval for the probability p is obtained by searching for the proportion p_U such that the probability of observing C_N or fewer primary efficacy cases out of n total primary efficacy cases is $\leqslant \alpha/2$. The upper and lower bounds of the $100*(1-\alpha)\%$ confidence interval for vaccine efficacy can be computed from the upper and lower bounds of the confidence interval for p.

Table 3: Planned Primary and Secondary Efficacy Analyses

Analysis Population or Method	PPE[†]	HN-TS	All-HN	FAS	S0P1	S1P0	S1P1	VE Estimation	Time-to-Event
Endpoints to Support the Primary Efficacy Hypothesis									
HPV 31/33/45/52/58-Related CIN 2/3, AIS, invasive cervical carcinoma, VIN 2/3, VaIN 2/3, vulvar cancer, or vaginal cancer	(P)	●		●	●	●	●	●	●
Sensitivity Analysis of the Primary Efficacy Endpoint									
HPV 31/33/45/52/58- Related CIN 2/3, AIS, invasive cervical carcinoma, VIN 2/3, VaIN 2/3, vulvar cancer, or vaginal cancer with Additional PCR Positivity[§]	(P)	●		●				●	
HPV 31/33/45/52/58- Related CIN 2/3, AIS, invasive cervical carcinoma, VIN 2/3, VaIN 2/3, vulvar cancer, or vaginal cancer -Imputing Case Status for Subjects Lost to Follow-up	(P)	●							
Endpoints to Support the Secondary Efficacy Hypothesis									
HPV 31/33/45/52/58-Related Persistent Infection ≥ 6 months (±1 month)	(P)	●		●	●	●	●	●	●
Endpoints for Supplementary Analyses of the Primary and Secondary Efficacy Endpoints									
HPV 31/33/45/52/58-Related CIN 2/3, AIS, invasive cervical carcinoma, VIN 2/3, VaIN 2/3, vulvar cancer, or vaginal cancer	(P)	●		●	●	●	●	●	
- By HPV Type	(P)	●		●	●	●	●	●	
- By Lesion Type									
HPV 31/33/45/52/58- Related Persistent Infection ≥ 6 months (±1 month)									
- By HPV Type	(P)	●		●	●	●	●	●	
Endpoints to Support Exploratory Efficacy Objectives									
HPV 31/33/45/52/58-Related CIN 1/2/3, AIS, invasive cervical carcinoma, genital wart, VIN 1/2/3, VaIN 1/2/3, vulvar cancer, or vaginal cancer	(P)	●		●	●	●	●	●	
- Overall	(P)	●		●	●	●	●	●	
- By HPV Type	(P)	●		●	●	●	●	●	
- By Lesion Type									
Pap Test Abnormalities (ASC-US [+ for HR HPV probe] or worse)									
- Overall			(P)	●				●[‖]	
- High Grade (ASC-H, HSIL or worse)			(P)	●					
- By Specific Abnormality			(P)	●					

[†] Endpoint cases are counted starting after Month 7 in the PPE population. For all other analysis populations, endpoint cases are counted starting after Day 1.
[‡] Disease is defined as any of genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN, cervical AIS, or cervical cancer.
[§] In addition to meeting all criteria for defining a case of the primary efficacy endpoint, subjects who are a case of the primary efficacy endpoint based on a cervical, vulvar, or vaginal biopsy, ECC, or definitive therapy specimen are also required to be PCR positive to the same HPV type for at least 1 specimen immediately prior to or immediately after the HPV 31/33/45/52/58-related disease specimen.
[‖] In addition to the estimation of vaccine efficacy of 9-valent HPV L1 VLP vaccine relative to Gardasil, efficacy of the 9-valent HPV L1 VLP vaccine will be estimated relative to the combined placebo population of Protocols 007 and 012 from the Gardasil (V501) clinical program using the methods in Hasselblad and Kong [3].
(P) indicates that the analysis population is the primary approach for evaluating the given endpoint.
AIS = Adenocarcinoma in-situ; CIN = Cervical intraepithelial neoplasia; HR = High-risk

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 9-6

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A summary of various efficacy analysis populations is provided in Table 4.

Per Protocol Efficacy (PPE) population consists of subjects who received all 3 doses of the 9vHPV vaccine or the qHPV vaccine within 1 year; had Month 7 PCR results on swab samples collected within 14 to 72 days post-dose 3; were HPV-naïve (i.e., seronegative at Day 1 and PCR negative from Day 1 through Month 7) to the vaccine HPV type being analyzed (HPV-naïve to both types 6 and 11 in analysis of HPV 6-related and HPV 11-related endpoints); and did not violate the protocol in ways that could interfere with the evaluation of immune response to injections of the 9vHPV or qHPV vaccines.

HPV-Naïve Type-Specific (HN-TS) population consists of subjects who: received at least 1 dose of the 9vHPV or qHPV vaccines; had at least 1 follow-up visit after Day 1; and were HPV-naïve at Day 1 to the HPV type being analyzed. HPV-naïve was defined as: seronegative and PCR negative if the HPV type being analyzed is one of the HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (i.e., the HPV types in the 9vHPV vaccine); PCR-negative if the HPV type being analyzed is one of the types 35, 39, 51, 56, and 59 (i.e., the HPV types not in the 9vHPV vaccine). In the analysis of HPV type 6, and similarly for HPV type 11, subjects were required to be HPV-naïve to both HPV types 6 and 11 (baseline serology testing was not conducted for the HPV types not in the 9vHPV vaccine, hence HPV-naïve was only defined by PCR-status for HPV types not in the 9vHPV vaccine.)

Full Analysis Set (FAS) population consists of subjects who received at least 1 dose of the 9vHPV or qHPV vaccines and had at least 1 follow-up visit after Day 1.

All-HPV Naive (All-HN or AHN) population consists of subjects who: received at least 1 dose of the 9vHPV or qHPV vaccines; had at least 1 follow-up visit after Day 1; were seronegative and PCR-negative at Day 1 to the HPV types in the 9vHPV vaccine; were PCR-negative at Day 1 to the HPV types not in the 9vHPV vaccine; and had a Day 1 Pap test result that was negative for squamous intraepithelial lesion (SIL).

The PPE population was the primary analysis population on which evaluations were performed to determine successful achievement of the primary efficacy objective and secondary efficacy objectives (1) and (2) enumerated in Section 6.1.1. Analyses were also performed on the HN-TS and FAS to support the results of the analyses based on the PPE population.

The AHN population was used for various exploratory efficacy evaluations. Additionally, a few other populations – Day 1 Seronegative and PCR Positive **(S0P1),**

Day 1 Seropositive and PCR Negative **(S1P0)**, and Day 1 Seropositive and PCR positive **(S1P1) –** were used in some exploratory efficacy analyses where appropriate.

The immunogenicity analyses were based on the **Per-Protocol Immunogenicity (PPI)** population, which consists of subjects who were PPE-population-eligible and in addition had their vaccination visits occur within acceptable day ranges relative to Day 1 and had at least one Month 7 serology result within 21 to 49 days post-dose 3.

Immunogenicity Substudy Cohort: All subjects enrolled during Part B comprise the immunogenicity substudy cohort. Among subjects in the immunogenicity substudy cohort, evaluations of Part B immunogenicity objectives were conducted on the analysis populations described above, e.g., S0P1, S1P0, S1P1, and PPI populations.

All (HPV Type-specific) Naïve Subjects with Serology (ANSS) population consists of subjects who received all 3 doses of 9vHPV or qHPV vaccine; had Month 7 PCR results on swab samples collected within 14 to 72 days post-dose 3; were HPV-naïve (i.e., seronegative at Day 1 and PCR negative from Day 1 through Month 7) to the vaccine HPV type being analyzed (HPV-naïve to both types 6 and 11 in analysis of HPV 6-related and HPV 11-related endpoints); and had an evaluable post-dose 3 serology result.

All safety analyses and summaries were provided separately for the dose-ranging cohort (comprised of all subjects randomized during Part A) and the efficacy cohort.

Table 4: Analysis Populations

Inclusion Criteria	Efficacy (PPE)	Immuno-genicity (PPI)	HPV- Naïve Type-Specific (HN-TS)	All-HPV Naive (AHN)	Full Analysis Set (FAS)	Sero-negative / PCR-positive (S0P1)	Sero-positive / PCR-negative (S1P0)	Sero-positive / PCR-positive (S1P1)
Have received all 3 injections with the correct dose of the correct clinical material within 1 year.	●							
Received ≥1 dose of 9vHPV or qHPV vaccine.			●	●	●	●	●	●
Received all 3 injections of 9vHPV or qHPV vaccine within acceptable day ranges.		●						
Inclusion Criteria Relating to Availability of Follow-up Data								
Have ≥1 follow-up visits with evaluable data following Month 7.	●	●						
Have ≥1 follow-up visits with evaluable data following Day 1.			●	●	●	●	●	●
Have valid PCR results on LVPP or EEC swab specimens within 14 days of the first vaccination.	●	●	●	●		●	●	●
Have valid PCR results on LVPP or EEC swab specimens within 14 to 72 days of the third vaccination.	●	●						
Have serum samples for testing antibodies to HPV collected within acceptable day ranges.		●						
Inclusion Criteria Relating to HPV 6 and 11 Status[†]								
Seronegative at Day 1 (HPV 6 <32 and HPV 11 <20 mMU/mL)	●	●	●	●		●		
Seropositive at Day 1 (HPV 6 ≥32 or HPV 11 ≥20 mMU/mL)							●	●
PCR-negative at Day 1	●	●	●	●			●	
PCR-positive at Day 1						●		●
PCR-negative at Month 7	●	●						
Inclusion Criteria Relating to HPV 16 Status[‡]								
Seronegative at Day 1 (HPV 16 <20 mMU/mL)	●	●	●	●		●		
Seropositive at Day 1 (HPV 16 ≥20 mMU/mL)							●	●
PCR-negative at Day 1	●	●	●	●			●	
PCR-positive at Day 1						●		●
PCR-negative at Month 7	●	●						
Inclusion Criteria Relating to Pap Abnormality Status								
Negative for SIL at Day 1				●				

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 9-7

6.1.10.1.1 Demographics

The demographic characteristics in the dose-ranging substudy (Part A) are presented in Table 5. The demographic characteristics in the efficacy substudy (Part B) are presented in Table 6. The distributions of the demographics were similar across the treatment groups.

Table 5: Demographic Characteristics: All Randomized Subjects, Dose-Ranging Study

	Low-Dose 9vHPV Vaccine		Mid-Dose 9vHPV Vaccine		High-Dose 9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	315		307		310		310		1,242	
Gender										
Female	315	(100.0)	307	(100.0)	310	(100.0)	310	(100.0)	1,242	(100.0)
Age (Years)										
Mean	21.7		22.0		21.9		21.9		21.9	
SD	2.4		2.5		2.4		2.5		2.4	
Median	22.0		22.0		22.0		22.0		22.0	
Race										
American Indian Or Alaska Native	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Asian	40	(12.7)	37	(12.1)	36	(11.6)	40	(12.9)	153	(12.3)
Black Or African American	18	(5.7)	10	(3.3)	14	(4.5)	14	(4.5)	56	(4.5)
Multi-Racial	92	(29.2)	99	(32.2)	98	(31.6)	101	(32.6)	390	(31.4)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.3)	1	(0.3)	2	(0.6)	4	(0.3)
Unknown	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	2	(0.2)
White	164	(52.1)	159	(51.8)	160	(51.6)	153	(49.4)	636	(51.2)
Ethnicity										
Hispanic Or Latino	125	(39.7)	127	(41.4)	117	(37.7)	125	(40.3)	494	(39.8)
Not Hispanic Or Latino	190	(60.3)	180	(58.6)	193	(62.3)	185	(59.7)	748	(60.2)
Region										
Asia-Pacific	34	(10.8)	32	(10.4)	35	(11.3)	34	(11.0)	135	(10.9)
Europe	58	(18.4)	58	(18.9)	57	(18.4)	57	(18.4)	230	(18.5)
Latin America	114	(36.2)	113	(36.8)	112	(36.1)	115	(37.1)	454	(36.6)
North America	109	(34.6)	104	(33.9)	106	(34.2)	104	(33.5)	423	(34.1)
Smoking Status										
Current smoker	53	(16.8)	46	(15.0)	50	(16.1)	46	(14.8)	195	(15.7)
Ex-smoker	21	(6.7)	25	(8.1)	24	(7.7)	18	(5.8)	88	(7.1)
Never smoked	240	(76.2)	236	(76.9)	235	(75.8)	246	(79.4)	957	(77.1)
Unknown	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.2)

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 10-12

Table 6: Demographic Characteristics: All Randomized Subjects, Efficacy Study

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	7,106		7,109		14,215	
Gender						
Female	7,106	(100.0)	7,109	(100.0)	14,215	(100.0)
Age (Years)						
Mean	21.9		21.8		21.9	
SD	2.5		2.5		2.5	
Median	22.0		22.0		22.0	
Range	16-26		16-26		16-26	
Race						
American Indian Or Alaska Native	6	(0.1)	10	(0.1)	16	(0.1)
Asian	1,022	(14.4)	1,006	(14.2)	2,028	(14.3)
Black Or African American	243	(3.4)	233	(3.3)	476	(3.3)
Multi-Racial	1,897	(26.7)	1,909	(26.9)	3,806	(26.8)
Native Hawaiian Or Other Pacific Islander	5	(0.1)	10	(0.1)	15	(0.1)
Unknown	10	(0.1)	13	(0.2)	23	(0.2)
White	3,923	(55.2)	3,928	(55.3)	7,851	(55.2)
Ethnicity						
Hispanic Or Latino	2,525	(35.5)	2,510	(35.3)	5,035	(35.4)
Not Hispanic Or Latino	4,580	(64.5)	4,599	(64.7)	9,179	(64.6)
Unknown	1	(0.0)	0	(0.0)	1	(0.0)
Region						
Asia-Pacific	905	(12.7)	909	(12.8)	1,814	(12.8)
Europe	2,406	(33.9)	2,409	(33.9)	4,815	(33.9)
Latin America	2,372	(33.4)	2,372	(33.4)	4,744	(33.4)
North America	1,423	(20.0)	1,419	(20.0)	2,842	(20.0)
Smoking Status						
Current smoker	1,071	(15.1)	1,005	(14.1)	2,076	(14.6)
Ex-smoker	382	(5.4)	358	(5.0)	740	(5.2)
Never smoked	5,647	(79.5)	5,744	(80.8)	11,391	(80.1)
Unknown	6	(0.1)	2	(0.0)	8	(0.1)

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 10-13

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Please refer to the clinical review.

6.1.10.1.3 Subject Disposition

A total of 1,242 subjects were enrolled in the dose-ranging substudy under Part A. The disposition of subjects is presented in Table 7. Three subjects in the low-dose 9vHPV group were discontinued prior to receiving their first vaccination. Around 95% of the subjects completed the substudy. As per protocol, the subjects who received either the mid-dose 9vHPV or qHPV in the dose-ranging study were also enrolled in the efficacy study. Of the 617 subjects meeting these criteria, 584 elected to continue in the study in the follow-up period after Month 7.

Table 7: Disposition of Subjects (Day 1 to Month 7) (Dose-Ranging Substudy) All Randomized Subjects

	Low-Dose 9vHPV Vaccine		Mid-Dose 9vHPV Vaccine		High-Dose 9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	315		307		310		310		1,242	
Vaccinated at										
Vaccination 1	312	(99.0)	307	(100.0)	310	(100.0)	310	(100.0)	1,239	(99.8)
Vaccination 2	305	(96.8)	300	(97.7)	306	(98.7)	305	(98.4)	1,216	(97.9)
Vaccination 3	300	(95.2)	291	(94.8)	297	(95.8)	300	(96.8)	1,188	(95.7)
Trial Disposition										
Completed	295	(93.7)	290	(94.5)	296	(95.5)	297	(95.8)	1,178	(94.8)
Discontinued	20	(6.3)	17	(5.5)	14	(4.5)	13	(4.2)	64	(5.2)
Adverse Event	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	2	(0.2)
Lost To Follow-Up	12	(3.8)	8	(2.6)	9	(2.9)	7	(2.3)	36	(2.9)
Protocol Violation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
Withdrawal By Subject	7	(2.2)	8	(2.6)	5	(1.6)	5	(1.6)	25	(2.0)
Subject Study Medication Disposition										
Completed	300	(95.2)	291	(94.8)	297	(95.8)	300	(96.8)	1,188	(95.7)
Did Not Take Study Medication	3	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.2)
Discontinued	12	(3.8)	16	(5.2)	13	(4.2)	10	(3.2)	51	(4.1)
Adverse Event	2	(0.6)	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.2)
Lost To Follow-Up	6	(1.9)	8	(2.6)	9	(2.9)	5	(1.6)	28	(2.3)
Pregnancy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
Protocol Violation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
Withdrawal By Subject	4	(1.3)	7	(2.3)	4	(1.3)	3	(1.0)	18	(1.4)
Protocol Milestone										
Continuing Into Next Trial Segment	2	(0.6)	287	(93.5)	0	(0.0)	297	(95.8)	586	(47.2)
Not Continuing Into Next Trial Segment	293	(93.0)	4	(1.3)	296	(95.5)	1	(0.3)	594	(47.8)
Unknown	20	(6.3)	16	(5.2)	14	(4.5)	12	(3.9)	62	(5.0)

Each subject is counted once for Trial Disposition, Study Medication Disposition, Protocol Milestone based on the latest corresponding disposition record.

Unknown: A disposition record did not exist at the time of reporting.

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 10-1

A total of 14,215 subjects were enrolled in the efficacy substudy. A summary of the number of subjects who were randomized, vaccinated, who completed or discontinued during the vaccination period (Day 1 through Month 7), by vaccination group, is provided in Table 8.

Table 8: Disposition of Subjects (Day 1 to Month 7) (Efficacy Substudy) All Randomized Subjects

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	7,106		7,109		14,215	
Vaccinated at						
Vaccination 1	7,099	(99.9)	7,105	(99.9)	14,204	(99.9)
Vaccination 2	7,015	(98.7)	7,015	(98.7)	14,030	(98.7)
Vaccination 3	6,928	(97.5)	6,934	(97.5)	13,862	(97.5)
Trial Disposition						
Completed	6,862	(96.6)	6,854	(96.4)	13,716	(96.5)
Discontinued	244	(3.4)	255	(3.6)	499	(3.5)
Adverse Event	6	(0.1)	2	(0.0)	8	(0.1)
Lost To Follow-Up	126	(1.8)	128	(1.8)	254	(1.8)
Physician Decision	3	(0.0)	2	(0.0)	5	(0.0)
Protocol Violation	4	(0.1)	4	(0.1)	8	(0.1)
Withdrawal By Subject	105	(1.5)	119	(1.7)	224	(1.6)
Subject Study Medication Disposition						
Completed	6,928	(97.5)	6,934	(97.5)	13,862	(97.5)
Did Not Take Study Medication	7	(0.1)	4	(0.1)	11	(0.1)
Discontinued	171	(2.4)	171	(2.4)	342	(2.4)
Adverse Event	8	(0.1)	4	(0.1)	12	(0.1)
Lost To Follow-Up	92	(1.3)	81	(1.1)	173	(1.2)
Physician Decision	2	(0.0)	4	(0.1)	6	(0.0)
Pregnancy	2	(0.0)	1	(0.0)	3	(0.0)
Protocol Violation	1	(0.0)	4	(0.1)	5	(0.0)
Withdrawal By Subject	66	(0.9)	77	(1.1)	143	(1.0)
Protocol Milestone						
Continuing Into Next Trial Segment	6,857	(96.5)	6,852	(96.4)	13,709	(96.4)
Not Continuing Into Next Trial Segment	10	(0.1)	8	(0.1)	18	(0.1)
Unknown	239	(3.4)	249	(3.5)	488	(3.4)

Each subject is counted once for Trial Disposition, Study Medication Disposition, Protocol Milestone based on the latest corresponding disposition record.

Unknown: A disposition record did not exist at the time of reporting.

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 10-2

Table 9: Disposition of Subjects (>Month 7) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population >Month 7 to Month 42	6,102		6,124		12,226	
Completed >Month 7 to Month 42	5,502	(90.2)	5,542	(90.5)	11,044	(90.3)
Subjects in population >Month 42 to Month 48	3,493		3,552		7,045	
Completed >Month 42 to Month 48	3,455	(98.9)	3,528	(99.3)	6,983	(99.1)
Subjects in population >Month 48 to Month 54	788		818		1,606	
Completed >Month 48 to Month 54	783	(99.4)	813	(99.4)	1,596	(99.4)

Source: Original BLA 125508/0; Clinical Study Report V503-001, Tables 10-3 through 10-5

A summary of subjects included in the PPE efficacy population is provided in Table 10.

Table 10: Subjects in the PPE Efficacy Analysis Population

	9vHPV Vaccine (N=7,106)	qHPV Vaccine (N=7,109)	Total (N=14,215)
Number of Subjects who received at least 1 injection	7,099	7,105	14,204
Included in Per-Protocol Efficacy Population			
HPV 6/11	4,833	4,878	9,711
HPV 16	4,895	4,944	9,839
HPV 18	5,533	5,556	11,089
HPV 31	5,403	5,332	10,735
HPV 33	5,730	5,714	11,444
HPV 45	5,830	5,808	11,638
HPV 52	5,422	5,297	10,719
HPV 58	5,465	5,423	10,888
Reason for Exclusion			
General protocol violation	136	167	303
Incorrectly randomized	1	0	1
Received incorrect clinical material or dose amount	7	13	20
Received non-study vaccination	111	141	252
Received vaccination of marketed HPV vaccine	1	3	4
Received immunosuppressives, IgG, or blood products	11	8	19
With a history of immune disorder	3	1	4
With a history of abnormal cervical biopsy result or positive HPV test result	1	0	1
With a history of genital warts or has genital warts at Day 1	1	2	3
Subject has 2 cervices	2	0	2
Missed 1st, 2nd and 3rd vaccination	7	4	11
Missed 2nd and 3rd vaccination	84	90	174
Missed 3rd vaccination	87	81	168
Missing Day 1 swab samples/results	243	245	488
Missing Day 1 serology samples/results	20	30	50
Missing Month 7 swab samples/results	162	153	315
Did not receive all 3 vaccinations within 1 year	50	55	105

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 10-8

Table 11 summarizes the number of subjects in the per-protocol efficacy population with disease and persistent infection follow-up after Month 7.

Table 11: Number of Subjects with Efficacy Phase Follow-Up in the PPE Population for HPV 31/33/35/52/58-related Persistent infection, CIN, or EGL

	9vHPV Vaccine (N = 7,106)	qHPV Vaccine (N = 7,109)	Total (N = 14,215)
With Follow-up for HPV 31/33/35/52/58-related Persistent infection, CIN, or EGL	6,016	6,017	12,033
With Follow-up for HPV 31-related Persistent infection, CIN, or EGL	5,308	5,252	10,560
With Follow-up for HPV 33-related Persistent infection, CIN, or EGL	5,624	5, 628	11,252
With Follow-up for HPV 45-related Persistent infection, CIN, or EGL	5,724	5,724	11,448
With Follow-up for HPV 52-related Persistent infection, CIN, or EGL	5,320	5,216	10,536
With Follow-up for HPV 58-related Persistent infection, CIN, or EGL	5,361	5,340	10,701

CIN = Cervical intraepithelial neoplasia; EGL = External genital lesions; HPV = Human papillomavirus; PPE = Per-Protocol efficacy

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 10-9

6.1.11 Efficacy and Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Efficacy

Table 12 presents the results of evaluation of efficacy against the primary efficacy endpoint of high grade cervical, vulvar, and vaginal disease related to HPV types 31, 33, 45, 52, and 58 in the PPE population (primary). In the PPE population, the single case of the primary efficacy endpoint in the 9vHPV group was a subject (SUBJID=18149) who was PCR-negative from Day 1 through Month 7 study visit for HPV type 58 who was diagnosed as a case of CIN 2 by the Pathology Panel and was also PCR-positive for HPV type 58 at approximately 11 months after vaccination dose 1. The subject was PCR-negative for HPV type 58 at all other times through Month 42. On the other hand, thirty (30) cases were identified in the qHPV group. As a result, the vaccine efficacy (VE) was 96.7% with the lower bound of the two-sided 95% confidence interval (CI) being 80.9%, exceeding the 25% lower bound VE criterion. Therefore, the pre-specified success criterion for the primary efficacy objective was met.

Table 12: Analysis of Efficacy against HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer (Per-Protocol Efficacy Populations)

	9vHPV	**9vHPV**	**9vHPV**	**9vHPV**	**qHPV**	**qHPV**	**qHPV**	**qHPV**	**Observed VE**	**95% CI**
Endpoint	n	# Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	# Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer (**PPE** Population)	6,016	1	19,005.1	0.0	6,017	30	18,976.6	0.2	96.7	(80.9, 99.8)
By HPV Type										
HPV 31-Related	5,308	0	16,744.4	0.0	5,252	7	16,560.7	0.0	100	(40.1, 100)
HPV 33-Related	5,624	0	17,771.4	0.0	5,628	7	17,803.0	0.0	100	(39.3, 100)
HPV 45-Related	5,724	0	18,102.7	0.0	5,724	2	18,079.2	0.0	100	(-246.8, 100)
HPV 52-Related	5,320	0	16,777.1	0.0	5,216	11	16,473.6	0.1	100	(67.3, 100)
HPV 58-Related	5,361	1	16,902.7	0.0	5,340	6	16,842.4	0.0	83.4	(-23.9, 99.3)

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 11-1; Results have been verified by the reviewer.

A summary of VE estimates against the primary efficacy endpoint in other analysis populations is provided in Table 13. The prophylactic efficacy can be seen in the VE result among the HPV-Naïve Type-Specific (HNTS) populations. In the HNTS population, subjects were naïve to the relevant HPV type at the time of administration of dose 1 of the vaccine. Six subjects in the 9vHPV group and 42 subjects in the qHPV group became cases. The vaccine efficacy was 85.7% with 95% CI of (68.4%, 94.1%).

On the other hand, the therapeutic efficacy of the 9vHPV vaccine in the S1P0, S0P1, and S1P1 analysis populations, where the subjects were HPV sero- or PCR positive at Day 1, was not evident, i.e., the lower limits of 95% CIs of the VEs were below zero.

In the FAS analysis population, which was comprised of all subjects who received at least one dose of the study vaccine, and a mixture of subjects who may or may not be HPV-naïve at the start of the vaccinations, the risk reduction estimate was observed at 16.5% with 95% CI of (-5.8%, 34.4%). The lowered risk reduction, compared to VE observed in the PPE population, was due to the low efficacy in the HPV-non-naïve subgroup. The applicant also performed N-weighted analysis, where the risk reduction was pooled based on the number of subjects in the subpopulations who were either ALL-HPV-naïve or not ALL-HPV-naïve. The N-weighted average of risk reduction is 80.1% (95% CI: 31.9% to 94.2%).

Table 13: Analysis of Efficacy against HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer in Secondary Analysis Populations

	9vHPV	9vHPV	9vHPV	9vHPV	qHPV	qHPV	qHPV	qHPV	
Analysis Population	**n**	**# Cases**	**Person-Years at Risk**	**Incidence Rate per 100 Person-Years**	**n**	**# Cases**	**Person-Years at Risk**	**Incidence Rate per 100 Person-Years**	**VE or Risk Reduction (95% CI) (%)**
FAS	7,024	129	24,866.4	0.5	7,022	155	24,936.6	0.6	16.5 (-5.8, 34.4)
HN-TS	6,873	6	24,659.4	0.0	6,866	42	24,668.0	0.2	85.7 (68.4, 94.1)
S1P0	1,153	1	4,152.0	0.0	1,146	3	4,155.7	0.1	66.6 (-202.5, 98.7)
S0P1	849	71	2,860.5	2.5	865	68	2,926.4	2.3	-6.8 (-51.2, 24.0)
S1P1	425	56	1,425.6	3.9	395	45	1,334.3	3.4	-16.5 (-75.7, 22.7)

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 11-45

Immunogenicity

Dose-Ranging Substudy

Two versions of the serology assay were used for the dose-ranging substudy. The pre-validated version of the HPV-9 cLIA assay was used earlier for all 9vHPV dose groups and the qHPV group. The Day 1 serology samples were retested from the mid-dose 9vHPV vaccine group and the qHPV vaccine group using the validated version of the HPV-9 cLIA assay. The GMTs at Day 1, Month 3, and Month 7 for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 for all vaccination groups are presented in Table 14. The

GMTs for HPV types contained in the vaccine increased substantially following the 2nd and 3rd vaccinations in both the qHPV vaccine group and the 9vHPV vaccine groups.

Table 14: Summary of Anti-HPV cLIA Geometric Mean Titers by Vaccination Group (Per-Protocol Immunogenicity Population - Dose-Ranging Substudy)

Assay (cLIA) Time Point	Low-Dose 9vHPV (N=312)	Low-Dose 9vHPV (N=312)	Mid-Dose 9vHPV (N=307)	Mid-Dose 9vHPV (N=307)	High-Dose 9vHPV (N=310)	High-Dose 9vHPV (N=310)	qHPV (N=310)	qHPV (N=310)
	n	GMT (mMU/mL)	n	GMT (mMU/mL)	n	GMT (mMU/mL)	n	GMT (mMU/mL)
Anti-HPV 6								
Day 1	200	< 10	186	< 16	207	< 10	196	< 16
Month 03	198	480.7	184	550.2	204	574.1	192	553.3
Month 07	200	598.3	186	673.1	207	689.0	196	542.1
Anti-HPV 11								
Day 1	200	< 7	186	< 6	207	< 7	196	< 6
Month 03	198	508.9	184	543.7	204	504.5	192	631.7
Month 07	200	571.3	186	549.6	207	564.7	196	660.6
Anti-HPV 16								
Day 1	198	< 9	205	< 12	194	< 9	201	< 12
Month 03	196	1,350.0	201	1,432.7	191	1,602.7	197	1,524.0
Month 07	198	1,874.6	205	2,310.9	194	2,422.4	201	1,847.9
Anti-HPV 18								
Day 1	218	< 15	229	< 8	233	< 15	223	< 8
Month 03	215	322.1	225	422.4	231	448.4	219	353.6
Month 07	218	603.8	229	785.2	233	788.8	223	635.5
Anti-HPV 31								
Day 1	212	< 6	217	< 4	221	< 6	212	< 4
Month 03	209	311.8	212	323.5	218	337.4	208	8.0
Month 07	212	585.7	217	545.0	221	599.4	212	8.0
Anti-HPV 33								
Day 1	230	< 4	239	< 4	230	< 4	224	< 4
Month 03	227	175.8	234	164.8	228	177.5	220	< 4
Month 07	230	293.9	239	296.0	230	330.0	224	< 4
Anti-HPV 45								
Day 1	229	< 4	239	< 3	237	< 4	225	< 3
Month 03	226	109.3	235	112.7	234	116.3	221	< 4
Month 07	229	235.5	239	225.9	237	250.2	225	< 4
Anti-HPV 52								
Day 1	200	< 2	215	< 3	213	< 2	12	< 3
Month 03	198	192.6	211	201.5	211	219.2	208	< 2
Month 07	200	319.6	215	351.2	213	406.7	212	< 2
Anti-HPV 58								
Day 1	222	< 3	231	< 4	223	< 3	210	< 4
Month 03	219	206.4	226	194.6	221	234.7	206	4.0
Month 07	222	369.5	231	371.5	223	444.1	210	<3

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 11-90

A statistical analysis was conducted (at a multiplicity-adjusted [due to the dose-selection interim analysis] 1-sided α=0.0247 level) to assess whether or not: Anti-HPV 6, 11, 16 and 18 cLIA GMTs at 4 weeks post-dose 3 in subjects vaccinated with selected 9vHPV vaccine were non-inferior to anti-HPV 6, 11, 16 and 18 cLIA GMTs at 4 weeks post-dose in subjects vaccinated with qHPV vaccine. As a result, the GMT ratios and corresponding 95.06% CIs were 1.24 (1.03, 1.50), 0.83 (0.71, 0.98), 1.25 (1.02, 1.53), 1.24 (1.02, 1.50) for anti-HPV 6, 11, 16, and 18, respectively. Because the lower bounds were above 0.5, the non-inferiority criteria were met.

Immunogenicity Substudy
Table 15 presents the results of the per-protocol analysis of non-inferiority comparing Month 7 cLIA GMTs between subjects who received the mid-dose 9vHPV vaccine and subjects who received qHPV vaccine. The lower bounds of the 95% CIs for the fold-differences in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs (9vHPV vaccine/qHPV vaccine) were above 0.67. Therefore, the non-inferiority criteria were met.

Table 15: Non-inferiority Comparisons of Month 7 HPV cLIA Geometric Mean Titers (HPV-types 6, 11, 16 and 18) Between Subjects Who Received 9vHPV Vaccine and Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population - Immunogenicity Substudy)

	9vHPV (N = 6,792)	9vHPV (N = 6,792)	qHPV (N=6,795)	qHPV (N=6,795)		
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	Estimated Fold Difference 9vHPV / qHPV (95% CI)	p-Value for Non-inferiority
Anti-HPV 6	3,993	893.1	3,975	875.2	1.02 (0.99, 1.06)	<0.001
Anti-HPV 11	3,995	666.3	3,982	830.0	0.80 (0.77, 0.83)	<0.001
Anti-HPV 16	4,032	3,131.1	4,062	3,156.6	0.99 (0.96, 1.03)	<0.001
Anti-HPV 18	4,539	804.6	4,541	678.7	1.19 (1.14, 1.23)	<0.001

Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 11-95. Results have been verified by the reviewer.

6.1.11.2 Analyses of Secondary Endpoints

A summary of VEs (or risk reductions) with regard to a series of secondary or exploratory efficacy endpoints related to HPV types 31/33/45/52/58 is presented in Table 16 for the PPE analysis population. The efficacy endpoints summarized in the tables include:

- HPV 31/33/45/52/58-related cervical, vulvar, or vaginal diseases (Secondary #4)
- HPV 31/33/45/52/58-related persistent infection of ≥ 6 months (Secondary #1)
- HPV 31/33/45/52/58-related persistent infection of ≥ 12 months (Exploratory #1)
- HPV 31/33/45/52/58-related Pap test abnormalities (Exploratory #8)
- HPV 31/33/45/52/58-related cervical and external genital procedures and cervical definitive therapy (Exploratory #9)

The 9vHPV vaccine was highly efficacious in reducing the incidences of these composite HPV 31/33/45/52/58-related endpoints. The point estimates of VE were ≥90%. The results for the HNTS population were consistent with those for the PPE population, with point estimates of VE ≥ 80%.

Table 16: Vaccine Efficacy against the Secondary and Exploratory Efficacy Endpoints Related (or Possibly Related) to HPV Types 31/33/45/52/58 in the PPE Population

	9vHPV	9vHPV	9vHPV	9vHPV	qHPV	qHPV	qHPV	qHPV	
HPV 31/33/45/52/58-Related Disease Endpoint	**n**	**# Cases**	**Person-Years at Risk**	**Incidence Rate per 100 Person-Years**	**n**	**# Cases**	**Person-Years at Risk**	**Incidence Rate per 100 Person-Years**	**VE or Risk Reduction (95% CI) (%)**
Disease	6,016	3	19,002.1	0.0	6,017	103	18,886.8	0.5	97.1 (91.8, 99.2)
Persistent infection ≥ 6 Months	5,939	35	16, 561.4	0.2	5,953	810	15,451.6	5.2	96.0 (94.4, 97.2)
Persistent Infection ≥12 Months	5,939	21	16,580.5	0.1	5,953	544	15,761.9	3.5	96.3 (94.4, 97.7)
Pap Test Abnormality	5,881	35	16,423.2	0.2	5,882	462	15,999.7	2.9	92.6 (89.7, 94.8)
Cervical or External Genital Biopsy	6,016	7	19,000.8	0.0	6,017	222	18,719.8	1.2	96.9 (93.6, 98.6)
Cervical Definitive Therapy	6,012	4	17,977.8	0.0	6,014	32	17,979.2	0.2	87.5 (65.7, 96.0)

Source: Original BLA 125508/0; Clinical Study Report V503-001, Tables 11-3, 11-5, 11-6, and 11-8.

6.1.11.3 Subpopulation Analyses

A summary of efficacy results regarding two HPV 31/33/45/52/58-Related efficacy endpoints by age, race, and study region for the PPE population is provided in Table 17. There was no apparent trend in the efficacy estimates across different categories of subgroups.

Table 17: Efficacy Results against HPV 31/33/45/52/58-Related Endpoints by Age, Race, and Demographic Region Per-Protocol Efficacy Population

Subgroup	CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer Efficacy (%) (95% CI)	Persistent Infection ≥6 Months (±1 Month Visit Window) Efficacy (%) (95% CI)
All Subjects	96.7 (80.9, 99.8)	96.0 (94.4, 97.2)
Age		
≤20 yrs.	100 (79.8, 100)	95.9 (93.4, 97.8)
≥21 yrs	91.1 (47.4, 99.6)	96.0(93.8, 97.6)
Race		
Asian	100 (≤ -999, 100)	95.8 (88.0, 98.9)
Black	NA (no cases)	97.3 (84.3, 99.9)
White	100 (82.9, 100)	97.4 (95.4, 98.5)
Other	87.3 (19.0, 99.4)	93.7 (90.0, 96.2)
Region		
Asia-Pacific	NA (no cases)	94.2 (84.9, 98.1)
Europe	100 (69.7, 100)	97.1 (94.5, 98.8)
Latin America	90.9 (46.2, 99.6)	94.8 (92.0, 96.9)
North America	100 (38.3, 100)	97.8 (93.7, 99.4)

Source: Original BLA 125508/0; Clinical Study Report V503-001, Tables 11-78 and 11-82

The subgroup analysis by age, race, and study region was performed by the reviewer for the primary immunogenicity results, comparing Month 7 cLIA GMTs between subjects who received the mid-dose 9vHPV vaccine and subjects who received qHPV vaccine. The GMT ratios (9vHPV/qHPV) and the corresponding 95% CIs are presented in Table 18. The lower bounds of the 95% CIs exceeded 0.67 for all serotypes and subgroups except for anti-HPV in the black racial group.

Table 18: Immunogenicity Results by Age, Race, and Demographic Region Per-Protocol Immunogenicity Population

Subgroup	Anti-HPV 6			Anti-HPV 11			Anti-HPV 16			Anti-HPV 18		
	GMT Ratio	95% LL	95% UL	GMT Ratio	95% LL	95% UL	GMT Ratio	95% LL	95% UL	GMT Ratio	95% LL	95% UL
Age												
≤20 yrs.	1.04	0.98	1.11	0.83	0.78	0.89	0.99	0.93	1.06	1.21	1.13	1.30
≥21 yrs	1.02	0.97	1.06	0.79	0.76	0.83	0.99	0.96	1.04	1.18	1.12	1.23
Race												
Asian	1.07	0.98	1.17	0.86	0.79	0.94	1.05	0.97	1.14	1.19	1.08	1.31
Black	0.86	0.72	1.02	0.68	0.56	0.82	1.04	0.86	1.26	0.99	0.81	1.20
White	1.01	0.96	1.05	0.79	0.75	0.83	0.96	0.92	1.01	1.16	1.10	1.22
Other	1.04	0.97	1.11	0.81	0.75	0.87	1.01	0.94	1.08	1.27	1.17	1.36
Region												
Asia-Pacific	1.08	0.99	1.19	0.88	0.80	0.97	1.03	0.95	1.12	1.21	1.09	1.34
Europe	0.99	0.93	1.05	0.78	0.73	0.83	0.93	0.88	0.99	1.15	1.07	1.23
Latin America	1.06	1.00	1.12	0.82	0.77	0.87	1.03	0.97	1.09	1.25	1.17	1.33
North America	0.97	0.90	1.05	0.77	0.71	0.83	0.99	0.92	1.07	1.13	1.04	1.24

Source: Reviewer's analysis based on raw data submitted in the application.

6.1.12 Safety Analyses

Vaccine safety was reported separately for the dose-ranging substudy cohort and the efficacy substudy.

6.1.12.1 Methods

All subjects who received at least one dose of 9vHPV vaccine or qHPV vaccine were followed for safety. Each subject was observed for at least 30 minutes after each study vaccination for any untoward effects, including allergic reactions or syncope. The observation period was documented in the subject's study chart. Each subject was to record her oral temperature 4 hours after each study vaccination and then daily for 4 days on a Vaccination Report Card (VRC). All subjects were followed for adverse experiences for 15 total days (day of vaccination plus 14 calendar days) after each injection. In addition, all subjects were followed for serious adverse experiences occurring from Day 1 through Month 7 in the Dose-ranging Substudy, or Day 1 through 180 days post-dose 3 in the Efficacy Substudy, regardless of causality. The cut-off date for the safety data was April 10, 2013.

Summary

A summary of clinical adverse experiences occurring by vaccination group from Day 1 through Month 7 following any vaccination visit during the study in the dose-ranging substudy is provided in Table 19. The proportion of dose-ranging substudy subjects reporting at least one adverse experience during the 7 month follow-up was slightly higher among subjects who received one of the 3 dose formulations of 9vHPV vaccine

(92.6%, 92.4%, and 92.8% in the low-dose, mid-dose and high-dose 9vHPV vaccine cohorts, respectively) compared to those who received qHPV vaccine (90.3%). The proportion of subjects who reported at least one injection-site adverse experience was higher in the 9vHPV groups (88.1%, 89.1%, and 91.5% in the low-dose, mid-dose, and high-dose 9vHPV vaccine cohorts, respectively) compared to those who received qHPV vaccine (83.8%). The proportions of subjects who reported at least one systemic adverse experience were similar across treatment groups in the dose-ranging substudy.

Table 19: Adverse Event Summary: 001 Dose-Ranging Substudy (Vaccination and Follow-up Periods, Day 1 to Month 7)

	Low-Dose 9vHPV Vaccine		Mid-Dose 9vHPV Vaccine		High-Dose 9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	310		303		305		308	
with one or more adverse events	287	(92.6)	280	(92.4)	283	(92.8)	278	(90.3)
injection-site	273	(88.1)	270	(89.1)	279	(91.5)	258	(83.8)
non-injection-site	166	(53.5)	172	(56.8)	157	(51.5)	165	(53.6)
with no adverse event	23	(7.4)	23	(7.6)	22	(7.2)	30	(9.7)
with vaccine-related[†] adverse events	279	(90.0)	275	(90.8)	283	(92.8)	268	(87.0)
injection-site	273	(88.1)	270	(89.1)	279	(91.5)	258	(83.8)
non-injection-site	104	(33.5)	93	(30.7)	91	(29.8)	90	(29.2)
with serious adverse events	4	(1.3)	3	(1.0)	3	(1.0)	8	(2.6)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	2	(0.6)	1	(0.3)	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related adverse event	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the vaccine.
[‡] Study medication withdrawn.
Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 12-2

Similarly, a summary of clinical adverse experiences occurring by vaccination group from Day 1 through the visit cut-off date of 10-Apr-2013, by vaccination group in this substudy cohort is provided in Table 20. The proportion of subjects in the efficacy substudy cohort reporting at least one adverse experience was higher among the subjects who received 9vHPV vaccine (94.2%) compared to those who received qHPV vaccine (91.0%). The proportion of subjects in this substudy who reported at least one injection-site adverse experience (within 15 days of any vaccination) was higher among subjects who received 9vHPV vaccine (90.8%) compared to those who received qHPV vaccine (85.1%). The proportion of subjects in this substudy who reported at least one systemic adverse experience was generally comparable between the 9vHPV group (57.3%) and the qHPV group (55.9%).

Table 20: Adverse Event Summary: 001 Efficacy Substudy (Vaccination and Follow-up Periods, Day 1 through Visit Cut-Off Date)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population with follow-up	7,071		7,078	
with one or more adverse events	6,661	(94.2)	6,444	(91.0)
injection-site	6,423	(90.8)	6,024	(85.1)
non-injection-site	4,052	(57.3)	3,957	(55.9)
with no adverse event	410	(5.8)	634	(9.0)
with vaccine-related[†] adverse events	6,519	(92.2)	6,202	(87.6)
injection-site	6,422	(90.8)	6,024	(85.1)
non-injection-site	2,088	(29.5)	1,930	(27.3)
with serious adverse events	233	(3.3)	183	(2.6)
with serious vaccine-related adverse events	2	(0.0)	2	(0.0)
who died	5	(0.1)	5	(0.1)
discontinued[‡] due to an adverse event	8	(0.1)	4	(0.1)
discontinued due to a vaccine-related adverse event	5	(0.1)	3	(0.0)
discontinued due to a serious adverse event	3	(0.0)	1	(0.0)
discontinued due to a serious vaccine-related adverse event	1	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the vaccine.
[‡] Study medication withdrawn.
Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 12-4

6.1.12.3 Deaths

No subject died during the dose-ranging substudy.

At the time of the closing of the study database for the current analyses, 10 subjects (5 in the 9vHPV vaccine group and 5 in the qHPV vaccine group) had died during the efficacy substudy. In the 9vHPV vaccine group, 1 death was due to trauma, 1 was due to hypovolemic and septic shock, 1 was a sudden death, 1 was due to cancer, and 1 was due to suicide. In the qHPV vaccine group, 1 death was due to cerebral hemorrhage, 3 were due to trauma, and 1 was due to cancer. None of the deaths were considered by the investigator to be vaccine related.

Please refer to the clinical review for more details.

6.1.12.4 Nonfatal Serious Adverse Events

Dose-Ranging Substudy
Eighteen (18) subjects reported serious adverse experiences between Day 1 and Month 7 in the dose-ranging substudy (4, 3, and 3 in the low-dose, mid-dose, and high-dose 9vHPV vaccine groups, respectively, and 8 in the qHPV vaccine group). No vaccine-related serious adverse experiences or subject deaths were reported in the dose-ranging substudy. The most commonly reported serious adverse experiences were induced abortion and spontaneous abortion.

Efficacy Substudy
Approximately 2.9% (n=416) of subjects reported one or more serious adverse experiences during the safety follow-up period in the efficacy substudy (3.3% [n=233] in the 9vHPV vaccine group, 2.6% [n=183] in the qHPV vaccine group). The proportion of subjects with serious adverse experiences occurring between Day 1 and the visit cut-off

date in the efficacy substudy was low and comparable between the 9vHPV vaccine groups and the qHPV vaccine group. Most SAEs were related to pregnancy. There were 4 reports of vaccine-related serious adverse experiences: 2 in the 9vHPV vaccine group (Pyrexia and Allergy to vaccine) and 2 in the qHPV vaccine group (Headache and Hypoaesthesia).

6.1.12.5 Adverse Events of Special Interest (AESI)

Pregnancy Outcomes
Dose-ranging substudy - Table 21 presents the pregnancy outcomes in Protocol 001 database from Day 1 through Month 7 for the dose ranging-substudy. During this time frame, 33 subjects reported a total of 34 pregnancies. At the time of the closing of the study database for the current analyses, outcomes were available for 31 of the pregnancies reported (5, 3, and 10 in the low-dose, mid-dose, and high-dose 9vHPV vaccine groups, and 13 in the qHPV vaccine group). Among the 31 pregnancies with known outcomes, 17 were live births (12 vaginal deliveries and 5 by C-Section) and 14 pregnancies were terminated early (3 spontaneous abortions, 1 late fetal death, and 10 elective abortions).

Table 21: Pregnancy Outcome Summary (Day 1 Through Month 7) (All Vaccinated Subjects, Dose-Ranging Substudy)

	Low-Dose 9vHPV Vaccine (N=312)	Mid-Dose 9vHPV Vaccine (N=307)	High-Dose 9vHPV Vaccine (N=309)	qHPV Vaccine (N=308)
Subjects with pregnancies	5 (1.6)	2 (0.7)	12 (3.9)	14 (4.5)
Number of pregnancies with known outcome*	5	3	10	13
Live Births	3 (60.0)	1 (33.3)	6 (60.0)	7 (53.8)
Abnormal Infant Outcome	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Fetal Loss	2 (40.0)	2 (66.7)	4 (40.0)	6 (46. 2)
Ectopic Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spontaneous Abortion	1 (20.0)	0 (0.0)	1 (10.0)	1 (7.7)
Late Fetal Death	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Elective Abortion	1 (20.0)	2 (66.7)	2 (20.0)	5 (38.5)

**Denominator for the percentage results in the categories below.*
Source: Original BLA 125508/0; Clinical Study Report V503-001, Tables 11-3

Efficacy substudy – Table 22 presents the pregnancy outcomes in Protocol 001 database from Day 1 through the closing of the study database for the efficacy substudy cohorts. During this time frame, 16.4% (n=2321) of subjects reported one or more pregnancies (16.8% [n=1192] in the 9vHPV vaccine and 15.9% [n=1129] in the qHPV group). At the time of the closing of the study database for the current analyses, outcomes were available for 1161 pregnancies in the 9vHPV vaccine group and 1108 of pregnancies in the qHPV vaccine group. The great majority of pregnancies whose outcomes were not available at the time of the visit cut-off date were ongoing (i.e., subjects had not completed their pregnancies).

The proportions of pregnancies with known outcome resulting in live births were comparable between the 2 vaccination groups. Likewise, the proportions of pregnancies

with known outcome resulting in fetal loss were comparable between the 2 vaccination groups.

The proportions of spontaneous fetal losses (spontaneous abortions and late fetal deaths) among pregnancies that had as an outcome a live birth or non-elective pregnancy loss (i.e., spontaneous abortion or late fetal death), were 12.3% in subjects who received 9vHPV vaccine, and 14.9% in subjects who received qHPV vaccine, and therefore do not appear to differ between the 2 vaccination groups.

Table 22: Pregnancy Outcome Summary (Day 1 Through Visit Cut-Off Date) (All Vaccinated Subjects, Efficacy Substudy)

	9vHPV Vaccine (N=7092)	qHPV Vaccine (N=7093)
Subjects with pregnancies	1,192 (16.8)	1,129 (15.9)
Number of pregnancies with known outcome*	1,161	1,108
Live Births	888 (76.5)	841 (75.9)
Abnormal Infant Outcome	18 (1.6)	25 (2.3)
Fetal Loss	273 (23.5)	267 (24.1)
Ectopic Pregnancy	12 (1.0)	7 (0.6)
Spontaneous Abortion	121 (10.4)	143 (12.9)
Late Fetal Death	3 (0.3)	4 (0.4)
Elective Abortion	137 (11.8)	113 (10.2)

**Denominator for the percentage results in the categories below.*
Source: Original BLA 125508/0; Clinical Study Report V503-001, Table 12-39

Reviewer's comment:

- *The rates of spontaneous abortion observed in the study is consistent with the background rate 13-20% reported in the literature.*

Reviewer's Analysis on Spontaneous Abortion Rates in Study 001

In the pregnancy data in Study 001, the observed rate of spontaneous abortion (SAB) tended to be higher in the 9vHPV group than in the qPHV group when the estimated conception dates were within 30 days of any vaccination. Among the pregnancies where the estimated conception dates were within 30 days of any vaccination the SAB rates were 28.4% (19/67) and 12.7% (7/55) for the 9vHPV (including all low, medium, high-dose groups) and the qHPV groups, respectively. The spontaneous abortion rates by baseline demographics and characteristics are presented in Table 23 through Table 25. The rates in Latin-American countries were higher than those in the non-Latin American countries.

Table 23: Spontaneous Abortion Rates by Country

Conceive within 30 days of Vaccination?	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Treatment	**9vHPV**	**9vHPV**	**9vHPV**	**qHPV**	**qHPV**	**qHPV**	**9vHPV**	**9vHPV**	**9vHPV**	**qHPV**	**qHPV**	**qHPV**
	N	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
All Subjects	***960***	***106***	***11.0%***	***934***	***137***	***14.7%***	***67***	***19***	***28.4%***	***55***	***7***	***12.7%***
Austria	5	1	20.0%	0	N/A	N/A	0	N/A	N/A	0	N/A	N/A
Brazil	54	8	14.8%	53	8	15.1%	3	0	0.0%	4	1	25.0%
Canada	61	5	8.2%	55	9	16.4%	2	1	50.0%	2	0	0.0%
Chile	5	0	0.0%	4	1	25.0%	1	0	0.0%	1	1	100%
Columbia	173	31	17.9%	182	48	26.4%	24	7	29.2%	16	4	25.0%
Germany	1	0	0.0%	8	0	0.0%	0	N/A	N/A	0	N/A	N/A
Denmark	229	21	9.2%	208	19	9.1%	8	1	12.5%	4	0	0.0%
Hong Kong	10	0	0.0%	11	4	36.4%	0	N/A	N/A	0	N/A	N/A
Japan	19	1	5.3%	22	5	22.7%	0	N/A	N/A	1	0	0.0%
Korea, Republic of	32	5	15.6%	26	4	15.4%	1	1	100%	3	1	33.3%
Mexico	53	4	7.5%	53	2	3.8%	7	4	57.1%	3	0	0.0%
Norway	40	3	7.5%	45	8	17.8%	2	0	0.0%	0	N/A	N/A
New Zealand	6	1	16.7%	4	1	25.0%	1	0	0.0%	0	N/A	N/A
Peru	85	8	9.4%	71	7	9.9%	4	3	75.0%	0	N/A	N/A
Sweden	6	2	33.3%	5	2	40.0%	0	N/A	N/A	0	N/A	N/A
Thailand	66	3	4.5%	59	3	5.1%	7	1	14.3%	6	0	0.0%
Taiwan, Province of China	36	2	5.6%	41	2	4.9%	2	0	0.0%	2	0	0.0%
United States	79	11	13.9%	87	14	16.1%	5	1	20.0%	13	0	0.0%

Note: Restricted to pregnancies which resulted in either live birth or non-elective fetal loss (spontaneous abortion or late fetal death). N=#pregnancies; n=#spontaneous abortions.
Source: Reviewer's analysis based on raw data provided in the application.

Table 24: Spontaneous Abortion Rates by Baseline Demographics

Conceive within 30 days of Vaccination?	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Treatment	**9vHPV**	**9vHPV**	**9vHPV**	**qHPV**	**qHPV**	**qHPV**	**9vHPV**	**9vHPV**	**9vHPV**	**qHPV**	**qHPV**	**qHPV**
	N	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
All	960	106	11.0%	934	137	14.7%	67	19	28.4%	55	7	12.7%
REGION												
Asia-Pacific	169	12	7.1%	163	19	11.7%	11	2	18.2%	12	1	8.3%
Europe	281	27	9.6%	266	29	10.9%	10	1	10.0%	4	0	0.0%
Latin America	370	51	13.8%	363	66	18.2%	39	14	35.9%	24	6	25.0%
North America	140	16	11.4%	142	23	16.2%	7	2	28.6%	15	0	0.0%
REGION 2												
Latin America	370	51	13.8%	363	66	18.2%	39	14	35.9%	24	6	25.0%
Non-Latin America	590	55	9.3%	571	71	12.4%	28	5	17.9%	31	1	3.2%
RACE												
American Indian Or Alaska Native	0	N/A	N/A	1	0	0.0%	0	N/A	N/A	0	N/A	N/A
Asian	165	11	6.7%	160	19	11.9%	10	2	20.0%	12	1	8.3%
Black Or African American	38	2	5.3%	44	8	18.2%	4	1	25.0%	7	0	0.0%
Multi-Racial	302	43	14.2%	313	57	18.2%	36	14	38.9%	21	5	23.8%
Native Hawaiian Or Other Pacific Islander	1	0	0.0%	0	N/A	N/A	0	N/A	N/A	0	N/A	N/A
Unknown	3	1	33.3%	0	N/A	N/A	1	0	0.0%	0	N/A	N/A
White	451	49	10.9%	416	53	12.7%	16	2	12.5%	15	1	6.7%
RACE GROUP 2												
Multi-racial	302	43	14.2%	313	57	18.2%	36	14	38.9%	21	5	23.8%
Not multi-racial	658	63	9.6%	621	80	12.9%	31	5	16.1%	34	2	5.9%
AGE GROUP												
16-22	408	54	13.2%	419	61	14.6%	37	7	18.9%	33	5	15.2%
23-26	552	52	9.4%	515	76	14.8%	30	12	40.0%	22	2	9.1%

Note: Restricted to pregnancies which resulted in either live birth or non-elective fetal loss (spontaneous abortion or late fetal death). N=#pregnancies; n=#spontaneous abortions.
Source: Reviewer's analysis based on raw data provided in the application.

Table 25: Spontaneous Abortion Rates by Baseline Characteristics

Conceive within 30 days of Vaccination?	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Treatment	9vHPV	9vHPV	9vHPV	qHPV	qHPV	qHPV	9vHPV	9vHPV	9vHPV	qHPV	qHPV	qHPV
	N	n	%	N	n	%	N	n	%	N	n	%
HISTORY OF ABORTION												
No	800	91	11.4%	792	120	15.2%	52	13	25.0%	39	4	10.3%
Yes	160	15	9.4%	142	17	12.0%	15	6	40.0%	16	3	18.8%
Smoking status												
Current-smoker	142	19	13.4%	143	24	16.8%	17	4	23.5%	7	3	42.9%
Ex-smoker	69	7	10.1%	51	7	13.7%	5	2	40.0%	2	0	0.0%
Non-smoker	749	80	10.7%	740	106	14.3%	44	13	29.5%	46	4	8.7%
Unknown	0	N/A	N/A	0	N/A	N/A	1	0	0.0%	0	N/A	N/A
Chlamydia positive at Day 1 (Y/N)												
No	912	103	11.3%	886	133	15.0%	62	17	27.4%	55	7	12.7%
Yes	48	3	6.3%	48	4	8.3%	5	2	40.0%	0	N/A	N/A
Con. med. use NSAID												
No	813	91	11.2%	796	117	14.7%	61	16	26.2%	46	7	15.2%
Yes	147	15	10.2%	138	20	14.5%	6	3	50.0%	9	0	0.0%

Note: Restricted to pregnancies which resulted in either live birth or non-elective fetal loss (spontaneous abortion or late fetal death). N=#pregnancies; n=#spontaneous abortions.
Source: Reviewer's analysis based on raw data provided in the application.

6.1.12.6 Clinical Test Results

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

6.1.12.7 Dropouts and/or Discontinuations

Dose-ranging substudy – 3 subjects (2 subjects in the low-dose 9vHPV vaccine group and 1 subject in the mid-dose 9vHPV vaccine group) did not complete the 3-dose regimen due to nonserious clinical adverse experiences. One subject in the low-dose 9vHPV vaccine group discontinued study vaccination due to a vaccine-related nonserious adverse experience of rash.

Efficacy substudy – 12 subjects (8 from the 9vHPV vaccine group, 4 from the qHPV vaccine group) did not complete the 3-dose regimen due to serious or nonserious clinical adverse experiences. The adverse experiences of 8 of the 12 subjects (5 from the 9vHPV vaccine group, 3 from the qHPV vaccine group) were judged by the investigator to be vaccine related. One subject in the 9vHPV vaccine group discontinued study vaccination due to a vaccine-related serious adverse experience of allergy to vaccine.

6.2 Trial #2: Protocol 002

Protocol V503-002 (also referred to as 002) is entitled "*A Safety, Immunogenicity, and Manufacturing Lot Consistency Study of Multivalent HPV L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents with a Comparison to Young Women.*"

This protocol has been extended through Month 36 to assess HPV antibody persistence in preadolescent and adolescent girls and boys. Subjects enrolled in the 16-26 year-old group had their final visit at Month 12. Subjects enrolled in the 9- 15 year-old groups will continue to be followed for an additional 24 months under Study Extension 002-10.

The submitted Clinical Study Report (CSR) includes Day 1 and Month 7 immunogenicity data, and safety data collected from Day 1 through Month 12. Because Study Extension 002-10 is ongoing, immunogenicity data from Month 12 through Month 36 and post-Month 12 safety data to be collected under the extension are not included in the CSR.

6.2.1 Objectives

Primary Safety Objective:

- To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine in preadolescent and adolescent boys and girls 9 to 15 years of age and young women 16-26 years of age.

Primary Immunogenicity Objectives:

Adolescent-Adult Immunobridging Substudy

- To demonstrate that administration of the 9-valent HPV L1 VLP vaccine induces non-inferior Geometric Mean Titers (GMTs) for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 in preadolescent and adolescent girls 9 to 15 years of age compared to young women 16-26 years of age.
- To demonstrate that administration of the 9-valent HPV L1 VLP vaccine induces non-inferior GMTs for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 in preadolescent and adolescent boys 9 to 15 years of age compared to young women 16-26 years of age.

Manufacturing Lot Consistency Substudy

- To demonstrate that the Final Manufacturing Process (FMP) results in 9-valent HPV L1 VLP vaccine that induces consistent serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti- HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 responses.

6.2.2 Design Overview

Protocol 002 was a multicenter immunogenicity and safety/tolerability study with a target enrollment of approximately 2800 subjects (1800 preadolescent and adolescent girls, 600 preadolescent and adolescent boys, and 400 young women). Two immunogenicity substudies were conducted: an adult-adolescent immunobridging substudy, which was to enroll approximately 600 girls, 600 boys, and 400 young women; and a lot manufacturing

consistency substudy, which was to enroll all 1800 girls equally randomized to 3 FMP lots. The manufacturing lot consistency substudy was double-blinded (with in-house blinding procedures) with respect to FMP lot number. All subjects were followed for safety/tolerability.

6.2.3 Population

Subjects enrolled in the study were healthy preadolescent and adolescent girls and boys (9 to 15 years of age), and healthy young women (16-26 years of age).

6.2.4 Study Treatments or Agents Mandated by the Protocol

All subjects were to receive 9vHPV vaccine as a series of 0.5-mL IM injections administered at Day 1, Month 2, and Month 6. The formulation of the vaccine is 30/40/60/40/20/20/20/20/20 μg/0.5 mL.

The three final manufacturing process (FMP) lot numbers were identified by the three corresponding formulation numbers: WL00033284, WL00033286, and WL00033286. Six hundred (600) girls, 600 boys, and 400 women were assigned to Lot 1, 600 girls were assigned to Lot 2, and 600 girls were assigned to Lot 3.

Reviewer's comment: It is unclear from the protocol which formulation numbers corresponded to the Lot Numbers referred to in the study.

6.2.6 Sites and Centers

A total of 72 study sites participated in Study 002. The study sites were located in 1 country in Africa (South Africa), 4 countries in the Asia-Pacific region (India, Korea, Taiwan, and Thailand), 6 countries in Europe (Austria, Belgium, Finland, Poland, Spain, and Sweden), 5 countries in Latin America (Brazil, Chile, Colombia, Costa Rica, and Peru), and 1 country in North America (the United States). Enrollment at each study site ranged from 1 to 228 subjects.

6.2.8 Endpoints and Criteria for Study Success

<u>Adolescent-Adult Immunobridging Substudy</u>
The hypotheses in the adolescent-adult immunobridging substudy is that the 9vHPV vaccine induces non-inferior immune responses in preadolescent and adolescent girls or boys 9 to 15 years of age who are seronegative at Day 1 to the relevant HPV type compared to young women 16-26 years of age who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type, as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at 4 weeks post-dose 3.

Each vaccine component will be analyzed separately for girls and boys. The statistical criterion for non-inferiority requires that the lower bound of the two-sided 95% CI of GMT ratio [girls/boys vs. young women] be greater than 0.67 for each HPV type.

<u>Lot-Consistency Substudy</u>

Hypothesis: Three separate FMP lots of the 9vHPV vaccine induce similar immune responses, as measured by anti-HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at 4 weeks post-dose 3.

Each vaccine component will be analyzed separately. The statistical criterion for lot consistency requires that the two-sided 95% CI of the ratio of GMTs for each of the three pairs of lots [Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3] be contained entirely within the interval [0.5, 2.0] for each HPV type.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The primary hypotheses of non-inferiority of GMTs for each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be addressed by 9 one-sided tests of non-inferiority (one corresponding to each HPV type) conducted at the ≤ 0.025 level (1-sided). For each HPV type, the hypotheses to be tested are

H0: GMT1/GMT2 ≤ 0.67

Ha: GMT1/GMT2 > 0.67,

where GMT1 represents the GMTs at 4 weeks post-dose 3 in the 9-15 year-old boys or girls group and GMT2 represents the GMTs at 4 weeks post-dose 3 in the 16-26 year-old young women group. The test will be conducted using an analysis of variance (ANOVA) model with a response of log individual titers and a fixed effect for comparison group. The statistical criterion for non-inferiority requires that the lower bound of the two-sided 95% CI of GMT ratio (9-15 year-old boys vs. 16-26 year-old young women or 9-15 year-old girls vs. 16-26 year-old young women) be greater than 0.67.

The primary hypothesis regarding consistency of the 3 lots of 9vHPV vaccine with respect to the GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post-dose 3, will be addressed by 3 pairwise (Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3) comparisons for each HPV type (27 comparisons total). Each pairwise comparison will test the equivalence of the 2 lots (within 2-fold) using 2 one-sided tests at the 0.025 level. For each HPV type, the hypotheses to be tested are:

H0: GMT1/GMT2≤ 0.5 or GMT1/GMT2≥ 2.0

Ha: $0.5 <$ GMT1/GMT2 <2.0,

where GMT1 and GMT2 are the GMTs of the two HPV vaccine lots being compared. The tests will be conducted using an ANCOVA model with a response of the natural log of individual titers and fixed effects for vaccine lot and age strata. Statistical significance for the two one-sided equivalence tests for each pair of lots is established if the p-values for the hypothesis tests are each < 0.025. This corresponds to the 95% CI for the fold difference in the two lots being contained entirely within (0.5, 2.0).

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Approximately 2800 subjects were to be enrolled in the study, including approximately 1800 healthy preadolescent and adolescent girls (9 to 15 years of age), 600 healthy preadolescent and adolescent boys (9 to 15 years of age), and 400 healthy young women

(16-26 years of age). Enrollment in the study was expected to be complete approximately 7 months after the first subject had been enrolled. Preadolescent and adolescent subjects were to be enrolled within 2 age strata (9 to 12 years of age and 13 to 15 years of age, at the time of enrollment) in an approximately 2:1 ratio. All enrolled subjects were to receive a 3-dose regimen (Day 1, Month 2, and Month 6) of 9vHPV vaccine. The 1800 preadolescent and adolescent girls (9 to 15 years of age) were to be equally randomized within each age stratum to 1 of 3 different FMP lots of vaccine. Preadolescent and adolescent boys (9 to 15 years of age) and young women (16-26 years of age) were all to be assigned the same FMP lot of vaccine as one of the cohorts of girls.

The primary analysis population was the Per-Protocol Immunogenicity (PPI) population. To be included in the primary immunogenicity analysis for the HPV 6 and HPV 11 components, subjects must have been seronegative to both HPV 6 and 11 at Day 1 and (for 16-26 year-old women) must have been PCR negative to HPV 6 and 11 from Day 1 through Month 7. To be included in the primary immunogenicity analysis for the other vaccine HPV types, subjects were required to be seronegative at Day 1 and (for 16-26 year-old women) PCR negative from Day 1 through Month 7 only for the HPV type being analyzed. In addition, subjects must have received all 3 doses of the correct clinical material within acceptable day ranges and must have had at least 1 post-dose 3 serology result within acceptable day ranges. A subject who had any protocol violation that could interfere with the evaluation of the subject's immune response to the study vaccine was excluded from the primary immunogenicity analysis.

6.2.10.1.1 Demographics

Table 26 displays the demographic characteristics of subjects randomized into this study, by vaccination group. Subjects in all cohorts were within the age ranges specified in the protocol. The 9-15 year-old groups were well-balanced with respect to the baseline characteristics of age, weight, and Body Mass Index (BMI). The 16-26 year-old females were heavier and had a somewhat larger BMI than the 9-15 year-olds.

Approximately 5.4% of the subjects were from Africa, approximately 23.8% were from the Asia-Pacific region, approximately 29.2% were from Europe, approximately 20.4% were from Latin America, and approximately 21.1% were from North America. The largest race category was White (52.6%), followed by Asian (24.2%), Multi-racial (15%), and Black or African American (8%). For ethnicity, 28.7% were Hispanic or Latino and 71.3% were not Hispanic or Latino. All vaccination groups were diverse with respect to geographic region, race, and ethnicity.

The demographic characteristics of subjects who are in the PPI population for at least one HPV type were generally comparable with those of the all-randomized subject population.

Table 26: Subject Characteristics (All Randomized Population) – Study 002

	9-15 yo Females (Lot 1) n (%)	9-15 yo Females (Lot 2) n (%)	9-15 yo Females (Lot 3) n (%)	9-15 yo Males n (%)	16-26 yo Females n (%)	Total n (%)
Subjects in population	648	643	644	669	470	3,074
Male	0 (0.0)	0 (0.0)	0 (0.0)	669 (100.0)	0 (0.0)	669 (21.8)
Female	648 (100.0)	643 (100.0)	644 (100.0)	0 (0.0)	470 (100.0)	2,405 (78.2)
Age (Years)						
9 to 12 Years of Age	440 (67.9)	432 (67.2)	432 (67.1)	450 (67.3)	0 (0.0)	1,754 (57.1)
13 to 15 Years of Age	208 (32.1)	211 (32.8)	212 (32.9)	219 (32.7)	0 (0.0)	850 (27.7)
16-26 Years of Age	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	470 (100.0)	470 (15.3)
Mean	11.7	11.6	11.6	11.7	21.3	13.1
SD	1.8	1.8	1.9	1.8	2.7	4.0
Median	12.0	11.0	11.0	12.0	21.0	12.0
Range	9 to 15	9 to 15	9 to 15	9 to 15	16 to 26	9 to 26
Race						
American Indian Or Alaska native	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	4 (0.1)
Asian	150 (23.1)	141 (21.9)	139 (21.6)	186 (27.8)	128 (27.2)	744 (24.2)
Black Or African American	50 (7.7)	59 (9.2)	52 (8.1)	37 (5.5)	48 (10.2)	246 (8.0)
Multi-Racial	81 (12.5)	91 (14.2)	86 (13.4)	149 (22.3)	53 (11.3)	460 (15.0)
Native Hawaiian Or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	1 (0.2)	4 (0.1)
White	366 (56.5)	351 (54.6)	367 (57.0)	292 (43.6)	240 (51.1)	1,616 (52.6)
Ethnicity						
Hispanic Or Latino	176 (27.2)	191 (29.7)	193 (30.0)	195 (29.1)	128 (27.2)	883 (28.7)
Not Hispanic Or Latino	472 (72.8)	452 (70.3)	451 (70.0)	474 (70.9)	342 (72.8)	2,191 (71.3)
Weight						
Mean	45.4	45.3	45.1	45.4	60.0	47.5
SD	13.2	14.1	13.6	15.1	13.1	14.9
Median	43.5	43.3	43.5	42.0	58.0	45.8
Range	19.5 to 132.0	18.0 to 109.3	20.0 to 152.0	15.4 to 115.2	35.0 to 126.1	15.4 to 152.0
Body Mass Index						
Subjects with data	647	643	644	669	468	3071
Mean	19.7	19.7	20.0	19.6	22.6	20.2
SD	4.4	4.3	4.5	4.2	4.6	4.5
Median	18.9	18.8	19.2	18.6	21.6	19.3
Range	11.1 to 58.8	5.6 to 46.4	10.5 to 57.5	10.1 to 43.0	15.4 to 47.5	5.6 to 58.8
Region						
Africa	32 (4.9)	34 (5.3)	29 (4.5)	30 (4.5)	40 (8.5)	165 (5.4)
Asia-Pacific	148 (22.8)	137 (21.3)	138 (21.4)	185 (27.7)	125 (26.6)	733 (23.8)
Europe	206 (31.8)	182 (28.3)	185 (28.7)	143 (21.4)	183 (38.9)	899 (29.2)
Latin America	125 (19.3)	147 (22.9)	136 (21.1)	160 (23.9)	60 (12.8)	628 (20.4)
North America	137 (21.1)	143 (22.2)	156 (24.2)	151 (22.6)	62 (13.2)	649 (21.1)

Source: Original BLA 125508/0; Clinical Study Report V503-002, Table 10-4

6.2.10.1.3 Subject Disposition

A total of 3111 subjects were screened for inclusion in this study, 3074 were randomized, and 3066 received at least 1 vaccination. A summary of the number of subjects who were randomized, vaccinated, who completed or discontinued during the study, by vaccination group, is provided in Table 27. Among the 3074 randomized subjects, a total of 104 subjects (3.4 %) discontinued during the entire study period (Day 1 through Month 12). Most subjects who discontinued prior to Month 12 were either lost to follow-up or the subject withdrew. Only 1 subject discontinued due to a clinical adverse experience.

Table 27: Subject Disposition in Study 002

	9-15 yo Females (Lot 1) n (%)	9-15 yo Females (Lot 2) n (%)	9-15 yo Females (Lot 3) n (%)	9-15 yo Males n (%)	16-26 yo Females n (%)	Total n (%)
Subjects in population	648	643	644	669	470	3,074
Vaccinated at						
Vaccination 1	646 (99.7)	642 (99.8)	644 (100.0)	666 (99.6)	468 (99.6)	3,066 (99.7)
Vaccination 2	637 (98.3)	633 (98.4)	638 (99.1)	658 (98.4)	462 (98.3)	3,028 (98.5)
Vaccination 3	635 (98.0)	627 (97.5)	637 (98.9)	653 (97.6)	455 (96.8)	3,007 (97.8)
Study Disposition						
COMPLETED	623 (96.1)	621 (96.6)	631 (98.0)	647 (96.7)	444 (94.5)	2,966 (96.5)
DISCONTINUED	25 (3.9)	22 (3.4)	13 (2.0)	22 (3.3)	22 (4.7)	104 (3.4)
ADVERSE EVENT	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
LOST TO FOLLOW-UP	12 (1.9)	8 (1.2)	10 (1.6)	8 (1.2)	11 (2.3)	49 (1.6)
PHYSICIAN DECISION	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)
PREGNANCY	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)
PROTOCOL VIOLATION	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.1)
WITHDRAWAL BY SUBJECT	12 (1.9)	13 (2.0)	2 (0.3)	13 (1.9)	8 (1.7)	48 (1.6)
UNKNOWN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	4 (0.1)

Source: Original BLA 125508/0; Clinical Study Report V503-002, Page 5.

Table 28 provides the subject accounting for the PPI analysis population by vaccination group. The most common reasons subjects were excluded from the PPI population were: missing Month 7 serology samples/results, positive to HPV at Day 1 and/or at Month 7, vaccination 2 or 3 out of acceptable day range, received non-study vaccination, and incomplete vaccinations.

Table 28: Subject Accounting for the Immunogenicity Analysis Population by Vaccination Group (All Randomized Subjects)

	9-15 yo Females (Lot 1) (N=646)	9-15 yo Females (Lot 2) (N=642)	9-15 yo Females (Lot 3) (N=644)	9-15 yo Males (N=666)	16-26 yo Females (N=468)	Total (N=3,066)
Number of Subjects who received at least 1 injection Included in PPI Population	517	536	544	559	333	2,489
HPV 16	529	542	556	569	329	2,525
HPV 18	531	547	563	567	345	2,553
HPV 31	522	542	553	564	340	2,521
HPV 33	534	543	560	567	354	2,558
HPV 45	534	548	565	570	368	2,585
HPV 52	533	547	562	568	337	2,547
HPV 58	531	539	560	566	332	2,528

Source: Original BLA 125508/0; Clinical Study Report V503-002, Table 10-2.

6.2.11 Immunobridging and Lot Consistency Analyses

The primary analysis population was the PPI population. The immunobridging and lot consistency analyses results are described in the following subsections.

6.2.11.1 Analyses of Primary Endpoint(s)

Immunobridging Analyses

Table 29 displays the statistical analysis of non-inferiority of Month 7 HPV cLIA geometric mean titers (GMTs) comparing 9-15 year-old girls or boys to 16-26 year-old young women for each vaccine HPV type in the PPI population. The table displays the GMTs for each group, along with the ratios in GMTs (9-15 year-old girls or boys divided by 16-26 year-old young women), and the 95% CI on the fold difference. For each HPV type, the statistical criterion for success required that the lower confidence bound exceed 0.67. Therefore, the criterion was met, supporting the conclusion that GMTs in both 9-15 year-old girls and boys are non-inferior to those in 16-26 year-old young women. Numerically, the GMT ratios for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 ranged from 1.83 to 2.62, with related lower bound of confidence intervals exceeding 1.

Table 29: Statistical Analysis of Non-inferiority of Month 7 HPV cLIA Geometric Mean Titers Comparing 9-15 Year-Old Females and Males (Lot 1) vs. 16-26 Year-Old Females (Lot 1) (Per-Protocol Immunogenicity Population)

	Female 9-15 yo	Female 9-15 yo	Male 9-15 yo	Male 9-15 yo	Female 16-26 yo	Female 16-26 yo	Female 9-15 yo vs Female 16-26 yo	Male 9-15 yo vs Female 16-26 yo
Assay (cLIA)	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**	**GMT Ratio (95%CI)**	**GMT Ratio (95%CI)**
Anti-HPV 6	517	1,715.4	559	2,084.7	328	900.8	1.90 (1.70, 2.14)	2.31 (2.07, 2.59)
Anti-HPV 11	517	1,295.1	559	1,487.1	332	706.6	1.83 (1.63, 2.06)	2.10 (1.88, 2.36)
Anti-HPV 16	529	6,979.8	569	8,628.9	329	3,522.6	1.98 (1.77, 2.22)	2.45 (2.19, 2.74)
Anti-HPV 18	531	2,153.7	567	2,822.8	345	882.7	2.44 (2.13, 2.80)	3.20 (2.80, 3.65)
Anti-HPV 31	522	1,891.6	564	2,221.2	340	753.9	2.51 (2.21, 2.85)	2.95 (2.60, 3.34)
Anti-HPV 33	534	980.4	567	1,198.7	354	466.8	2.10 (1.87, 2.36)	2.57 (2.29, 2.88)
Anti-HPV 45	534	714.4	570	907.0	368	272.2	2.62 (2.27, 3.03)	3.33 (2.89, 3.84)
Anti-HPV 52	533	932.9	568	1,037.8	337	419.6	2.22 (1.97, 2.51)	2.47 (2.19, 2.79)
Anti-HPV 58	531	1,286.7	566	1,567.7	332	590.5	2.18 (1.93, 2.45)	2.66 (2.37, 2.98)

Source: Original BLA 125508/0; Clinical Study Report V503-002, Tables 11-5 and 11-6.

Table 30 displays the results of type-specific Month 7 GMT comparisons among subjects randomized to the 3 manufacturing lots of 9vHPV vaccine in the PPI population. For each comparison, the lower bound of the 95% CI of GMT ratio between the comparison lots was greater than 0.5 and the upper bound was less than 2.0. Therefore, equivalence can be concluded for all 3 pairwise comparisons for each vaccine HPV type. Overall, for all HPV vaccine types, the Month 7 anti-HPV GMT responses from the 3 manufacturing lots of 9vHPV vaccine were consistent.

Table 30 Statistical Analysis of Equivalence of Geometric Mean Titers at Month 7 Comparing 9-Valent HPV Vaccine Consistency Lots 1, 2, and 3 (Per Protocol Immunogenicity Population)

		Group A	Group A	Group A	Group B	Group B	Group B	
Assay (cLIA)	**Group A vs. Group B**	**N**	**n**	**GMT***	**N**	**n**	**GMT***	**GMT Ratio (95% CI)**
Anti-HPV 6	Lot 1 vs. Lot 2	646	517	1,603.6	642	536	1,645.8	0.97 (0.88, 1.08)
Anti-HPV 6	Lot 1 vs. Lot 3	646	517	1,603.6	644	544	1,550.0	1.03 (0.93, 1.16)
Anti-HPV 6	Lot 2 vs. Lot 3	642	536	1,645.8	644	544	1,550.0	1.06 (0.95, 1.19)
Anti-HPV 11	Lot 1 vs. Lot 2	646	517	1,221.9	642	536	1,223.2	1.00 (0.90, 1.11)
Anti-HPV 11	Lot 1 vs. Lot 3	646	517	1,221.9	644	544	1,143.6	1.07 (0.95, 1.20)
Anti-HPV 11	Lot 2 vs. Lot 3	642	536	1,223.2	644	544	1,143.6	1.07 (0.95, 1.20)
Anti-HPV 16	Lot 1 vs. Lot 2	646	529	6,465.1	642	542	6,764.7	0.96 (0.86, 1.06)
Anti-HPV 16	Lot 1 vs. Lot 3	646	529	6,465.1	644	556	6,456.5	1.00 (0.90, 1.12)
Anti-HPV 16	Lot 2 vs. Lot 3	642	542	6,764.7	644	556	6,456.5	1.05 (0.94, 1.17)
Anti-HPV 18	Lot 1 vs. Lot 2	646	531	1,976.8	642	547	1,969.5	1.00 (0.89, 1.14)
Anti-HPV 18	Lot 1 vs. Lot 3	646	531	1,976.8	644	563	1,778.3	1.11 (0.98, 1.26)
Anti-HPV 18	Lot 2 vs. Lot 3	642	547	1,969.5	644	563	1,778.3	1.11 (0.97, 1.26)
Anti-HPV 31	Lot 1 vs. Lot 2	646	522	1,742.3	642	542	1,736.2	1.00 (0.89, 1.13)
Anti-HPV 31	Lot 2 vs. Lot 3	642	542	1,736.2	644	553	1,701.7	1.02 (0.90, 1.15)
Anti-HPV 33	Lot 1 vs. Lot 2	646	534	913.6	642	543	873.0	1.05 (0.94, 1.16)
Anti-HPV 33	Lot 1 vs. Lot 3	646	534	913.6	644	560	868.6	1.05 (0.94, 1.17)
Anti-HPV 33	Lot 2 vs. Lot 3	642	543	873.0	644	560	868.6	1.01 (0.90, 1.12)
Anti-HPV 45	Lot 1 vs. Lot 2	646	534	643.3	642	548	770.3	0.84 (0.73, 0.95)
Anti-HPV 45	Lot 1 vs. Lot 3	646	534	643.3	644	565	620.8	1.04 (0.91, 1.18)
Anti-HPV 45	Lot 2 vs. Lot 3	642	548	770.3	644	565	620.8	1.24 (1.08, 1.42)
Anti-HPV 52	Lot 1 vs. Lot 2	646	533	862.7	642	547	934.1	0.92 (0.83, 1.03)
Anti-HPV 52	Lot 1 vs. Lot 3	646	533	862.7	644	562	905.4	0.95 (0.85, 1.07)
Anti-HPV 52	Lot 2 vs. Lot 3	642	547	934.1	644	562	905.4	1.03 (0.92, 1.16)
Anti-HPV 58	Lot 1 vs. Lot 2	646	531	1,197.7	642	539	1,255.5	0.95 (0.86, 1.06)
Anti-HPV 58	Lot 1 vs. Lot 3	646	531	1,197.7	644	560	1,118.3	1.07 (0.96, 1.20)
Anti-HPV 58	Lot 2 vs. Lot 3	642	539	1,255.5	644	560	1,118.3	1.12 (1.00, 1.26)

*Based on an ANCOVA model with a response of the natural log of individual titers and fixed effects for lots and age strata.
Source: Original BLA 125508/0; Clinical Study Report V503-002, Table 11-9

6.2.11.3 Subpopulation Analyses

Subgroup analyses are not performed for this study because the primary analyses have been performed based on different genders (males and females) and age groups (9-15 year olds and 16-26 year olds). Because the immune responses in the boys or girls 9 through 15 years of age were substantially higher than those among females 16 through 26 years of age, subgroup analysis by race is unlikely to provide meaningful information to the analysis for the immunobridging objective. Lot consistency analysis was performed among females 9 through 15 years of age. Given such narrowly restricted demographics in the study subjects, subgroup analysis for lot consistency is not necessary.

6.2.11.5 Exploratory and Post Hoc Analyses

The reviewer performed additional analyses on the primary endpoints excluding the subjects in the (b)(3)(b)(4)(b)(7) sites, due to a potential ethical issue at these sites. There were about 230 subjects who were enrolled in seven (b)(3)(b)(4)(b)(7) sites and excluded in the analyses. As shown in Table 31 and Table 32, the GMTs for which the (b)(3)(b)(4)(b)(7) sites are excluded are similar to those for which all sites are included. The lot consistency criteria are also met.

In conclusion, there appears to be no impact on the study conclusion regarding the immunogenicity objectives when excluding the (b)(3)(b)(4)(b)(7) sites.

Table 31: Month 7 Anti-HPV cLIA Geometric Mean Titers Excluding (b)(3)(b)(4)(b)(7) Sites (Per-Protocol Immunogenicity Population)

	Serotype	6	6	11	11	16	16	18	18	31	31	33	33	45	45	52	52	58	58
Group	**Sites**	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**
16- to 26-Year-Old Females	**All**	328	901	332	707	329	3523	345	883	340	754	354	467	368	272	337	420	332	590
16- to 26-Year-Old Females	**Excluding (b)(3)(b)(4)(b)(7) Sites**	319	889	323	697	320	3462	336	869	331	737	345	458	359	269	328	411	323	581
9- to 15-Year-Old Females (Lot 1)	**All**	517	1715	517	1295	529	6980	531	2154	522	1892	534	980	534	714	533	933	531	1287
9- to 15-Year-Old Females (Lot 1)	**Excluding (b)(3)(b)(4)(b)(7) Sites**	488	1693	488	1285	499	6874	501	2128	491	1877	503	970	503	703	502	913	501	1274
9- to 15-Year-Old Females (Lot 2)	**All**	536	1763	536	1312	542	7293	547	2134	542	1868	543	923	548	828	547	1008	539	1345
9- to 15-Year-Old Females (Lot 2)	**Excluding (b)(3)(b)(4)(b)(7) Sites**	510	1778	510	1321	516	7320	519	2157	516	1898	515	938	520	845	520	1035	511	1356
9- to 15-Year-Old Females (Lot 3)	**All**	544	1660	544	1232	556	6948	563	1967	553	1879	560	931	565	678	562	971	560	1208
9- to 15-Year-Old Females (Lot 3)	**Excluding (b)(3)(b)(4)(b)(7) Sites**	517	1683	517	1244	529	7001	536	1974	527	1865	534	943	538	673	536	976	533	1220
9- to 15-Year-Old Males	**All**	559	2085	559	1487	569	8629	567	2823	564	2221	567	1199	570	907	568	1038	566	1568
9- to 15-Year-Old Males	**Excluding (b)(3)(b)(4)(b)(7) Sites**	507	2088	507	1492	516	8669	514	2868	513	2281	514	1219	517	912	515	1067	514	1602

Source: Reviewer's analysis based on raw data provided by the applicant.

Table 32: Lot-Consistency Comparisons of Month 7 Anti-HPV cLIA Excluding (b)(3)(b)(4)(b)(7) **Sites**

	Lot1 vs. Lot 2	Lot1 vs. Lot 2	Lot1 vs. Lot 2	Lot 1 vs. Lot 3	Lot 1 vs. Lot 3	Lot 1 vs. Lot 3	Lot 2 vs. Lot 3	Lot 2 vs. Lot 3	Lot 2 vs. Lot 3
Serotype	**GMT Ratio**	**95% Lower Limit**	**95% Upper Limit**	**GMT Ratio**	**95% Lower Limit**	**95% Upper Limit**	**GMT Ratio**	**95% Lower Limit**	**95% Upper Limit**
6	0.95	0.85	1.06	1.01	0.90	1.12	1.06	0.95	1.18
11	0.97	0.87	1.08	1.03	0.92	1.15	1.06	0.95	1.19
16	0.94	0.85	1.04	0.98	0.88	1.09	1.05	0.94	1.16
18	0.99	0.87	1.12	1.08	0.95	1.22	1.09	0.96	1.24
31	0.99	0.88	1.11	1.01	0.89	1.14	1.02	0.90	1.15
33	1.03	0.93	1.15	1.03	0.92	1.14	0.99	0.89	1.11
45	0.83	0.73	0.95	1.04	0.91	1.19	1.26	1.10	1.44
52	0.88	0.79	0.98	0.94	0.84	1.05	1.06	0.95	1.19
58	0.94	0.84	1.05	1.04	0.94	1.16	1.11	0.99	1.24

Source: Reviewer's analysis based on raw data provided by the applicant.

6.2.12 Safety Analyses

6.2.12.1 Methods

The following measures were collected from each study subject to assess safety: 1) temperatures (within 5 days following any vaccination); 2) all adverse events (within 14 days following any vaccination); 3) all serious adverse experiences (SAEs) that occurred from Days 1 through 180 following the last vaccination; 4) all SAEs that resulted in death or were determined to be related to the study vaccine that occurred at any time during the study. All subjects who received at least one injection of study vaccine and had safety follow-up data were included in the safety summary (Table 33).

Summary

The proportions of subjects reporting at least one adverse experience during the 7-month follow-up period were generally comparable among the 9-15 year-old females (86.6% the 9-15 year-old males (81.0%), and the 16-26 year-old females (85.4%).

The proportion of subjects who reported at least one injection-site adverse experience within 15 days of any vaccination was generally comparable between the 9-15 year-old females (1577/1923 [82.0%]) and the 16-26 year-old females (398/466 [85.4%]). The percentage of subjects with injection-site adverse experiences was numerically lower in the 9-15 year-old males (483/662 [73.0%]).

The proportion of subjects who reported at least one systemic adverse experience within 15 days of any vaccination was generally lower in the 9-15 year-old females (45.6%) and the 9-15 year-old males (42.9%) as compared to the 16-26 year-old females (59.0).

Table 33: Adverse Event Summary (Days 1 to 15 Following Any Vaccination Visit) (All Vaccinated Subjects)

	9- to 15-Year-Old Females n (%)	9- to 15-Year-Old Males n (%)	16- to 26-Year-Old Females n (%)
Subjects in population with follow- up with one or more	1,923	662	466
adverse events	1,663 (86.5)	533 (80.5)	418 (89.7)
injection-site	1,577 (82.0)	483 (73.0)	398 (85.4)
non-injection-site	865 (45.0)	277 (41.8)	266 (57.1)
with no adverse event	260 (13.5)	129 (19.5)	48 (10.3)
with vaccine-related[†] adverse events	1,614 (83.9)	500 (75.5)	406 (87.1)
injection-site	1,577 (82.0)	483 (73.0)	398 (85.4)
non-injection-site	401 (20.9)	144 (21.8)	121 (26.0)
with serious adverse events	3 (0.2)	5 (0.8)	2 (0.4)
with serious vaccine-related adverse events who died	0 (0.0)	1 (0.2)	1 (0.2)
discontinued[‡] due to an adverse event	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to a vaccine-related adverse event	0 (0.0)	1 (0.2)	0 (0.0)
discontinued due to a serious adverse event	0 (0.0)	1 (0.2)	0 (0.0)
discontinued due to a serious vaccine-related adverse event	0 (0.0)	1 (0.2)	0 (0.0)
	0 (0.0)	1 (0.2)	0 (0.0)

[†] Determined by the investigator to be related to the vaccine.
[‡] Study medication withdrawn.
Source: Original BLA 125508/0; Clinical Study Report V503-002, Table12-1

6.2.12.3 Deaths

No subject died during the entire course of the study.

6.2.12.4 Nonfatal Serious Adverse Events

Thirty-four (34) subjects (15 from the 9-15 year-old female cohort, 11 from the 9-15 year-old male cohort, and 8 from the 16-26 year-old female cohort) experienced nonfatal serious clinical adverse experiences (excluding events of fetal loss) during the entire study period. The most common SAEs (excluding events of fetal loss) were appendicitis and asthma among the 9-15 year-old male and female cohorts.

Two subjects (1 from the 9-15 year-old male cohort, and 1 from the 16-26 year-old female cohort) experienced SAEs that were considered by the investigator to be vaccine-related. Among the 9-15 year-old males, the 1 subject who experienced an SAE that was judged to be vaccine-related reported an asthmatic crisis. Among the 16-26 year-old females, the 1 subject who experienced an SAE that was judged to be vaccine-related reported a headache.

6.2.12.5 Adverse Events of Special Interest (AESI)

There were 8 subjects who reported events of fetal loss (1 from the 9-15 year-old cohort and 7 from the 16-26 year-old female cohort), including:

- 6 elective abortions (1 from the 9-15 year-old cohort and 5 from the 16-26 year-old female cohort)
- 1 spontaneous abortion (16-26 year-old female cohort)
- 1 ectopic pregnancy (16-26 year-old female cohort).
-

None of these events were considered by the investigator to be vaccine-related. All the events of elective abortion were due to personal decision.

6.2.12.7 Dropouts and/or Discontinuations

One subject discontinued study medication due to an adverse experience (asthmatic crisis). The adverse experience was judged by the investigator to be vaccine-related.

6.3 Trial #3: Protocol 009 (GDS01C)

Protocol V503-009 (also referred to as 009) is entitled "*A Randomized, Double-Blinded, Controlled with GARDASIL® (Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)), Phase III Clinical Trial to Study the Immunogenicity and Tolerability of V503 (9-Valent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescent and Adolescent Girls (9- to 15-year-olds).*"

The study was conducted solely in European countries and NOT under US Investigational New Drug (IND) regulation. It was sponsored and conducted by ----------(b)(4)----------, a joint venture between ---(b)(4)--- and the applicant.

Based on the study results, the applicant concluded that the 9vHPV vaccine and qHPV vaccine have generally comparable immunogenicity and safety profiles in preadolescent and adolescent girls, 9 to 15 years of age. A detailed review was not performed by the reviewer. Some key safety results will be presented in the integrated summary presented in Section 8 of this review.

6.4 Trial #4: Protocol 006

Protocol V503-006 (also referred to as 006) is entitled "*A Phase III Randomized, International, Placebo-Controlled, Double-Blind Clinical Trial to Study the Tolerability and Immunogenicity of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, Given to Females 12-26 Years of Age Who Have Previously Received GARDASIL™.*"

6.4.1 Objectives

Primary Objective: To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine in adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of qHPV .

Secondary Objective: To demonstrate that the 9-valent HPV L1 VLP vaccine is immunogenic with respect to HPV Types 31, 33, 45, 52, and 58 in adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of qHPV.

6.4.2 Design Overview

This was a randomized, double-blinded, placebo-controlled, international, multi-centered, safety/tolerability and immunogenicity study of the 9vHPV vaccine in females 12 to 26 years of age who were previously vaccinated with GARDASIL. Approximately 180 healthy females 12 to 15 years of age and 720 healthy females 16-26 years of age were to be enrolled in the study. Subjects were randomized in a 2:1 ratio to 9vHPV vaccine or placebo.

6.4.3 Population

Females between the ages of 12 years, 0 days and 26 years, 364 days on the day of enrollment, who had previously received a 3-dose regimen of qHPV and in good physical health were enrolled.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Subjects received one 0.5-mL intramuscular dose of 9vHPV vaccine at Day 1, Month 2, and Month 6. Normal saline placebo was given in the control group.

6.4.6 Sites and Centers

A total of 32 sites (10 in US and 22 in Ex-US countries) participated in this clinical study.

6.4.8 Endpoints and Criteria for Study Success

The objective was to demonstrate that 9-valent HPV L1 VLP vaccine generates acceptable immune responses in adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of GARDASIL measured by the percentage of subjects who are seropositive to each of HPV Types 31, 33, 45, 52, and 58 at 4 weeks post-dose 3.

Each vaccine component was to be analyzed separately. Acceptability is defined as the lower bound of the two-sided 95% confidence interval for the seropositivity percentage being greater than 90%. A subject was defined to be seropositive to HPV Types 6, 11, 16, or 18 if his or her anti-HPV serum cLIA level was ≥ 30, ≥ 16, ≥ 20, or ≥ 24 milli Merck Units/mL, respectively. A subject was defined to be seropositive to HPV Types 31, 33, 45, 52, or 58 if his or her anti-HPV serum cLIA level was ≥ 10, ≥ 8, ≥ 8, ≥ 8, or ≥ 8 milli Merck Units/mL, respectively.

6.4.9 Statistical Considerations & Statistical Analysis Plan

The study sample size of 600 was planned to achieve > 99% power to demonstrate the lower bound of the two-sided 95% CI of the seropositiveity percentage being greater than 90%, assuming the true seropositivity percentage is 95% and 15% of the subjects would be lost to follow-up.

The percentage of seropositivity to a given HPV type at 4 weeks post-dose 3 in the 9vHPV group was calculated. The associated 95% CI was constructed based on the exact binomial method for a single proportion proposed by Clopper and Pearson.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

The primary population for the immunogenicity analyses was based on the modified per-protocol immunogenicity population (mPPI). To be included in this population, subjects must:

- Have received all 3 vaccinations with the correct dose of the correct clinical material, and each vaccination visit must occur within acceptable day ranges
- Have provided Month 7 serology result within 21 to 49 days Post-dose 3.
- Have no other protocol violations that could interfere with the evaluation of subject's immune response to the study vaccine.

Unlike the Per-Protocol Immunogenicity (PPI) population used in other V503 studies, the mPPI population does not require subjects to be seronegative at Day 1 and PCR negative from Day 1 through Month 7, because subjects enrolled in this study have already received 3 doses of GARDASIL .

All subjects who received at least 1 study vaccination and had follow-up data were included in the primary analysis of safety. Subjects were summarized according to what clinical material they received.

6.4.10.1.1 Demographics

A total of 924 were randomized, including 618 subjects in the 9vHPV vaccine group and 306 subjects in the placebo group. Table 34 presents the demographic characteristics randomized into this study by vaccination group. The two vaccination groups were well balanced with respect to these demographic characteristics. The mean age of the subjects was 19 years. The largest race/ethnicity category was White (77.3%).

Table 34: Subject Characteristics (All Randomized Subjects): Study 006

	9vHPV vaccine n (%)	Placebo n (%)	Total n (%)
Subjects in population	618	306	924
Gender			
Female	618 (100.0)	306 (100.0)	924 (100.0)
Age (Years)			
12 to 15 Years of Age	122 (19.7)	60 (19.6)	182 (19.7)
16-26 Years of Age	496 (80.3)	246 (80.4)	742 (80.3)
Mean	19.0	18.9	19.0
SD	3.7	3.7	3.7
Median	19.0	19.0	19.0
Range	12 to 26	12 to 26	12 to 26
Race			
American Indian Or Alaska Native	1 (0.2)	0 (0.0)	1 (0.1)
Asian	40 (6.5)	14 (4.6)	54 (5.8)
Black Or African American	3 (0.5)	3 (1.0)	6 (0.6)
Multi-Racial	91 (14.7)	58 (19.0)	149 (16.1)
White	483 (78.2)	231 (75.5)	714 (77.3)
Ethnicity			
Hispanic Or Latino	128 (20.7)	68 (22.2)	196 (21.2)
Not Hispanic Or Latino	490 (79.3)	238 (77.8)	728 (78.8)
Region			
Asia-Pacific	37 (6.0)	12 (3.9)	49 (5.3)
Europe	268 (43.4)	140 (45.8)	408 (44.2)
Latin America	108 (17.5)	63 (20.6)	171 (18.5)
North America	205 (33.2)	91 (29.7)	296 (32.0)
Smoking Status			
Current smoker	32 (5.2)	12 (3.9)	44 (4.8)
Ex-smoker	6 (1.0)	12 (3.9)	18 (1.9)
Never smoked	579 (93.7)	282 (92.2)	861 (93.2)
Missing or unknown	1 (0.2)	0 (0.0)	1 (0.1)

Source: Original BLA 125508/0; Clinical Study Report V503-006, Table10-4.

6.4.10.1.3 Subject Disposition

The disposition of the subjects and subjects accounting for the primary immunogenicity analysis population is summarized in Table 35. A total of 897 (97%) subjects completed their three study vaccinations. Three subjects, all in the 9vHPV group, discontinued due to a clinical adverse experience.

Table 35: Disposition of Subjects (All Randomized Subjects): Study 006

	9vHPV vaccine (N=618) n (%)	Placebo (N=306) n (%)	Total (N=924) n (%)
Vaccinated at			
Vaccination 1	615 (99.5)	306 (100.0)	921 (99.7)
Vaccination 2	604 (97.7)	304 (99.3)	908 (98.3)
Vaccination 3	597 (96.6)	300 (98.0)	897 (97.1)
Study Disposition			
Completed	595 (96.3)	300 (98.0)	895 (96.9)
Discontinued	22 (3.6)	6 (2.0)	28 (3.0)
Adverse Event	3 (0.5)	0 (0.0)	3 (0.3)
Lost To Follow-Up	4 (0.6)	1 (0.3)	5 (0.5)
Protocol Violation	3 (0.5)	1 (0.3)	4 (0.4)
Withdrawal By Subject	12 (1.9)	4 (1.3)	16 (1.7)
Unknown	1 (0.2)	0 (0.0)	1 (0.1)
Modified PPI Population	515 (83.7)	261 (85.3)	776 (84.3)
Excluded from Modified PPI population	100 (16.3)	45 (14.7)	145 (15.7)
Key Reasons for Exclusion:			
General protocol violation	23 (3.7)	10 (3.3)	33 (3.6)
Missed at least one vaccination	21 (3.4)	6 (2.0)	27 (2.9)
Vaccination 2 or 3 out of window	31 (5.0)	15 (4.9)	46 (5.0)
Missing Month 7 serology samples/results	43 (7.0)	29 (9.5)	72 (7.8)

Source: Original BLA 125508/0; Clinical Study Report V503-006, Tables10-1 and 10-2.

6.4.11 Efficacy Analyses

Immunogenicity analyses are presented in the following subsections.

6.4.11.1 Analyses of Primary Endpoint(s)

The immunogenicity objective was listed as secondary in the protocol.

A summary by vaccination group of the geometric mean titers (GMTs) for the immune responses to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7, with associated 95% CIs is presented in Table 36. Table 37 shows that GMTs for HPV Types 6, 11, 16, and 18 increased substantially following the 1st vaccine administration in the 9vHPV vaccine group, but did not change much with further vaccine administrations. GMTs for HPV Types 31, 33, 45, 52, and 58 increased substantially following each of the 1st and 3rd vaccine administrations in the 9vHPV vaccine group, while GMTs for subjects in the placebo group remained around or below the limits of detection of the assay for HPV Types 31, 33, 45, 52 and 58.

Table 36: Summary of Anti-HPV cLIA Geometric Mean Titers by Vaccination Group (Modified Per-Protocol Immunogenicity Population†)

		9vHPV	9vHPV	9vHPV	Placebo	Placebo	Placebo
Serotype	**Visit**	**N**	**GMT**	**95% CI**	**N**	**GMT**	**95% CI**
Anti-HPV 6	Day 1	499	348.2	(320.2, 378.8)	248	372.4	(330.6, 419.6)
	Month 02	505	2,426.7	(2,254.2, 2,612.3)	245	363.4	(326.9, 404.0)
	Month 07	511	2,207.4	(2,052.7, 2,373.9)	251	323.8	(291.9, 359.2)
Anti-HPV 11	Day 1	513	253.0	(232.3, 275.6)	261	263.6	(233.8, 297.1)
	Month 02	511	2,077.8	(1,925.9, 2,241.6)	256	253.3	(227.6, 282.0)
	Month 07	515	1,824.0	(1,695.5, 1,962.2)	261	225.4	(203.4, 249.7)
Anti-HPV 16	Day 1	513	1,066.1	(973.8, 1,167.1)	261	1,103.7	(972.2, 1,253.1)
	Month 02	511	13,877.6	(12,846.3, 14,991.7)	256	1,076.1	(964.9, 1,200.1)
	Month 07	515	11,192.8	(10,393.6, 12,053.6)	261	966.9	(871.3, 1,072.9)
Anti-HPV 18	Day 1	513	154.2	(135.4, 175.5)	261	136.1	(113.4, 163.2)
	Month 02	511	2,187.9	(1,975.2, 2,423.5)	256	130.1	(112.6, 150.3)
	Month 07	515	2,285.8	(2,067.4, 2,527.3)	261	112.8	(98.0, 129.9)
Anti-HPV 31	Day 1	513	4.1	(<4, 4.5)	261	4.3	(<4, 5.0)
	Month 02	511	201.1	(180.5, 224.0)	256	4.3	(<4, 5.0)
	Month 07	515	260.0	(237.6, 284.5)	261	4.7	(4.1, 5.3)
Anti-HPV 33	Day 1	513	< 4	(<4, <4)	261	< 4	(<4, <4)
	Month 02	511	70.0	(63.2, 77.4)	256	< 4	(<4, <4)
	Month 07	515	175.2	(162.5, 188.9)	261	< 4	(<4, <4)
Anti-HPV 45	Day 1	513	< 3	(<3, <3)	261	< 3	(<3, <3)
	Month 02	511	15.1	(13.5, 16.8)	256	< 3	(<3, <3)
	Month 07	515	97.4	(89.8, 105.7)	261	< 3	(<3, <3)
Anti-HPV 52	Day 1	513	< 3	(<3, <3)	261	< 3	(<3, <3)
	Month 02	511	56.0	(51.2, 61.2)	256	< 3	(<3, <3)
	Month 07	515	264.1	(244.6, 285.1)	261	< 3	(<3, <3)
Anti-HPV 58	Day 1	513	< 4	(<4, <4)	261	< 4	(<4, <4)
	Month 02	511	83.2	(76.4, 90.5)	256	< 4	(<4, <4)
	Month 07	515	269.7	(250.8, 290.0)	261	< 4	(<4, <4)

Source: Original BLA 125508/0; Clinical Study Report V503-006, Table 11-1

The statistical criterion of acceptability required that the lower bound of the 95% CI for the proportion of subjects seroconverting be greater than 90% for HPV Types 31, 33, 45, 52, and 58. A p-value < 0.025 corresponds to a lower bound of the 2-sided 95% confidence interval of > 0.90 and supports the conclusion that the given anti-HPV seroconversion percentage is acceptable. The table shows that acceptability hypothesis of the seroconversion rates for HPV Types 31, 33, 45, 52, and 58 was met for the 9vHPV vaccine.

Table 37: Statistical Analysis of Acceptability of Anti-HPV cLIA Seropositivity Percentages for HPV-Types 31, 33, 45, 52 and 58 at Month 7 (Modified Per-Protocol Immunogenicity Population)

HPV-Type	N	# seropositive subjects	Percent	95% CI	p-Value
Anti-HPV 31	515	514	99.8%	(98.9%, 100%)	<0.001
Anti-HPV 33	515	514	99.8%	(98.9%, 100%)	<0.001
Anti-HPV 45	515	506	98.3%	(96.7%, 99.2%)	<0.001
Anti-HPV 52	515	513	99.6%	(98.6%, 100%)	<0.001
Anti-HPV 58	515	514	99.8%	(98.9%, 100%)	<0.001

Source: Original BLA 125508/0; Clinical Study Report V503-006, Table 11-3

6.4.11.3 Subpopulation Analyses

The study subjects consisted of adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of GARDASIL. Because of the high anti-HPV seropositivity rates (> 98%) in the study, subgroup analysis by age, race, or site is unlikely to provide any additional meaningful information. Therefore, subgroup analyses were not performed.

6.4.12 Safety Analyses

6.4.12.1 Methods

All subjects who received at least one dose of 9vHPV vaccine or qHPV vaccine were followed for safety. Each subject was observed for at least 30 minutes after each study vaccination for any untoward effects, including allergic reactions or syncope. The observation period was documented in the subject's study chart. Each subject was to record her oral temperature 4 hours after each study vaccination and then daily for 4 days after each study vaccination on a Vaccination Report Card (VRC). All subjects were followed for adverse experiences for 15 total days (day of vaccination plus 14 calendar days) after each injection. In addition, all subjects were followed for serious adverse experiences occurring from Day 1 through Month 7 regardless of causality.

Summary

A summary of clinical adverse experiences occurring by vaccination during the study is provided in Table 38. Most of the events occurred during the Day 1 to Day 15 vaccination period. The proportion of subjects reporting at least one adverse experience was higher among the subjects who received 9vHPV vaccine (583/608 [95.9%]) compared to those who received placebo (229/305 [75.1%]). The proportion of subjects who reported at least one injection-site adverse experience was higher among subjects who received 9vHPV vaccine (91.1%) compared to those who received placebo (43.9%). The proportion of subjects who reported at least one systemic adverse experience was slightly higher among subjects who received 9vHPV vaccine compared to those who received placebo (59.7% vs. 55.7%).

Table 38: Adverse Event Summary – Study 006 (Day 1 to End of Study) (All Vaccinated Subjects)

	9vHPV vaccine n (%)	Placebo n (%)
Subjects in population with follow-up	608	305
with one or more adverse events	583 (95.9)	229 (75.1)
injection-site	554 (91.1)	135 (44.3)
non-injection-site	374 (61.5)	177 (58.0)
with no adverse event	25 (4.1)	76 (24.9)
with vaccine-related† adverse events	566 (93.1)	175 (57.4)
injection-site	554 (91.1)	135 (44.3)
non-injection-site	186 (30.6)	79 (25.9)
with serious adverse events	3 (0.5)	3 (1.0)
with serious vaccine-related adverse events	1 (0.2)	1 (0.3)
who died	0 (0.0)	0 (0.0)
discontinued‡ due to an adverse event	3 (0.5)	0 (0.0)
discontinued due to a vaccine-related adverse event	3 (0.5)	0 (0.0)
discontinued due to a serious adverse event	0 (0.0)	0 (0.0)
discontinued due to a serious vaccine-related adverse event	0 (0.0)	0 (0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.
Source: Original BLA 125508/0; Clinical Study Report V503-006, Table 12-2

6.4.12.3 Deaths
No subject died during the course of the study.

6.4.12.4 Nonfatal Serious Adverse Events

SAEs were reported in 3 subjects in the 9vHPV vaccine group and 3 subjects in the placebo group during the entire course of the study, including 2 subjects with vaccine-related SAEs (1 subject in the 9vHPV vaccine group and 1 subject in the placebo group).

6.4.12.5 Adverse Events of Special Interest (AESI)

There was 1 subject who reported an event of fetal loss in the placebo group. This event was considered by the investigator to be not related to the vaccine. The event of elective abortion was due to personal decision.

6.4.12.6 Clinical Test Results
No routine laboratory safety tests were conducted within the context of the study.

6.4.12.7 Dropouts and/or Discontinuations
There were three subjects in the 9vHPV vaccine group (3/608 [0.5%]) who discontinued study medication due to an adverse experience.

6.5 Trial #5: Protocol 005 and Protocol 007

There were two concomitant vaccination studies submitted in the application.

Protocol V503-005 (also referred to as 005) is entitled "*Open-label, randomized, study of 9vHPV vaccine given concomitantly with Menactra™ and Adacel™ in healthy preadolescents and adolescents.*"

Protocol V503-007 (also referred to as 007) is entitled "*Open-label, randomized, study of 9vHPV vaccine given concomitantly with Repevax™ in healthy preadolescents and adolescents.*"

Note that Protocol 007 was conducted outside the US. The concomitant vaccine used, Repevax™ (a diphtheria, tetanus, polio, and pertussis vaccine), was not a US licensed vaccine. Success in this study was declared since the non-inferiority criterion was met for all HPV types contained in the 9vHPV vaccine and all antigens in the Repevax™ vaccine. Because of the regulatory status of Protocol 007, results in Protocol 007 are not reviewed in detail. However, some key safety results may be presented in the integrated summary presented in Section 8.

6.5.1 Objectives

The primary immunogenicity objectives were:

(1) To demonstrate that a first dose of the 9-valent HPV L1 VLP vaccine administered concomitantly with Menactra™ and Adacel™ induces non-inferior anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 Geometric Mean Titers (GMTs) in preadolescent and adolescent boys and girls 11 to 15 years of age compared with the administration of the 9-valent HPV L1 VLP vaccine alone.

(2) To demonstrate that Menactra™ administered concomitantly with Adacel™ and a first dose of the 9-valent HPV L1 VLP vaccine induces non-inferior immune responses with respect to seroconversion percentages to *Neisseria meningitidis* serogroups A, C, Y, and W-135 in preadolescent and adolescent boys and girls 11 to 15 years of age compared with the administration of Menactra™ concomitantly with Adacel

(3) To demonstrate that Adacel™ administered concomitantly with Menactra™ and a first dose of the 9-valent HPV L1 VLP vaccine induces non-inferior immune responses to diphtheria, tetanus, and pertussis in preadolescent and adolescent boys and girls.

6.5.2 Design Overview

This study was an open-label, randomized, multicenter, comparative study to evaluate the tolerability and immunogenicity of the concomitant administration of the first dose of the 9vHPV vaccine with Menactra™ and Adacel™ versus the administration of 9vHPV vaccine non-concomitantly with Menactra™ and Adacel™. The study was designed to enroll 1240 healthy, preadolescent, and adolescent boys and girls 11 to 15 years of age, who met the eligibility criteria, were randomized into the study and received vaccination within the context of the study. Subjects were stratified by gender (1:1 ratio) and randomly assigned to 1 of 2 vaccination groups in a 1:1 ratio. Subjects in Vaccination Group 1 (also referred to as the Concomitant Group) received the first dose of 9vHPV vaccine in the deltoid muscle of the non-dominant arm, and Menactra™ and Adacel™ were administered concomitantly at separate injection sites at least 2 inches apart in the deltoid muscle of the dominant arm on Day 1. Subjects in Vaccination Group 2 (also referred to as Non-concomitant Group) received the first dose of the 9vHPV vaccine on

Day 1 and Menactra™ and Adacel™ at Month 1. Subjects in both vaccination groups received the second dose of the 9vHPV vaccine at Month 2 and the third dose at Month 6.

6.5.3 Population

Healthy preadolescent and adolescent boys and girls 11 to 15 years of age were the target study population.

6.5.4 Study Treatments or Agents Mandated by the Protocol

Subjects received a 0.5-mL intramuscular dose of 9vHPV vaccine (30/40/60/40/20/20/20/20/20 μg HPV Types 6/11/16/18/31/33/45/52/58 L1 VLPs formulated with 500 μg of amorphous aluminum hydoxyphosphate sulfate [AAHS]) at Day 1, Month 2, and Month 6. Subjects also received a 0.5-mL dose of Menactra™ and a 0.5-mL intramuscular dose of Adacel™ either on Day 1 (Group 1, Concomitant Group) or at Month 1 (Non-concomitant Group).

6.5.6 Sites and Centers

There were 41 sites/investigators involved in the study: 34 sites in the U.S. and 7 sites in 4 countries in Latin America (Chile, Colombia, Mexico, and Peru).

6.5.7 Surveillance/Monitoring

Please refer to the clinical review.

6.5.8 Endpoints and Criteria for Study Success

Success in this study will be declared if the primary hypothesis of non-inferiority is achieved for the 9vHPV vaccine and at least one of Menactra™ and Adacel™. The first primary hypothesis will be tested at the 0.025 level (one-sided) and if met, the second primary hypothesis related to Menactra™, and hypotheses 3a and 3b related to Adacel™ will each be tested at the 0.0125 level (one-sided). A summary of the primary endpoints and the corresponding statistical success criteria is given in Table 39.

The hypotheses and corresponding statistical criteria for the primary immunogenicity objectives are described below:

(1) The anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at Week 4 post-vaccination 3 in subjects receiving a first dose of the 9-valent HPV L1 VLP vaccine concomitantly with Menactra™ and Adacel™ will be non-inferior to the GMTs of subjects receiving the 9-valent HPV L1 VLP vaccine alone.

Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of the two-sided 95% confidence interval (CI) of the GMT ratio [Concomitant Group/Non-concomitant Group] be greater than 0.5 for each HPV type.

(2) The percentages of subjects with a 4-fold or greater rise in antibody titers for *Neisseria meningitidis* serogroups A, C, Y, and W-135 one month postvaccination in subjects receiving Menactra™ concomitantly with Adacel™ and a first dose of the 9-valent HPV L1 VLP vaccine will be non-inferior to the percentages of subjects receiving Menactra™ concomitantly with Adacel™ .

Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of the two-sided 97.5% CI for the difference [Concomitant Group minus Non-concomitant Group] in percentages be greater than -10% for each Menactra™ serogroup.

(3a) The percentages of subjects who achieve the World Health Organization (WHO) defined protective anti-diphtheria and anti-tetanus titer of $\geq$ 0.1 IU/mL one month post-vaccination in subjects receiving Adacel™ concomitantly with Menactra™ and a first dose of the 9-valent HPV L1 VLP vaccine will be non-inferior to the percentages in subjects receiving Adacel™ concomitantly with Menactra.

Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of the two-sided 97.5% CI for the difference [Concomitant Group minus Non-concomitant Group] in percentages be greater than -10%.

(3b) The anti-pertussis (anti-pertussis toxin [anti-PT], anti-filamentous hemagglutinin [anti-FHA], anti-fimbrial agglutinogens [anti-FIM], anti-pertactin [anti-PRN]) GMTs one month post-vaccination in subjects receiving Adacel™ concomitantly with Menactra™ and a first dose of the 9-valent HPV L1 VLP vaccine will be non-inferior to the GMTs in subjects receiving Adacel™ concomitantly with Menactra™ .

Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of the two-sided 97.5% CI of the GMT ratio [Concomitant Group/Non-concomitant Group] be greater than 0.67 for each pertussis component.

Table 39: Summary of Primary Endpoints and Statistical Success Criteria

Antigen	Endpoint	Non-inferiority Margin	Type I Error (One-sided)
HPV type 6, 11, 16, 18, 31, 33, 45, 52, and 58 (each type is tested separately)	GMT	2-fold	0.025
Menactra Serogroup A	% ≥4-fold rise	10%	0.0125
Menactra Serogroup C	% ≥4-fold rise	10%	
Menactra Serogroup Y	% ≥4-fold rise	10%	
Menactra Serogroup W-135	% ≥4-fold rise	10%	
Diphtheria	% Titer≥0.1 IU/mL	10%	0.0125
Tetanus	% Titer≥0.1 IU/mL	10%	
Pertussis PT	GMT	1.5-fold	0.0125
Pertussis FHA	GMT	1.5-fold	
Pertussis PRN	GMT	1.5-fold	
Pertussis FIM	GMT	1.5-fold	

Source: Reviewer's summary based on information given in the CSR for Study 005.

6.5.9 Statistical Considerations & Statistical Analysis Plan

With 620 subjects per group, this study was expected to have overall power > 90% for the primary immunogenicity hypotheses, accounting for multiplicity.

The hypotheses on non-inferiority of GMTs (primary hypotheses for HPV and pertussis GMTs, and secondary hypotheses for meningococcal serogroups) were based on one-sided tests of non-inferiority comparing GMTs for each component. An ANOVA model with a response of log individual titers and fixed effects for vaccination group and gender was used. The hypotheses tested were:

H_0: $GMT_{Concomitant}/GMT_{Non\text{-}concomitant} \leq 1/\delta$ versus
H_1: $GMT_{Concomitant}/GMT_{Non\text{-}concomitant} > 1/\delta$,

where $GMT_{Concomitant}$ represents the GMT in subjects receiving a first dose of 9vHPV vaccine concomitantly with Menactra™ and Adacel™, and $GMT_{Non\text{-}concomitant}$ represents the GMT in subjects receiving 9vHPV vaccine alone (δ =2 for 9vHPV vaccine and Menactra™ components and =1.5 for pertussis). The statistical criterion for non-inferiority in these tests corresponds to the lower bound of the associated CI for the fold-difference in GMTs between the 2 groups (Concomitant Group/Non-concomitant Group) excluding a decrease of δ-fold or more (i.e., the lower bound of CI > $1/\delta$) for each component. The 95% CIs are provided for these HPV-related analyses and for the meningococcal analyses; 97.5% CI are provided for these analyses related to pertussis.

The hypotheses of non-inferiority of response rates (primary hypotheses for meningococcal serogroups, diphtheria, and tetanus, and secondary hypothesis for HPV seroconversion endpoint) were tested by one-sided tests of non-inferiority comparing proportions of responders for each component. These tests were conducted based on methods developed by Miettinen and Nurminen, stratified by gender. Cochran-Mantel-

Haenszel (CMH) weights were used for calculating the overall seroconversion percentage across the gender strata. The hypotheses tested were:

H_0: $P_{Concomitant} - P_{Non\text{-}concomitant} \leq -\delta$ (δ= 0.05 for each HPV type and δ= 0.10 for each Menactra™ versus

H_1: $P_{Concomitant} - P_{Non\text{-}concomitant} > -\delta$,

where $P_{Concomitant}$ represents the true response rate of subjects receiving a first dose of 9vHPV vaccine concomitantly with Menactra™ and Adacel™ and $P_{Non\text{-}concomitant}$ represents the true response rate of subjects receiving 9vHPV vaccine alone. Rejection of the null hypothesis in these tests corresponds to the lower bound of the associated CI for the difference in proportions between the 2 groups (Concomitant Group and Non-concomitant Group) excluding a decrease of 5 percentage points or more for each HPV type, and excluding a decrease of 10 percentage points or more for each Menactra™ and Adacel™ component. Ninety-five percent (95%) CIs are provided for these HPV-related analyses, and 97.5% CIs are provided for these analyses related to meningococcal serogroups, diphtheria, and tetanus.

6.5.10 Study Population and Disposition

6.5.10.1 Populations Enrolled/Analyzed

The primary analyses used to determine success with respect to the study primary and secondary immunogenicity hypotheses were based on the PP population. Analyses supportive of primary results from hypotheses relating to immune responses to vaccination with 9vHPV vaccine were conducted on the All Type-Specific Naïve Subjects with Serology (ANSS) Population. Analyses supportive of primary analysis results from hypotheses relating to immune response to vaccination with Menactra™ and Adacel™ were conducted on the Full Analysis Set (FAS) population.

Per-Protocol (PP) Population

For the PP analyses, evaluable subjects were those who met the inclusion criteria, were not protocol violators, and had serology and vaccinations within the specified day ranges and criteria.

All Type-Specific Naïve Subjects with Serology (ANSS) Population

A supportive immunogenicity analysis was carried out on the ANSS population for the HPV endpoints. To be included in this population, subjects must:
(1) Have received all 3 vaccinations with 9vHPV vaccine.
(2) Have provided post dose 3 serology data.
(3) Have been seronegative to the appropriate HPV type at Day 1.
(4) Have received one dose of Menactra™ and Adacel™

To be included in the ANSS population for HPV 6 and 11, subjects must have been seronegative to both HPV 6 and 11 at Day 1. To be included in the ANSS population for any other vaccine HPV type, subjects needed to be seronegative at Day 1 only for the HPV type being analyzed.

Unlike the PP population for HPV endpoints, the ANSS population was to include general protocol violators. The ANSS population was analyzed as randomized. In addition, no ranges on the timing of the vaccination were to be applied. Acceptable day range for serum samples at Month 7 was broader than in the PP population, extending from Day 1 post-dose 3 to Day 105 post-dose 3.

Full Analysis Set (FAS) Population
A randomized subject was to be excluded from the FAS population only if the subject failed to receive Menactra™ or Adacel™ and at least 1 injection of 9vHPV vaccine, or if the subject did not have data, post-injection of Menactra™ or Adacel™ related to the immune response to injection of Menactra™ or Adacel™.

The numbers of subjects included in these populations are summarized in Table 40. The proportions of subjects in the PPI for 9vHPV ranged from 81% to 87%, varying by type. The proportions of subjects in the PPI for Adacel and Menactra were 96% in the Concomitant group and 92% in the Non-concomitant group.

The most common reason for exclusion from the per-protocol immunogenicity analysis for 9vHPV vaccine was serum sample or results missing at Month 7 (n=78 and n=60 for the Concomitant Group and the Non-concomitant Group, respectively). The most common reason for exclusion from the per-protocol immunogenicity analysis for Adacel was serum sample or results missing at 4 weeks post-injection of Adacel (n=18 and n=31 for the Concomitant Group and the Non-concomitant Group, respectively).

Table 40: Summary of Subjects in the Per-Protocol Immunogenicity Populations

	Concomitant	Non-Concomitant	Total
Randomized and Received at least 1 injection	619	618	1237
Subjects included in PPI for 9vHPV Vaccine			
HPV 6/11	502 (81.1)	514 (83.2)	1,016 (82.1)
HPV 16	513 (82.9)	530 (85.8)	1,043 (84.3)
HPV 18	516 (83.4)	535 (86.6)	1,051 (85.0)
HPV 31	514 (83.0)	536 (86.7)	1,050 (84.9)
HPV 33	520 (84.0)	537 (86.9)	1,057 (85.4)
HPV 45	523 (84.5)	539 (87.2)	1,062 (85.9)
HPV 52	521 (84.2)	538 (87.1)	1,059 (85.6)
HPV 58	519 (83.8)	537 (86.9)	1,056 (85.4)
Subjects included in PPI for Adacel ™ Vaccine	595 (96.1)	566 (91.6)	1161 (93.9)
Subjects included in PPI for Menactra™ Vaccine	595 (96.1)	567 (91.7)	1162 (93.9)

Source: Original BLA 125508/0; Clinical Study Report V503-005, Table 10-2 and 10-3, and Table 1 in Section 16.2.6.

6.5.10.1.1 Demographics

Table 41 displays the demographic characteristics of subjects randomized into this study by vaccination group (Concomitant and Non-concomitant). With respect to baseline demographics, the Concomitant and Non-concomitant groups were comparable. The median age in each vaccination group at enrollment was 12.0 years. All subjects were between 11 and 15 years of age, as specified in the protocol. Boys and girls were evenly distributed within the Concomitant and Non-concomitant groups. Approximately 56% were from North America and approximately 43% from Latin America. The largest race category was White (47.4%), followed by Multi-racial (35.0%). Among two categories of ethnicity, the number of Hispanic or Latino (60.4%) was larger than the number of not Hispanic or Latino (39.6%).

Table 41: Subject Demographics in Study 005 (All Randomized Subjects)

	Concomitant	Non-Concomitant	Total
Subjects in population	621	620	1,241
Gender			
Male	310 (49.9)	310 (50.0)	620 (50.0)
Female	311 (50.1)	310 (50.0)	621 (50.0)
Age (Years)			
Mean	12.2	12.1	12.2
SD	1.4	1.3	1.4
Median	12.0	12.0	12.0
Range	11 to 15	11 to 15	11 to 15
Race			
American Indian Or Alaska Native	60 (9.7)	59 (9.5)	119 (9.6)
Asian	6 (1.0)	8 (1.3)	14 (1.1)
Black Or African American	38 (6.1)	41 (6.6)	79 (6.4)
Multi-Racial	217 (34.9)	217 (35.0)	434 (35.0)
Native Hawaiian Or Other Pacific Islander	2 (0.3)	5 (0.8)	7 (0.6)
White	298 (48.0)	290 (46.8)	588 (47.4)
Ethnicity			
Hispanic Or Latino	384 (61.8)	366 (59.0)	750 (60.4)
Not Hispanic Or Latino	237 (38.2)	254 (41.0)	491 (39.6)
Region			
North America	344 (55.4)	357 (57.6)	701 (56.5)
Latin America	277 (44.6)	263 (42.4)	540 (43.5)

Source: Original BLA 125508/0; Clinical Study Report V503-005, Table 10-5

6.5.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Overall, 51% of subjects had at least one medical condition reported at Day 1. The most common (> 5% in any one vaccination group) specific medical history conditions were seasonal allergy, attention deficit/hyperactivity disorder, asthma, and allergic rhinitis.

6.5.10.1.3 Subject Disposition

A total of 1241 subjects were randomized and 1237 received vaccination. A summary of the subject disposition is provided in Table 42. The completion rate was 94% for both treatment groups.

Table 42: Disposition of Subjects

	9vHPV Vaccine + [Menactra Adacel n (%)	9vHPV Vaccine + [Menactra Adacel - concomitant n (%)	Total n (%)
Not Randomized			13
Subjects in population	621	620	1,241
Vaccinated at			
Vaccination 1A	619 (99.7)	618 (99.7)	1,237 (99.7)
Vaccination 1B	0 (0.0)	600 (96.8)	600 (48.3)
Vaccination 2	602 (96.9)	596 (96.1)	1,198 (96.5)
Vaccination 3	587 (94.5)	589 (95.0)	1,176 (94.8)
Study Disposition			
COMPLETED	586 (94.4)	584 (94.2)	1,170 (94.3)
DISCONTINUED	35 (5.6)	36 (5.8)	71 (5.7)
ADVERSE EVENT	0 (0.0)	1 (0.2)	1 (0.1)
LOST TO FOLLOW-UP	20 (3.2)	16 (2.6)	36 (2.9)
PROTOCOL VIOLATION	0 (0.0)	1 (0.2)	1 (0.1)
WITHDRAWAL BY SUBJECT	15 (2.4)	18 (2.9)	33 (2.7)

Source: Original BLA 125508/0; Clinical Study Report V503-005, Table 10-1

6.5.11 Efficacy Analyses

Immunogenicity analyses are presented in the following subsections.

6.5.11.1 Analyses of Primary Endpoint(s)

Table 43 presents the results of the PP analysis of non-inferiority of anti-HPV responses in the group that received concomitant 9vHPV vaccine + Menactra™ and Adacel™ injections compared with the group that received non-concomitant 9vHPV vaccine + Menactra™ and Adacel™ injections one month later, with respect to GMT's for each vaccine HPV type at 4 weeks post-dose 3 (Month 7) of 9vHPV vaccine. The lower bounds of the two-sided 95% CIs exceeded the pre-specified criterion of 0.5 for all nine serotypes, indicating that non-inferiority of all anti-HPV GMT responses in the Concomitant Group relative to the Non-concomitant Group at 4 weeks post-dose 3 of 9vHPV vaccine was established. The results performed based on the ANSS population (not shown) were consistent with those observed in the PPI population. In addition, all (100%) subjects seroconverted for HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in both the Concomitant and Non-concomitant Groups. The non-inferiority criteria based on the comparison of seroconversion rates were also met (data not shown).

Table 43: Statistical Analysis of Non-Inferiority Comparing Month 7 HPV cLIA Geometric Mean Titers (HPV-types 6, 11, 16, 18, 31, 33, 45, 52, and 58) Between Concomitant vs. Non-concomitant Vaccination Group (Per-Protocol Immunogenicity Population - HPV)

	Concomitant Group	Concomitant Group	Non-Concomitant Group	Non-Concomitant Group	Concomitant/Non-Concomitant
Assay (cLIA)	**N**	**GMT**	**N**	**GMT**	**GMT Ratio (95% CI)**
Anti-HPV 6	501	2,198.7	514	2,260.7	0.97 (0.88, 1.08)
Anti-HPV 11	502	1,495.0	514	1,547.2	0.97 (0.87, 1.07)
Anti-HPV 16	513	8,882.6	530	9,027.6	0.98 (0.89, 1.09)
Anti-HPV 18	516	2,610.4	535	2,633.9	0.99 (0.88, 1.12)
Anti-HPV 31	514	2,439.4	536	2,334.3	1.04 (0.93, 1.17)
Anti-HPV 33	520	1,268.5	537	1,276.3	0.99 (0.89, 1.11)
Anti-HPV 45	523	947.8	539	863.8	1.10 (0.97, 1.25)
Anti-HPV 52	521	1,082.7	538	1,103.7	0.98 (0.88, 1.10)
Anti-HPV 58	519	1,532.8	537	1,555.1	0.99 (0.88, 1.10)

Source: Original BLA 125508/0; Clinical Study Report V503-005, Table 11-1

Table 44 presents the results of the analysis of non-inferiority of anti-diphtheria, anti-tetanus, and anti-pertussis responses in the Concomitant Group and the Non-concomitant Group at 4 weeks post vaccination with Adacel™. The non-inferiority criterion was met for each component of the vaccine.

Table 44: Non-Inferiority Test of Immune Response to Adacel™ at 4 Weeks Post Injection of Adacel™ Concomitant vs. Non-Concomitant Group (Per-Protocol Population - Adacel ™)

	Concomitant Group	Concomitant Group	Non-Concomitant Group	Non-Concomitant Group	Concomitant vs. Non-Concomitant	
Assay	**N**	**% subjects or GMT**	**N**	**% subjects or GMT**	**Difference in % or GMT Ratio (97.5% CI)**	**NI Criterion Met**
% Diphtheria titer ≥ 0.1 IU/mL	595	100%	566	100%	0.0% (-0.8%, 0.9%)	Yes
% Tetanus titer ≥ 0.1 IU/mL	594	99.8%	562	100%	-0.2% (-1.2%, 0.7%)	Yes
Anti-PT （GMT）	595	28.5	566	35.7	0.80 (0.69, 0.92)	Yes
Anti-FHA（GMT）	595	184.1	566	201.4	0.91 (0.83, 1.01)	Yes
Anti-PRN （GMT）	595	328.4	566	344.0	0.95 (0.84, 1.08)	Yes
Anti-FIM 2/3（GMT）	595	653.0	566	681.4	0.96 (0.76, 1.21)	Yes

Source: Original BLA 125508/0; Clinical Study Report V503-005, Tables 11-3 and 11-4

Table 45 presents comparison of the proportion of subjects in the PPI population with at least 4-fold rise in titer for *N. meningitidis* Serogroups A, C, W-135, and Y at one month post-vaccination with Menactra™. The results show that the lower bounds of the two-sided 97.5% CIs of the differences in proportion exceeded the pre-specified non-inferiority margin of -10% for each serogroup. Therefore, the non-inferiority criteria were met.

Table 45: Non-Inferiority Test of Percent of Subjects with ≥ 4-Fold Rise in Titer for *Neisseria meningitides* Serogroups from Day 1 to 4 Weeks Post Injection of Menactra™ Concomitant vs. Non-Concomitant Group (Per-Protocol Population - Menactra ™)

	Concomitant Group	Concomitant Group	Non-Concomitant Group	Non-Concomitant Group	Concomitant vs. Non-Concomitant	
Neisseria meningitidis	N	% subjects ≥ 4-Fold Rise	N	% subjects ≥ 4-Fold Rise	Difference in %	NI Criterion Met
Serogroup A	590	79.0	564	75.4	3.8 (-1.7, 9.3)	Yes
Serogroup C	590	92.9	566	95.1	-2.1 (-5.4, 1.1)	Yes
Serogroup W-135	589	95.6	566	97.7	-2.1 (-4.7, 0.3)	Yes
Serogroup Y	590	91.5	566	89.4	2.1 (-1.8, 6.1)	Yes

Source: Original BLA 125508/0; Clinical Study Report V503-005, Table 2 in Section 16.2.6

6.5.11.2 Analyses of Secondary Endpoints

Analyses with regard to the following secondary endpoints were also performed:

- Non-inferiority of the percent of subjects with Diphtheria titer ≥ 1.0 IU/mL
- Non-inferiority of the percent of subjects with Tetanus titer ≥ 1.0 IU/mL
- Non-inferiority of GMTs to *N. meningitides* serogroups A, C, W-135, and Y

The results support the non-inferiority conclusions that the concomitant vaccination of 9vHPV, Menactra™, and Adacel™ does not impair the immune response to any of the components in each of the vaccines. The details of the results are not presented in the review.

6.5.11.3 Subpopulation Analyses

The study was performed among adolescents 11 to 15 years of age, equally stratified between boys and girls. Since the objective of the study was to investigate whether there might be interference between the 9vHPV vaccine and other vaccines (Adacel™ and Menactra™) when administered concomitantly, subgroup analyses by gender or by race will not have adequate statistical power and therefore be unlikely to provide meaningful conclusions with regard to the non-inferiority objectives in this study. Therefore, subgroup analyses are not performed and reported for this study.

6.5.12 Safety Analyses

6.5.12.1 Methods

All subjects were observed for at least 30 minutes after each study vaccination for any untoward effects, including allergic reactions. This observation period was documented in the subject's study chart. On the Vaccination Report Card (VRC), the subject's oral temperature was recorded in the evening of the day of each study vaccination and daily for a total of 5 days for the purpose of identifying febrile events. Temperatures were to be collected at the same time of day whenever possible. Also, beginning after each study vaccination and for a total of 15 days including the day of vaccination, injection site and

systemic adverse experiences, concomitant medications, and concomitant vaccinations were recorded on the VRC. All VRC information was recorded in the Electronic Data Capture (EDC) system. In addition, serious adverse experiences were collected, regardless of causality, for the duration of the study.

Summary

All subjects who received at least one dose of 9vHPV vaccine + Menactra and Adacel were followed for safety (613 subjects in the Concomitant Group and 611 subjects in the Non-concomitant Group). Table 46 presents a summary of clinical AEs occurring by vaccination group during the study period. Vaccine-related injection-site events were observed in 86.6% of the subjects in the concomitant group and 83.3% in the non-concomitant group. The most reported symptom was pain. The proportions of subjects who reported at least one systemic (non-injection-site) AE were 56.1% in the Concomitant Group and 55.5% in the Non-concomitant Group. Overall, the rates of adverse events are comparable between the two treatment groups.

Table 46: Adverse Event Summary (Days 1 to End of study): Protocol 005

	Concomitant n (%)	Non-Concomitant n (%)	Total n (%)
Subjects in population with follow-up	613	611	1,224
with one or more adverse events	553 (90.2)	542 (88.7)	1,095 (89.5)
injection-site	531 (86.6)	509 (83.3)	1,040 (85.0)
non-injection-site	344 (56.1)	339 (55.5)	683 (55.8)
with no adverse event	60 (9.8)	69 (11.3)	129 (10.5)
with vaccine-related adverse events	538 (87.8)	522 (85.4)	1,060 (86.6)
injection-site	531 (86.6)	509 (83.3)	1,040 (85.0)
non-injection-site	168 (27.4)	168 (27.5)	336 (27.5)
with serious adverse events	5 (0.8)	5 (0.8)	10 (0.8)
with serious vaccine-related adverse events	0 (0.0)	0 (0.0)	0 (0.0)
who died	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to an adverse event	1 (0.2)	1 (0.2)	2 (0.2)
discontinued due to a vaccine-related adverse event	1 (0.2)	1 (0.2)	2 (0.2)
discontinued due to a serious adverse event discontinued	0 (0.0)	0 (0.0)	0 (0.0)
due to a serious vaccine-related adverse event	0 (0.0)	0 (0.0)	0 (0.0)

Source: Original BLA 125508/0; Clinical Study Report V503-005, Table 12-2.

6.5.12.3 Deaths

No deaths occurred during the study.

6.5.12.4 Nonfatal Serious Adverse Events

There were 11 nonfatal serious adverse events (SAEs) in 10 subjects reported during this study, all of which were considered to be not related to study vaccine by the investigators. The number of subjects with SAEs in the study was comparable in the two groups. Five events occurred in the Concomitant Group (2 Appendicitis, Seroma, Affective disorder, and Testicular torsion), and 6 occurred in the Non-concomitant Group

(Appendicitis, Depression, Gastroenteritis, Orthostatic hypotension, Bronchitis, and Dengue fever). One SAE was mild, 5 were moderate, and 4 were severe in intensity. None of the SAEs were considered to be vaccine-related by the investigators.

Reviewer's comment: It appears the applicant may have made a mistake in reporting the number of SAEs in the two treatment groups. On page 191 of the CSR, the applicant described the number of SAEs as "… 6 in the Concomitant Group and 5 in the Non-Concomitant Group." The correct counts according to Table 12-26 in the CSR should be 5 in the Concomitant group and 6 in the Non-concomitant group.

6.5.12.5 Adverse Events of Special Interest (AESI)

No pregnancies were reported in the study.

6.5.12.6 Clinical Test Results

Please refer to the clinical review.

6.5.12.7 Dropouts and/or Discontinuations

One subject (0.2%) in each group (1/613 in the Concomitant group and 1/611 in the Non-concomitant group) was discontinued due to an AE. One subject in the Concomitant group discontinued from study vaccination due to the adverse experiences of pyrexia and headache. One subject in the Non-concomitant group not only discontinued from study vaccination but also discontinued from the study altogether due to the adverse experience of pain in extremity.

7. INTEGRATED OVERVIEW OF EFFICACY

Since there was only one pivotal study (Study 001) on the efficacy of the 9vHPV vaccine, an integrated overview of efficacy is not necessary.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Please refer to the clinical review.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety of the 9vHPV vaccine was assessed in six clinical trials. The description of the studies is provided in Section 5.3. Protocols V503-005, V503-006, V503-007, and V503-009/GDS01C are complete, whereas extension phases of Protocols V503-001 and V503-002 are ongoing. The safety data included in the application for Protocol V503-001 include Day 1 through the visit cut-off date April 10, 2013; for Protocol V503-002 the

data include Day 1 through Month 12; and for the rest of the protocols, include Day 1 though the end of the study (Month 7).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

These studies collectively were conducted in female subjects 9 through 26 years of age at enrollment and male subjects 9 through 15 years of age at enrollment. Safety analyses were performed on the All-Subjects-As-Treated (ASaT) population, where subjects were administered at least one dose of 9vHPV vaccine. A total of 13,360 subjects received at least one dose of 9vHPV vaccine and 7391 subjects received at least one dose of qHPV vaccine. The demographics of these subjects who received 9vHPV vaccine are presented in Table 47. In addition, HPV serostatus at enrollment was assessed for all vaccine types in all study subjects. Among subjects 16-26 years of age who received 9vHPV vaccine in Protocols 001 and 002, 61.3% were seronegative and 52.2% were negative by both serology and PCR at baseline. Most (91%-99%) of the subjects 9 to 15 years of age were seronegative at baseline to the vaccine HPV types.

Table 47: Demographics of Subjects Who Received 9vHPV Vaccine (Protocols 001, 002, 005, 006, 007, and 009)

	9vHPV Vaccine n (%)
Subjects in population	13,360
Gender	
Male	1,809 (13.5)
Female	11,551 (86.5)
Age (Years)	
Under 9	0 (0.0)
9 to 15	5,307 (39.7)
16 to 17	301 (2.3)
18 to 26	7,752 (58.0)
Over 26	0 (0.0)
Mean (SD)	17.9 (5.3)
Median	19.0
Range	9 to 26
Race	
Asian	1,964 (14.7)
Black	575 (4.3)
Other	3,046 (22.8)
White	7,775 (58.2)
Ethnicity	
Hispanic Or Latino	4,290 (32.1)
Not Hispanic Or Latino	9,069 (67.9)
Unknown	1 (0.0)
Region	
Africa	165 (1.2)
Asia-Pacific	1,813 (13.6)
Europe	4,773 (35.7)
Latin America	3,642 (27.3)
North America	2,967 (22.2)

Source: Original BLA 125508/0.3, Module 2 Summary of Clinical Safety, Table 2.7.4:9

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

There are dissimilarities across studies due to different study population demographics and study designs, such as follow-up time. Pooling data across studies could potentially mask the results observed in a sub-population or individual studies. In addition, since Study 001 has a much larger sample size than the other studies, the results from Study 001 would have a large influence on the pooled results.

8.4 Safety Results

A summary of adverse events that occurred between Day 1 and Day 15 following any vaccination visit, as well as during the entire study period is presented in Table 48. Overall, 92.2% of subjects who received 9vHPV vaccine reported an adverse experience. Most adverse experiences were injection-site events. Few subjects reported an SAE.

Overall, 5 SAEs were determined to be related to 9vHPV vaccine. These SAEs included pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis. Few subjects (0.1%) discontinued due to an adverse experience.

Table 48 Adverse Event Summary: Subjects Who Received 9vHPV Vaccine (Protocols 001, 002, 005, 006, 007, and 009)

	Day 1- Day 15 post Vaccintaion n (%)	Entire Study Period n (%)
Subjects in population with follow-up	13,307	13,307
with one or more adverse events	12,231 (91.9)	12,270 (92.2)
injection-site	11,751 (88.3)	11,753 (88.3)
non-injection-site	7,138 (53.6)	7,324 (55.0)
with no adverse event	1,076 (8.1)	1,037 (7.8)
with vaccine-related[†] adverse events	11,956 (89.8)	11,958 (89.9)
injection-site	11,750 (88.3)	11,752 (88.3)
non-injection-site	3,736 (28.1)	3,742 (28.1)
with serious adverse events	48 (0.4)	305 (2.3)
with serious vaccine-related adverse events	5 (0.0)	5 (0.0)
who died	1 (0.0)	5 (0.0)
discontinued[‡] due to an adverse event	14 (0.1)	15 (0.1)
discontinued due to a vaccine-related adverse event	11 (0.1)	11 (0.1)
discontinued due to a serious adverse event	4 (0.0)	5 (0.0)
discontinued due to a serious vaccine-related adverse event	2 (0.0)	2 (0.0)

Source: Original BLA 125508/0, Module 2 Summary of Clinical Safety, Tables 2.7.4:12 and 2.7.4:13.

8.4.1 Deaths

There were 5 subjects, all in Study 001, who received 9vHPV vaccine who died during the study. Of the 5 deaths, one each was due to trauma (road traffic accident); completed suicide; cancer (acute lymphocytic leukemia); hypovolemic and septic shock; and sudden death. None of the deaths were considered related to the 9vHPV vaccine.

An SAE (acute promyelocytic leukemia) was reported in Protocol V503-001 from the visit cut-off date of 10 APR 2013 through the database lock date for the primary efficacy analyses for that study (26 JUL 2013). The SAE occurred in a 29-year-old Multi-racial female subject on Day 1284 post-dose 3. This subject was randomized to and received the 9vHPV vaccine group. This SAE was considered severe in intensity and lasted 6 days. The subject died as a result of the SAE. The reporting investigator considered that this event was not related to the study vaccine.

During the Protocol V503-002-10 study extension, an SAE (Sepsis) occurred in a 15-year-old Multi-racial female subject on Day 557 post-dose 3. The subject received 9vHPV vaccine. This SAE was considered severe in intensity and lasted 4 days. The subject died as a result of the SAE. The reporting investigator considered that this event was not related to the study vaccine.

8.4.2 Nonfatal Serious Adverse Events

There were 305 (2.3%) subjects who reported one or more serious adverse events during the entire study period across all six studies. Most serious adverse experiences were

related to pregnancy. Because events of fetal loss were required to be reported as serious adverse experiences, a large proportion of the serious adverse experiences were events of elective and spontaneous abortion. Among the serious adverse experiences that were not of fetal loss, appendicitis was the most frequent.

Five (5) subjects administered 9vHPV vaccine had at least one SAE that was determined to be related to 9vHPV vaccine by the investigators. These SAEs included pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis.

8.4.3 Study Dropouts/Discontinuations

The disposition of the subjects who received 9vHPV vaccine from Day 1 through Month 7 across all studies is presented in Table 49. Among the 13,360 vaccinated subjects, a total of 328 subjects (2.5%) discontinued study vaccinations during the vaccination period. Most subjects who discontinued during the vaccination period were either lost to follow-up or withdrew consent. Twelve (12) subjects withdrew early due to an adverse experience, and 5 subjects discontinued due to a protocol violation.

Table 49: Disposition of Subjects Who Received 9vHPV Vaccine (Protocols 001, 002, 005, 006, 007, and 009) (Day 1 Through Month 7)

	9vHPV Vaccine	
	n	(%)
Subjects in population	13,360	
Vaccinated at		
Vaccination 1	13,360	(100.0)
Vaccination 2	13,175	(98.6)
Vaccination 3	13,032	(97.5)
Trial Disposition		
Completed	12,915	(96.7)
Discontinued	412	(3.1)
Adverse Event	12	(0.1)
Lost To Follow-Up	201	(1.5)
Physician Decision	4	(0.0)
Pregnancy	1	(0.0)
Protocol Violation	5	(0.0)
Withdrawal By Subject	189	(1.4)
Unknown	33	(0.2)

Source: Original BLA 125508/0.3, Module 2 Summary of Clinical Safety, Table 2.7.4:8

A total of 15 subjects who received 9vHPV vaccine (0.1%) discontinued study vaccinations due to a clinical adverse experience during the entire study period. A total of 11 subjects who received 9vHPV vaccine (0.1%) discontinued due to an adverse experience determined by the investigator to be vaccine related.

Please refer to the clinical review with regard to the evaluation of the patterns of study discontinuation due to adverse events.

8.4.4 Common Adverse Events

Injections site reactions between Day 1 and Day 5 following any vaccination visit were observed in 86.7% of the subjects who received 9vHPV vaccine. The most common

injection-site adverse experiences reported were pain, swelling, and erythema. Over half (53.6%) of the subjects experienced one or more systemic adverse events within 15 days following any vaccination; 28.6% of the subjects reported one or more systemic adverse events related to vaccine. Table 50 summarizes the events where the incidence was ≥1% in one or more groups. The most common vaccine-related systemic adverse events were headache, pyrexia, nausea, dizziness, and fatigue.

Table 50: Subjects With Systemic Adverse Events by System Organ Class (Incidence ≥ 1%) - Overall and Vaccine Related Subjects Who Received 9vHPV Vaccine (Protocols 001, 002, 005, 006, 007, and 009) (Days 1 To 15 Following Any Vaccination Visit)

	Overall	Overall	Vaccine Related	Vaccine Related
	n	(%)	n	(%)
Subjects in population with follow-up	13,307		13,307	
With one or more injection site adverse events (Days 1 o 5)	7,138	(53.6)	3,736	(28.1)
with one or more systemic adverse events (Days 1 to 15)	6,169	(46.4)	9,571	(71.9)
Ear and labyrinth disorders	**133**	**(1.0)**	**34**	**(0.3)**
Gastrointestinal disorders	**2,019**	(15.2)	809	(6.1)
Abdominal pain	291	(2.2)	92	(0.7)
Abdominal pain upper	383	(2.9)	123	(0.9)
Diarrhoea	372	(2.8)	122	(0.9)
Nausea	750	(5.6)	457	(3.4)
Vomiting	292	(2.2)	104	(0.8)
General disorders and administration site conditions	**1,965**	**(14.8)**	**1,353**	**(10.2)**
Fatigue	376	(2.8)	258	(1.9)
Malaise	159	(1.2)	113	(0.8)
Pyrexia	1,200	(9.0)	883	(6.6)
Infections and infestations	**2,090**	**(15.7)**	**284**	**(2.1)**
Influenza	396	(3.0)	86	(0.6)
Nasopharyngitis	659	(5.0)	96	(0.7)
Upper respiratory tract infection	256	(1.9)	23	(0.2)
Injury, poisoning and procedural complications	**249**	**(1.9)**	**4**	**(0.0)**
Musculoskeletal and connective tissue disorders	**868**	**(6.5)**	**295**	**(2.2)**
Back pain	186	(1.4)	41	(0.3)
Myalgia	207	(1.6)	103	(0.8)
Pain in extremity	189	(1.4)	49	(0.4)
Nervous system disorders	**3,637**	(27.3)	2,099	(15.8)
Dizziness	522	(3.9)	321	(2.4)
Headache	3,230	(24.3)	1,845	(13.9)
Migraine	129	(1.0)	38	(0.3)
Reproductive system and breast	**572**	**(4.3)**	**55**	**(0.4)**
Dysmenorrhoea	343	(2.6)	22	(0.2)
Respiratory, thoracic and mediastinal disorders	**1,063**	**(8.0)**	**195**	**(1.5)**
Cough	269	(2.0)	34	(0.3)
Nasal congestion	127	(1.0)	21	(0.2)
Oropharyngeal pain	594	(4.5)	117	(0.9)
Skin and subcutaneous tissue disorders	**426**	**(3.2)**	**146**	**(1.1)**

Source: Original BLA 125508/0, Module 2 Summary of Clinical Safety, Table 2.7.4:17

8.4.5 Clinical Test Results

No clinical laboratory evaluations to assess the safety of the vaccine were performed in the conduct of the clinical trials in support of this application.

8.4.8 Adverse Events of Special Interest

Please refer to the clinical reviewer's review regarding the spontaneous abortion rates observed in the study. The majority of the pregnancies were observed in Study 001. Please refer to Section 6.1.12.5 of the review on the summary of this adverse event of interest.

8.4.9 Safety Subgroup Analysis

An adverse event summary by age and gender is provided in Table 51. It appears that the females tended to report more vaccine-related adverse events (local and systemic reactions) than the male subjects.

Table 51: Adverse Event Summary among Subjects Who Received 9vHPV Vaccine by Gender and Age Group: Entire Study Period

Gender	**Female**	**Female**	**Male**
Age	**16-26 yrs.**	**9-15 yrs.**	**9-15 yrs**
Subjects in population with follow-up	8027	3,481	1,799
with one or more adverse events	7,553 (94 .1)	3,143 (90.3)	1,574 (87.5)
injection-site	7,273 (90 .6)	3,009 (86.4)	1,471 (81.8)
non-injection-site	4,634 (57.7)	1,766 (50.7)	924 (51.4)
with no adverse event	474 (5.9)	338 (9.7)	225 (12.5)
with vaccine-related† adverse events	7,384 (92.0)	3,066 (88.1)	1,508 (83.8)
injection-site	7,272 (90.6)	3,009 (86.4)	1,471 (81.8)
non-injection-site	2,358 (29.4)	888 (25.5)	496 (27.6)
with serious adverse events	250 (3.1)	32 (0.9)	23 (1.3)
with serious vaccine-related adverse events	4 (0.0)	0 (0.0)	1 (0.1)
who died	5 (0.1)	0 (0.0)	0 (0.0)
discontinued‡ due to an adverse event	9 (0.1)	3 (0.1)	3 (0.2)
discontinued due to a vaccine-related adverse event	6 (0.1)	2 (0.1)	3 (0.2)
discontinued due to a serious adverse event	3 (0.0)	1 (0.0)	1 (0.1)
discontinued due to a serious vaccine-related adverse event	1 (0.0)	0 (0.0)	1 (0.1)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.
Source: Original BLA 125508/0, Module 2 Summary of Clinical Safety, Appendices 2.7.4:43 and 2.7.4:62.

Similarly, adverse event summaries by race in the two age groups are provided in Table 52 and Table 53 for the 16-26 year old and 9-15 year old subjects, respectively. It appears that the white subjects tended to report more vaccine-related adverse events (local and systemic reactions) than other racial groups.

Table 52: Adverse Event Summary among Subjects 16-26 Years of Age Who Received 9vHPV Vaccine by Race: Days 1 to 15 Following Any Vaccination Visit

Age	**16-26 yrs.**	**16-26 yrs.**	**16-26 yrs.**	**16-26 yrs.**
Race	**White**	**Black**	**Asian**	**Other**
Subjects in population with follow-up	4,514	291	1,185	2,037
with one or more adverse events	4,306 (95.4)	259 (89.0)	1,057 (89.2)	1,907 (93.6)
injection-site	4,192 (92.9)	239 (82.1)	1,019 (86.0)	1,823 (89.5)
non-injection-site	2,552 (56.5)	177 (60.8)	549 (46.3)	1,233 (60.5)
with no adverse event	208 (4.6)	32 (11.0)	128 (10.8)	130 (6.4)
with vaccine-related† adverse events	4,241 (94.0)	248 (85.2)	1,034 (87.3)	1,861 (91.4)
injection-site	4,191 (92.8)	239 (82.1)	1,019 (86.0)	1,823 (89.5)
non-injection-site	1,378 (30.5)	69 (23.7)	278 (23.5)	631 (31.0)
with serious adverse events	15 (0.3)	1 (0.3)	7 (0.6)	5 (0.2)
with serious vaccine-related adverse events	3 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
who died	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued‡ due to an adverse event	6 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)
discontinued due to a vaccine-related adverse event	4 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)
discontinued due to a serious adverse event	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
discontinued due to a serious vaccine-related adverse event	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.
Source: Original BLA 125508/0, Module 2 Summary of Clinical Safety, Appendices 2.7.4.80, 2.7.4.87, 2.7.4.94, and 2.7.4:101

Table 53: Adverse Event Summary among Subjects 9-15 Years of Age Who Received 9vHPV Vaccine by Race: Days 1 to 15 Following Any Vaccination Visit

Age	**9-15 yrs.**	**9-15 yrs.**	**9-15 yrs.**	**9-15 yrs.**
Race	**White**	**Black**	**Asian**	**Other**
Subjects in population with follow-up	3,230	280	769	1,001
with one or more adverse events	3,009 (93.2)	211 (75.4)	614 (79.8)	868 (86.7)
injection-site	2,881 (89.2)	196 (70.0)	588 (76.5)	813 (81.2)
non-injection-site	1,769 (54.8)	96 (34.3)	238 (30.9)	524 (52.3)
with no adverse event	221 (6.8)	69 (24.6)	155 (20.2)	133 (13.3)
with vaccine-related† adverse events	2,922 (90.5)	206 (73.6)	602 (78.3)	842 (84.1)
injection-site	2,881 (89.2)	196 (70.0)	588 (76.5)	813 (81.2)
non-injection-site	903 (28.0)	43 (15.4)	108 (14.0)	326 (32.6)
with serious adverse events	13 (0.4)	0 (0.0)	3 (0.4)	4 (0.4)
with serious vaccine-related adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued‡ due to an adverse event	4 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)
discontinued due to a vaccine-related adverse event	3 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)
discontinued due to a serious adverse event	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
discontinued due to a serious vaccine-related adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.
Source: Original BLA 125508/0, Module 2 Summary of Clinical Safety, Appendices 2.7.4.122, 2.7.4.129, 2.7.4.136, and 2.7.4:143

Reviewer's comment: The applicant did not provide adverse event summaries for different racial groups during the entire study period. Nevertheless, the observed differences are most likely to be similar when the events from the entire study period are considered, because most of the events summarized in the table were captured during the Day 1-15 period following any vaccination visit.

8.6 Safety Conclusions

Please refer to Section 10 conclusions regarding safety.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Six Phase III GARDASIL®9 clinical studies (V503-001, V503-002, V503-005, V503-006, V503-007, or V503-009/GDS01C) in female subjects 9 to 26 years of age and male subjects 9 to 15 years of age are included in this submission.

Efficacy
In the efficacy study (Study V503-001), the primary population was 16-26 year-old adolescent and young adult women who were seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type. Efficacy of 96.7% (with the lower

bound of the two-sided 95% confidence interval (CI) being 80.9%) was observed with regard to the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer, compared with GARDASIL™ (Table 12). The vaccine was also found to be efficacious (efficacy of 96%) against HPV 31-, 33-, 45-, 52-, and 58-related persistent infection of ≥ 6 or 12 months (Table 16).

Immunogenicity

The primary immunogenicity endpoint to evaluate responses to 9vHPV vaccine was Month 7 HPV Competitive Luminex Immunoassay (cLIA) Geometric Mean Titers (GMT) against HPV-types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Non-inferiority comparisons were made between age groups (boys or girls 9-15 years of age vs. women 16-26 years of age) or between vaccine groups (9vHPV vs. qHPV) using the margin of 0.67.

Among adolescent and young women 16 through 26 years of age, the non-inferiority criteria with regard to responses to anti-HPV 6, 11, 16, and 18 were met for the 9vHPV when compared with the qHPV group (Table 15).

The non-inferiority criteria were met with regard to responses to anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 when comparing girls or boys 9 through 15 years of age with young women 16-26 years of age (Table 43).

No interference was observed with GARDASIL®9 co-administered with Menactra™ and Adacel™.

Safety

Across all studies, 88% of the subjects reported at least one injection-site reaction, and about 53% reported at least one systemic reaction within 15 days of vaccination. There were 2% of the 9vHPV recipients who reported one or more serious adverse events (SAEs), the majority of which were related to pregnancy. Five of the SAEs (pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis) were determined to be related to 9vHPV vaccine by the investigators. There were 7 deaths reported, all in the 9vHPV vaccine group. None of these deaths were considered to be related to the 9vHPV vaccine by the investigators.

In a post hoc analysis, an imbalance was observed in spontaneous abortion rates between subjects who received 9vHPV and those who received qHPV (28.4% vs. 12.7%, respectively) when pregnancies were restricted to those with estimated conception dates within 30 days of any vaccination.

Please refer to the clinical review for more safety details and assessment of the clinical significance of some of the observed differences.

10.2 Conclusions and Recommendations

In conclusion, there were no major statistical issues related to the submission. Primary results were confirmed by the reviewer's independent analyses. The efficacy and immunogenicity objectives pre-specified in the studies were met and support the approval of the vaccine. The reviewer defers to the medical officers and epidemiologists on the review committee regarding the regulatory implications of the imbalance in spontaneous abortion rates noted in the above summary.