Application Type	BLA Supplement
STN	125508/153, /153.2 received on 5/6/2016
CBER Received Date	February 1, 2016
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Division / Office	OVRR/DVRPA
Clinical Reviewer (s)	Joohee Lee, M.D.
Project Manager	Bharat Khurana, Ph.D.; Laura Montague; Rebekah Wiesmann, Ph.D.
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
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	3-dose schedule: 0, 2 months, 6 months Alternative 2-dose schedule (0, (b) (4) months): for individuals 9 through 14 years of age

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 and men 9 through 26 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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TABLES

GLOSSARY

Abbreviation/Term	Definition
9vHPV vaccine	Nine-valent Human Papillomavirus vaccine
AEs	Adverse experiences
ANOVA	Analysis of variance
ANSS	All (HPV Type-specific) Naïve Subjects with Serology
ATS	All Type Specific
CI	Confidence interval
cLIA	Competitive Luminex Immunoassay
CRF	Case report form
CSR	Clinical study report
eCRF	Electronic case report form
FDA	Food and Drug Administration
FPE	First patient enrolled
GCP	Good Clinical Practice
GMR	Geometric mean ratio
GMTs	Geometric Mean Titers
HIV	Human immunodeficiency virus
HM	Heterosexual male
HPV	Human Papillomavirus
IgG	Immunoglobulin G
IM	Intramuscular
LLOQ	Lower Limit of quantitation
LMP	Last menstrual period
LOD	Limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
mMU/mL	milli-Merck Units per milliliter
MSM	Men-having-sex-with-men
PPI	Per Protocol Immunogenicity
RSD	Relative standard deviation
SAEs	Serious Adverse Experiences
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class
SUBJID	Subject identification number (a.k.a., AN)
VLP	Virus-Like Particle
VRC	Vaccination Report Card

1. EXECUTIVE SUMMARY

The applicant, Merck Sharp & Dohme Corporation, submitted the supplemental Biologics License Application (sBLA 125508/153) to seek a label change for an alternative 2-dose schedule for individuals 9 through 14 years of age 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.

Data from a Phase III GARDASIL®9 clinical study (V503-010) were submitted to support the proposed label change. In this study, immunogenicity results among preadolescents and adolescents 9 through 14 years of age in the 2-dose regimens -- 0, 6 months or 0, 12 months, -- were compared with young women 16 through 26 years of age following the approved 3-dose regimen (0, 2 months, 6 months). The pre-specified noninferiority criteria (>0.67 fold for geometric mean titer ratios and > -5% for differences in seroconversion rate) regarding the immune responses measured at four weeks post last dose via a cLIA HPV assay were met. A summary of additional findings through exploratory analyses is given in Section 10.1 of this review.

With regard to safety, vaccine report cards (VRCs) were not used in this study, given that extensive data on the three-dose regimen had already been obtained. Non-serious adverse events (AEs) occurring Day 1 to 15 following any vaccination and serious adverse events (SAEs) through 6 months following the last vaccination were collected in the study. In general, the proportion of subjects who reported at least one adverse event were higher among subjects who received the 0, 2, 6 regimen, compared to the corresponding proportion among subjects who received the 0, 6 or 0, 12 regimen. There were no deaths observed in the study as of the date of the clinical study report. There were 22 subjects reporting an SAE, but none of the SAEs were deemed to be associated with vaccination by the investigators.

Randomization between groups was not possible in this study because subjects cannot be randomized to sex/age groups. To reduce potential bias in the immunogenicity assessments, the laboratory personnel conducting HPV serology assays were blinded to age and sex of all subjects enrolled in the study. All decisions regarding the inclusion or exclusion of subjects in the per-protocol immunogenicity population based on protocol violations were made while the study team was blinded to immunogenicity results.

Conclusion and Recommendations:

There are no major statistical issues related to this submission. Primary results were confirmed by the reviewer's independent analyses. The primary immunogenicity objectives pre-specified in the study were met and, thus, the study results support approval of the license application. The reviewer defers to the other members of the review committee regarding implication of the additional observed immunogenicity findings through exploratory analyses noted in this review.

2. CLINICAL AND REGULATORY BACKGROUND

Gardasil 9 was approved on December 10, 2014 and indicated in girls and women 9 through 26 years of age, and boys 9 through 15 years of age for reduction in the incidence of HPV 6/11/16/18/31/33/45/52/58-related cervical, vulvar, vaginal, and anal cancers, and condyloma acuminate. This indication was extended to men 16 through 26 years of age on December 14, 2015. A 3-dose regimen at 0, 2, and 6 months was indicated.

2.1 Disease or Health-Related Condition (s) Studied

Please refer to the medical officer's clinical review.

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

Please refer to the medical officer's clinical review.

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

This product was licensed in the US on December 10, 2014 and indicated in girls and women 9 through 26 years of age, and boys 9 through 15 years of age. On December 14, 2015, CBER approved the extended indication in men 16 through 26 years of age.

As of October 31, 2015, the 9vHPV vaccine has been approved in 35 countries.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Submission quality is acceptable. The applicant has responded to all information requests from 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 appropriate discipline reviewers.

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review.

4.2 Assay Validation

N/A

4.3 Nonclinical Pharmacology/Toxicology

N/A

4.4 Clinical Pharmacology

N/A

4.5 Clinical

Please refer to the medical officer's 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

This review focuses on Study V503-010, which the applicant submitted as the basis for the proposed label change.

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

This review is based on the applicant's BLA supplement submission (STN 125508/153) dated February 1, 2016 and subsequent amendments to the submission, primarily Modules 1, 2, and 5 in the following location in the Electronic Document Room (EDR): (b) (4)

5.3 Table of Studies/Clinical Trials

A single study (Study V503-010) was submitted in the application. This study was designed to demonstrate noninferior antibody responses in a 2-dose regimen in boys and girls 9 through 14 years of age, compared to a 3-dose regimen in women 16 to 26 years of age. Please see Section 6 for details.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Protocol 010

The title of the protocol is "*A Phase III Clinical Trial to Study the Tolerability and Immunogenicity of a 2-dose regimen of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, administered in Preadolescents and Adolescents (9 to 14 year olds) with a Comparison to Young Women (16 to 26 year olds).*"

6.1.1 Objectives

The primary objectives were:

- To demonstrate that administration of a 2-dose 9-valent HPV L1 Virus Like Particle (VLP) vaccine at Day 1 and Month 6 induces noninferior 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 9 to 14 year-old girls compared to 16 to 26 year-old young women receiving 3 doses.

- To demonstrate that administration of a 2-dose 9-valent HPV L1 VLP vaccine at Day 1 and Month 6 induces noninferior 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 9 to 14 year-old boys compared to 16 to 26 year-old young women receiving 3 doses.
- To demonstrate that administration of a 2-dose 9-valent HPV L1 VLP vaccine at Day 1 and Month 12 induces noninferior 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 9 to 14 year-old boys and girls compared to 16 to 26 year-old young women receiving 3 doses.

The secondary objectives were:

- To demonstrate that the administration of a 2-dose 9-valent HPV L1 VLP vaccine at Day 1 and Month 6 induces noninferior immune responses with respect to seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 9 to 14 year-old girls compared to 16 to 26 year-old young adult women.
- To demonstrate that the administration of a 2-dose 9-valent HPV L1 VLP vaccine at Day 1 and Month 6 induces noninferior immune responses with respect to seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 9 to 14 year-old boys compared to 16 to 26 year-old young adult women.

6.1.2 Design Overview

This was a Phase III, open-label, international, multicenter, 3-year safety and immunogenicity study to compare the immunogenicity of 2 doses of 9vHPV vaccine administered at Day 1 and Month 6 (or Day 1 and Month 12) in girls and boys 9 to 14 years of age, and 3 doses of 9vHPV vaccine administered at Day 1, Month 2, and Month 6 in young women 16 to 26 years of age. Approximately 1500 subjects were to be enrolled including:

- 300 girls 9 to 14 years of age receiving 2 doses of 9vHPV vaccine at Day 1 and Month 6 (0, 6 regimen)
- 300 boys 9 to 14 years of age receiving 2 doses of 9vHPV vaccine at Day 1 and Month 6
- 300 girls and boys 9 to 14 years of age receiving 2 doses of 9vHPV vaccine at Day 1 and Month 12 (0, 12 regimen)
- 300 girls 9 to 14 years of age receiving 3 doses of 9vHPV vaccine at Day 1, Month 2 and 6 (0, 2, 6 regimen)
- 300 young women 16 to 26 years of age receiving 3 doses of 9vHPV vaccine at Day 1, Month 2 and 6.

6.1.3 Population

6.1.4 Study Treatments or Agents Mandated by the Protocol

All subjects received the same formulation of 9-Valent HPV L1 VLP Vaccine (0.5 mL) via intramuscular injection. The bulk product was described as "VSUV V503, 60/80/120/80/40/40/40/40/40 ug/mL, 0.5 mL (1000 ug/mL Alum)." The manufacturing lot numbers were WL00049589 and WL00053191.

6.1.6 Sites and Centers

This trial was conducted at 53 centers, of which 52 sites allocated subjects to study treatment. Four (4) of these trial centers were in Canada; 2 were in Chile; 4 were in Colombia; 4 were in the Czech Republic; 3 were in Denmark; 4 were in Israel; 3 were in the Republic of Korea; 3 were in Malaysia; 2 were in Norway; 2 were in South Africa; 3 were in Spain; 1 was in Taiwan; 2 were in Thailand; 3 were in Turkey, and 12 were in the United States. One site in Israel received drug supplies but did not enroll any subjects.

6.1.7 Surveillance/Monitoring

N/A

6.1.8 Endpoints and Criteria for Study Success

The primary immunogenicity endpoints for evaluating antibody response to 9vHPV vaccine were geometric mean titers (GMTs) to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Week 4 post last dose of vaccine.

The secondary endpoints for evaluating antibody response to 9vHPV vaccine are the percentages of subjects who seroconvert for each HPV type (6, 11, 16, 18, 31, 33, 45, 52, and 58) by Week 4 post-dose 2 (0, 6 and 0, 12 regimens only) or at Week 4 post-dose 3 (0, 2, 6 regimen only). Seroconversion is defined as changing serostatus from seronegative at baseline to seropositive by Week 4 after the last dose (post-dose 2 or post-dose 3). A subject with a cLIA titer at or above the serostatus cutoff for a given HPV type is considered seropositive for that type. The serostatus cutoffs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 are 30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/mL, respectively.

The safety endpoint included the incidence rates of clinical adverse events (AEs). The most important variable of interest for safety/tolerability was the incidence of any vaccine-related serious adverse events (SAEs) and vaccine-related discontinuations.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary hypotheses of noninferiority of GMTs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 were addressed by 9 one-sided tests of noninferiority (one corresponding to each HPV type) conducted at the 0.025 level (one-sided), each analyzed separately.

The secondary hypotheses of noninferiority of seroconversion percentages for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58) were addressed by 9 one-sided tests of noninferiority (one corresponding to each HPV type), each conducted at the α=0.025 level (one-sided). The noninferiority margin was -5%. The tests were conducted using the method of Miettinen and Nurminen. The statistical criterion for noninferiority required that the lower bound of the two-sided 95% confidence interval for the difference (girls (or boys) receiving the 0, 6 regimen minus women receiving the 0, 2, 6 regimen, or girls and boys receiving the 0, 12 regimen minus women receiving the 0, 2, 6 regimen) in seroconversion percentages is greater than -5 percentage points for each HPV type.

There are three primary hypotheses for noninferiority of peak immune response in a 2-dose regimen compared to a 3-dose regimen: 9 to 14 year-old girls receiving the 0, 6 regimen vs. 16 to 26 year-old women, 9 to 14 year-old boys receiving the 0, 6 regimen vs. 16 to 26 year-old women, and 9 to 14 year-old boys and girls receiving the 0, 12 regimen vs. 16 to 26 year-old women. For testing each of the three primary immunobridging hypotheses, success was required on all 9 vaccine HPV types. Therefore, no multiplicity adjustment was needed to account for the multiple HPV type-specific tests conducted for a specific hypothesis. Multiplicity adjustment for testing the 3 primary hypotheses was executed through a gate-keeping procedure in which the hypotheses were tested sequentially, provided statistical significance at the nominal 0.025 level was concluded in the preceding test.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Per-Protocol Immunogenicity (PPI) population served as the primary population for the analysis of antibody responses to each of the 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58). To be included in this population, subjects must:

1) Have received all planned vaccinations with the correct dose of the correct clinical material and each vaccination visit must occur within acceptable day range.
2) Have provided a serology sample with valid serology result within 21 to 49 days post last dose of the regimen (last dose is at Month 6 for the 0, 6 and 0, 2, 6regimens and Month 12 for the 0, 12 regimen.)
3) Be seronegative to the appropriate HPV type at Day 1.
4) Have no other protocol violations that could interfere with the evaluation of subject's immune response to the study vaccine.

Table 1 provides a summary of subjects in the PPI analysis population. The most common reasons subjects were excluded from the PPI population were: being positive to a vaccine HPV type at Day 1 and missing Day 1 or 4 weeks post last dose serology samples/results.

Table 1: Subject Composition in the Immunogenicity Analysis Population

	9-14-Year Old Females (0, 6 Regimen) (N=301)	9-14-Year Old Males (0, 6 Regimen) (N=301)	9-14-Year Old Females and Males (0, 12 Regimen) (N=301)	9-14-Year Old Females (0, 2, 6 Regimen) (N=301)	16-26-Year Old Females (0, 2, 6 Regimen) (N=314)	Total (N=1,518)
Number of Subjects who received at least 1 injection	301	301	300	300	314	1,516
Included in PPI Population n (%)						
HPV 6	258 (86)	263 (87)	257 (86)	254 (85)	238 (76)	1270 (84)
HPV 11	258 (86)	264 (88)	257 (86)	254 (85)	238 (76)	1271 (84)
HPV 16	272 (90)	273 (91)	264 (88)	269 (90)	249 (79)	1327 (88)
HPV 18	272 (90)	272 (90)	266 (89)	270 (90)	267 (85)	1347 (89)
HPV 31	272 (90)	271 (90)	268 (89)	271 (90)	264 (84)	1346 (89)
HPV 33	273 (91)	271 (90)	269 (90)	275 (92)	279 (89)	1367 (90)
HPV 45	274 (91)	273 (91)	268 (89)	275 (92)	280 (89)	1370 (90)
HPV 52	272 (90)	273 (91)	268 (89)	275 (92)	271 (86)	1359 (90)
HPV 58	270 (90)	270 (90)	265 (88)	273 (91)	261 (83)	1339 (88)
Reason for Exclusion						
General protocol violation	1	0	3	3	2	9
Did not complete the assigned vaccination regimen	8	5	9	7	3	32
Missing Day 1 or 4 weeks post last dose serology samples/results	25	25	27	23	20	120
Serology samples collected out of acceptable day range	10	10	14	12	10	56
Vaccination 2 or 3 out of acceptable day range	10	9	12	9	12	52
Positive to HPV 6 or 11 at Day 1	19	12	13	25	54	123
Positive to HPV 16 at Day 1	6	1	6	8	42	63
Positive to HPV 18 at Day 1	4	2	4	8	23	41
Positive to HPV 31 at Day 1	4	3	2	4	23	36
Positive to HPV 33 at Day 1	2	3	0	0	8	13
Positive to HPV 45 at Day 1	1	1	1	0	6	9
Positive to HPV 52 at Day 1	3	1	1	0	18	23
Positive to HPV 58 at Day 1	5	4	5	1	27	44

Source: Table 10-3 in the CSR for Study V503-010. The percentages are based on subjects with at least one injection, calculated by the reviewer.

6.1.10.1.1 Demographics

Table 2 displays the demographic characteristics of all subjects enrolled into this study. Subjects in all study groups were within the age ranges specified in the protocol. The applicant confirmed these results, despite that a few subjects appeared to be <9 years or >14 years of age due to calculation based on incomplete birth date. All study 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 2: Subject Characteristics (All Enrolled Subjects)

	9-14-Year Old Females (0, 6 Regimen) (N=301)	9-14-Year Old Males (0, 6 Regimen) (N=301)	9-14-Year Old Females and Males (0, 12 Regimen)	9-14-Year Old Females (0, 2, 6 Regimen) (N=301)	16-26-Year Old Females (0, 2, 6 Regimen) (N=314)	Total (N=1,518)
Gender						
Male	0 (0.0)	301 (100.0)	150 (49.8)	0 (0.0)	0 (0.0)	451 (29.7)
Female	301 (100.0)	0 (0.0)	151 (50.2)	301 (100.0)	314 (100.0)	1,067 (70.3)
Age (Years)						
8 and under	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)
9 to 10	99 (32.9)	98 (32.6)	99 (32.9)	101 (33.6)	0 (0.0)	397 (26.2)
11 to 12	102 (33.9)	102 (33.9)	106 (35.2)	100 (33.2)	0 (0.0)	410 (27.0)
13 to 14	99 (32.9)	100 (33.2)	95 (31.6)	98 (32.6)	0 (0.0)	392 (25.8)
15	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	3 (0.2)
16 to 26	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	314 (100.0)	314 (20.7)
Mean	11.4	11.5	11.4	11.4	21.0	13.4
SD	1.7	1.7	1.6	1.7	2.7	4.3
Median	11.0	12.0	11.0	12.0	21.0	12.0
Range	8 to 14	9 to 15	8 to 14	9 to 15	16 to 26	8 to 26
Race						
American Indian Or Alaska Native	13 (4.3)	12 (4.0)	8 (2.7)	10 (3.3)	8 (2.5)	51 (3.4)
Asian	64 (21.3)	30 (10.0)	46 (15.3)	63 (20.9)	45 (14.3)	248 (16.3)
Black Or African American	32 (10.6)	14 (4.7)	25 (8.3)	43 (14.3)	21 (6.7)	135 (8.9)
Multiple	32 (10.6)	34 (11.3	32 (10.6)	31 (10.3)	22 (7.0)	151 (9.9)
White	160 (53.2)	211 (70.1)	190 (63.1)	154 (51.2)	213 (67.8)	928 (61.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)	5 (0.3)
Region						
Asia-Pacific	79 (26.2)	39 (13.0)	58 (19.3)	81 (26.9)	63 (20.1)	320 (21.1)
Europe	56 (18.6)	132 (43.9)	102 (33.9)	66 (21.9)	114 (36.3)	470 (31.0)
Latin America	57 (18 9)	34 (11.3)	44 (14.6)	56 (18.6)	55 (17.5)	246 (16.2)
North America	83 (27.6)	85 (28.2)	77 (25.6)	60 (19.9)	70 (22.3)	375 (24.7)

Source: Table 10-6 in the CSR for Study V503-010.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All subjects were to be healthy at enrollment in the study.

6.1.10.1.3 Subject Disposition
A summary of subject disposition is provided in Table 3. Since the study is continuing, a summary of subjects who "Completed" the study is not available at this time. Among the 1,518 randomized subjects, a total of 44 subjects (2.9%) discontinued from the study during the vaccination period (Day 1 through Month 7 for subjects who received the 0, 6 or 0, 2, 6 regimens, Day 1 through Month 13 for subjects who received the 0, 12 regimen).

Table 3: Disposition of Subjects

	9-14-Year Old Females (0, 6 Regimen) n (%)	9-14-Year Old Males (0, 6 Regimen) n (%)	9-14-Year Old Females and Males (0, 12 Regimen) n (%)	9-14-Year Old Females (0, 2, 6 Regimen) n (%)	16-26-Year Old Females (0, 2, 6 Regimen) n (%)	Total n (%)
Subjects in population	301	301	301	301	314	1518
Vaccinated At						
Vaccination 1	301 (100.0)	301 (100.0)	300 (99.7)	300 (99.7)	314 (100.0)	1516 (99.9)
Vaccination 2	293 (97.3)	296 (98.3)	291 (96.7)	298 (99.0)	313 (99.7)	1491 (98.2)
Vaccination 3	0 (0.0)	0 (0.0)	0 (0.0)	293 (97.3)	311 (99.0)	604 (39.8)
Status for Trial						
Discontinued	11 (3.7)	7 (2.3)	9 (3.0)	11 (3.7)	6 (1.9)	44 (2.9)
Adverse Event	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Lost To Follow-Up	7 (2.3)	2 (0.7)	4 (1.3)	3 (1.0)	4 (1.3)	20 (1.3)
Physician Decision	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Protocol Violation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Withdrawal By Subject	3 (1.0)	5 (1.7)	4 (1.3)	7 (2.3)	2 (0.6)	21 (1.4)
Status Not Recorded	290 (96.3)	294 (97.7)	292 (97.0)	290 (96.3)	308 (98.1)	1474 (97.1)

Source: Table 10-1 in the CSR for Study V503-010.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Table 4 presents the results of the per-protocol analysis of noninferiority comparing Month 7 cLIA GMTs between 9 to 14 year-old girls in the 0, 6 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen. The GMT ratios (0, 6 regimen / 0, 2, 6 regimen) for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 ranged from 1.60 to 2.96, with the lower bounds of 95% CIs ranging from 1.36 to 2.50. Therefore, the objective to show noninferiority comparing Month 7 cLIA GMTs between 9 to 14 year-old girls in the 0, 6 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen was met. Similar findings were observed when comparing Month 7 cLIA GMTs between 9 to 14 year-old boys in the 0, 6 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen (Table 5). The fold differences appear to be even higher when comparing Month 7 cLIA GMTs between 9 to 14 year-old girls and boys in the 0, 12 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen (Table 6). The noninferiority objectives were met.

Table 4: Statistical Analysis of Noninferiority Comparing Month 7 HPV cLIA Geometric Mean Titers (Per-Protocol Immunogenicity Population): Girls 9-14 Years of Age (0, 6 Regimen) vs. Women 16-26 Years of Age (0, 2, 6 Regimen)

	9-14 yo Females (0, 6 Regimen) (Group A)	**9-14 yo Females (0, 6 Regimen) (Group A)**	**16-26 yo Females (0, 2, 6 Regimen) (Group B)**	**16-26 yo Females (0, 2, 6 Regimen) (Group B)**	
	n	GMT (mMU/mL)	n	GMT (mMU/mL)	Fold Difference Group A / Group B (95% CI)
Anti-HPV 6	258	1,657.9	238	770.9	2.15 (1.83, 2.53)
Anti-HPV 11	258	1,388.9	238	580.5	2.39 (2.03, 2.82)
Anti-HPV 16	272	8,004.9	249	3,154.0	2.54 (2.14, 3.00)
Anti-HPV 18	272	1,872.8	267	761.5	2.46 (2.05, 2.96)
Anti-HPV 31	272	1,436.3	264	572.1	2.51 (2.10, 3.00)
Anti-HPV 33	273	1,030.0	279	348.1	2.96 (2.50, 3.50)
Anti-HPV 45	274	357.6	280	213.6	1.67 (1.38, 2.03)
Anti-HPV 52	272	581 1	271	364.2	1.60 (1.36, 1.87)
Anti-HPV 58	270	1,251.2	261	491.1	2.55 (2.15, 3.01)

Source: Table 11-3 in the CSR for Study V503-010.

Table 5: Statistical Analysis of Noninferiority Comparing Month 7 HPV cLIA Geometric Mean Titers (Per-Protocol Immunogenicity Population): Boys 9-14 Years of Age (0, 6 Regimen) vs. Women 16-26 Years of Age (0, 2, 6 Regimen)

	9-14 yo Males (0, 6 Regimen) (Group A)	**9-14 yo Males (0, 6 Regimen) (Group A)**	**16-26 yo Females (0, 2, 6 Regimen) (Group B)**	**16-26 yo Females (0, 2, 6 Regimen) (Group B)**	
	n	GMT (mMU/mL)	n	GMT (mMU/mL)	Fold Difference Group A / Group B (95% CI)
Anti-HPV 6	263	1,557.4	238	770.9	2.02 (1.73, 2.36)
Anti-HPV 11	264	1,423.9	238	580.5	2.45 (2.09, 2.88)
Anti-HPV 16	273	8,474.8	249	3,154.0	2.69 (2.29, 3.15)
Anti-HPV 18	272	1,860.9	267	761.5	2.44 (2.04, 2.92)
Anti-HPV 31	271	1,498.2	264	572.1	2.62 (2.20, 3.12)
Anti-HPV 33	271	1,040.0	279	348.1	2.99 (2.55, 3.50)
Anti-HPV 45	273	352.3	280	213.6	1.65 (1.37, 1.99)
Anti-HPV 52	273	640.4	271	364.2	1.76 (1.51, 2.05)
Anti-HPV 58	270	1,325.7	261	491.1	2.70 (2.30, 3.16)

Source: Table 11-5 in the CSR for Study V503-010.

Table 6: Statistical Analysis of Noninferiority Comparing at 4 Weeks Post Last Dose HPV cLIA Geometric Mean Titers (Per-Protocol Immunogenicity Population): Girls and Boys 9-14 Years of Age (0, 12 Regimen) vs. Women 16-26 Years of Age (0, 2, 6 Regimen)

	9-14 yo Females and Males (0, 12 Regimen) (Group A)	9-14 yo Females and Males (0, 12 Regimen) (Group A)	16-26 yo Females (0, 2, 6 Regimen) (Group B)	16-26 yo Females (0, 2, 6 Regimen) (Group B)	
	n	GMT (mMU/mL)	n	GMT (mMU/mL)	Fold Difference Group A / Group B (95% CI)
Anti-HPV 6	257	2,678.8	238	770.9	3.47 (2.93, 4.11)
Anti-HPV 11	257	2,941.8	238	580.5	5.07 (4.32, 5.94)
Anti-HPV 16	264	14,329.3	249	3,154.0	4.54 (3.84, 5.37)
Anti-HPV 18	266	2,810.4	267	761.5	3.69 (3.06, 4.45)
Anti-HPV 31	268	2,117.5	264	572.1	3.70 (3.08, 4.45)
Anti-HPV 33	269	2,197.5	279	348.1	6.31 (5.36, 7.43)
Anti-HPV 45	268	417.7	280	213.6	1.96 (1.61, 2.37)
Anti-HPV 52	268	1,123.4	271	364.2	3.08 (2.64, 3.61)
Anti-HPV 58	265	2,444.6	261	491.1	4.98 (4.23, 5.86)

Source: Table 11-7 in the CSR for Study V503-010.

6.1.11.2 Analyses of Secondary Endpoints

Table 7 presents a summary of the proportion (with associated 95% CIs) of subjects in the PPI population with positive serostatus to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7. The differences in seroconversion percentages between the two vaccination groups (0, 6 regimen minus 0, 2, 6 regimen) ranged from 0% to 1.5%, with lower bounds of 95% CIs ranging from -1.8% to 0.1%. Therefore, the objective to show noninferiority comparing Month 7 seroconversion percentages between 9 to 14 year-old girls in the 0, 6 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen was met. Similarly, the objective to show noninferiority comparing Month 7 seroconversion percentages between 9 to 14 year-old boys in the 0, 6 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen was met (Table 8). The objective to show noninferiority comparing seroconversion percentages at 4 weeks post last dose between 9 to 14 year-old girls and boys in the 0, 12 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen was met (Table 9).

Table 7: Statistical Comparison of Month 7 Anti-HPV Seroconversion Rates Between (Per-Protocol Immunogenicity Population): Girls 9-14 Years of Age (0, 6 Regimen) vs. Women 16-26 Years of Age (0, 2, 6 Regimen)

	Group A	Group A	Group A	Group B	Group B	Group B	
	9-14 yo Females (0, 6 Regimen) (Group A)	9-14 yo Females (0, 6 Regimen) (Group A)	9-14 yo Females (0, 6 Regimen)	16-26 yo Females (0, 2, 6 Regimen) (Group	16-26 yo Females (0, 2, 6 Regimen) (Group B)	16-26 yo Females (0, 2, 6 Regimen) (Group B)	
Anti-HPV Response	n	m	Seroconversion (%)	n	m	Seroconversion (%)	Difference (95% CI) Group A - Group B
HPV 6 cLIA ≥30 mMU/mL	258	257	99.6	238	237	99.6	0.0 (-1.8, 2.0)
HPV 11 cLIA ≥16 mMU/mL	258	258	100	238	237	99.6	0.4 (-1.1, 2.3)
HPV 16 cLIA ≥20 mMU/mL	272	272	100	249	248	99.6	0.4 (-1.0, 2.2)
HPV 18 cLIA ≥24 mMU/mL	272	272	100	267	263	98.5	1.5 (0.1, 3.8)
HPV 31 cLIA ≥10 mMU/mL	272	271	99.6	264	263	99.6	0.0 (-1.7, 1.8)
HPV 33 cLIA ≥8 mMU/mL	273	272	99.6	279	278	99.6	0.0 (-1.7, 1.7)
HPV 45 cLIA ≥8 mMU/mL	274	272	99.3	280	274	97.9	1.4 (-0.7, 4.0)
HPV 52 cLIA ≥8 mMU/mL	272	271	99.6	271	270	99.6	0.0 (-1.7, 1.7)
HPV 58 cLIA ≥8 mMU/mL	270	270	100	261	260	99.6	0.4 (-1.0, 2.1)

Note: n=number of subjects in the analysis; m=#subjects with conversion
Source: Table 11-4 in the CSR for Study V503-010.

Table 8: Statistical Comparison of Month 7 Anti-HPV Seroconversion Rates (Per-Protocol Immunogenicity Population): Boys 9-14 Years of Age (0, 6 Regimen) vs. Women 16-26 Years of Age (0, 2, 6 Regimen)

	Group A	Group A	Group A	Group B	Group B	Group B	
	9-14 yo Males (0, 6 Regimen) (Group A)	9-14 yo Males (0, 6 Regimen) (Group A)	9-14 yo Males (0, 6 Regimen)	16-26 yo Females (0, 2, 6 Regimen) (Group B)	16-26 yo Females (0, 2, 6 Regimen) (Group B)	16-26 yo Females (0, 2, 6 Regimen) (Group B)	
Anti-HPV Response	n	m	Seroconversion (%)	n	m	Seroconversion (%)	Difference (95% CI) Group A - Group B
HPV 6 cLIA ≥30 mMU/mL	263	263	100	238	237	99.6	0.4 (-1.0, 2.3)
HPV 11 cLIA ≥16 mMU/mL	264	264	100	238	237	99.6	0.4 (-1.0, 2.3)
HPV 16 cLIA ≥20 mMU/mL	273	273	100	249	248	99.6	0.4 (-1.0, 2.2)
HPV 18 cLIA ≥24 mMU/mL	272	272	100	267	263	98.5	1.5 (0.1, 3.8)
HPV 31 cLIA ≥10 mMU/mL	271	271	100	264	263	99.6	0.4 (-1.0, 2.1)
HPV 33 cLIA ≥8 mMU/mL	271	271	100	279	278	99.6	0.4 (-1.0, 2.0)
HPV 45 cLIA ≥8 mMU/mL	273	271	99.3	280	274	97.9	1.4 (-0.7, 4.0)
HPV 52 cLIA ≥8 mMU/mL	273	273	100	271	270	99.6	0.4 (-1.0, 2.1)
HPV 58 cLIA ≥8 mMU/mL	270	270	100	261	260	99.6	0.4 (-1.0, 2.1)

Note: n=number of subjects in the analysis; m=#subjects with conversion
Source: Table 11-6 in the CSR for Study V503-010.

Table 9: Statistical Comparison of Anti-HPV Seroconversion Rates at 4 Weeks Post Last Dose (Per-Protocol Immunogenicity Population): Girls and Boys 9-14 Years of Age (0, 12 Regimen) vs. Women 16-26 Years of Age (0, 2, 6 Regimen)

	Group A	Group A	Group A	Group B	Group B	Group B	
	9-14 yo Females and Males (0, 12 Regimen)	9-14 yo Females and Males (0, 12 Regimen)	9-14 yo Females and Males (0, 12 Regimen)	16-26 yo Females (0, 2, 6 Regimen)	16-26 yo Females (0, 2, 6 Regimen)	16-26 yo Females (0, 2, 6 Regimen)	
Anti-HPV Response	**n**	**m**	**Seroconversion (%)**	**n**	**m**	**Seroconversion (%)**	**Difference (95% CI) Group A - Group B**
HPV 6 cLIA ≥30 mMU/mL	257	257	100	238	237	99.6	0.4 (-1.1, 2.3)
HPV 11 cLIA ≥16	257	257	100	238	237	99.6	0.4 (-1.1, 2.3)
HPV 16 cLIA ≥20	264	264	100	249	248	99.6	0.4 (-1.0, 2.2)
HPV 18 cLIA ≥24	266	266	100	267	263	98.5	1.5 (0.1, 3.8)
HPV 31 cLIA ≥10	268	268	100	264	263	99.6	0.4 (-1.0, 2.1)
HPV 33 cLIA ≥8 mMU/mL	269	269	100	279	278	99.6	0.4 (-1.1, 2.0)
HPV 45 cLIA ≥8 mMU/mL	268	268	100	280	274	97.9	2.1 (0.7, 4.6)
HPV 52 cLIA ≥8 mMU/mL	268	268	100	271	270	99.6	0.4 (-1.0, 2.1)
HPV 58 cLIA ≥8 mMU/mL	265	265	100	261	260	99.6	0.4 (-1.1, 2.1)

Note: n=number of subjects in the analysis; m=#subjects with conversion
Source: Table 11-8 in the CSR for Study V503-010.

6.1.11.3 Subpopulation Analyses

The subgroup analyses by age and/or sex are associated with the primary and secondary objectives. Please refer to Sections 6.1.11.1 and 6.1.11.2 for those subgroup analyses.

Subgroup analyses by race and by region for GMTs only are shown in Table 10 and Table 11, respectively. The findings within subgroups were consistent with those in the primary analysis. GMTs at Month 7 in the 9-14 year-old female 0, 6 regimen group were higher than those in the 16-26 year-old females 0, 2, 6 regimen group within each subgroup. GMTs at 4 weeks post last dose were higher in the 0, 12 regimen group than in the other groups, within each demographic subgroup.

Table 10: cLIA GMTs at 4 Weeks Post Last Dose by Race

		Asian	Asian	Black Or African American	Black Or African American	White	White	Other	Other
Serotype	**Group**	**n**	**GMT**	**n**	**GMT**	**n**	**GMT**	**n**	**GMT**
6	**16-26-Year Old Females (0, 2, 6 Regimen)**	34	719 8	9	872 6	173	734 4	25	971 8
	9-14-Year Old Females (0, 2, 6 Regimen)	56	1425	40	1472	166	1089	31	1592
	9-14-Year Old Females (0, 6 Regimen)	58	1657	29	1802	138	1667	33	1509
	9-14-Year Old Females and Males (0, 12 Regimen)	43	2514	20	3275	166	2516	28	3714
	9-14-Year Old Males (0, 6 Regimen)	27	1310	11	1846	189	1456	36	2399
11	**16-26-Year Old Females (0, 2, 6 Regimen)**	34	592 1	9	439 4	173	558 2	25	674 6
	9-14-Year Old Females (0, 2, 6 Regimen)	56	1235	40	1478	166	882 2	31	1260
	9-14-Year Old Females (0, 6 Regimen)	58	1385	29	1612	138	1371	33	1291
	9-14-Year Old Females and Males (0, 12 Regimen)	43	2853	20	3754	166	2804	28	3447
	9-14-Year Old Males (0, 6 Regimen)	28	1192	11	1445	189	1409	36	1719
16	**16-26-Year Old Females (0, 2, 6 Regimen)**	40	3648	11	4398	180	2783	25	4062
	9-14-Year Old Females (0, 2, 6 Regimen)	61	6524	43	7105	172	5168	32	7762
	9-14-Year Old Females (0, 6 Regimen)	61	8643	31	10250	145	7378	35	7886
	9-14-Year Old Females and Males (0, 12 Regimen)	43	13148	23	16018	169	13546	29	20679
	9-14-Year Old Males (0, 6 Regimen)	30	7481	13	11049	191	8083	39	10764
18	**16-26-Year Old Females (0, 2, 6 Regimen)**	39	932 0	13	934 9	195	679 6	27	806 2
	9-14-Year Old Females (0, 2, 6 Regimen)	61	1986	44	2223	172	1284	32	2020
	9-14-Year Old Females (0, 6 Regimen)	60	2009	30	2478	145	1740	37	1777
	9-14-Year Old Females and Males (0, 12 Regimen)	44	3351	23	2820	169	2459	30	4593
	9-14-Year Old Males (0, 6 Regimen)	30	1861	13	2775	190	1727	39	2340
31	**16-26-Year Old Females (0, 2, 6 Regimen)**	40	692 9	13	754 1	191	493 7	26	712 5
	9-14-Year Old Females (0, 2, 6 Regimen)	61	1865	46	1820	171	1094	32	1943
	9-14-Year Old Females (0, 6 Regimen)	61	1476	30	2025	144	1254	37	1762
	9-14-Year Old Females and Males (0, 12 Regimen)	44	2534	23	2223	170	1927	31	2655
	9-14-Year Old Males (0, 6 Regimen)	30	1445	12	1923	190	1433	39	1771
33	**16-26-Year Old Females (0, 2, 6 Regimen)**	41	391 3	16	343 2	200	323 8	28	397 9
	9-14-Year Old Females (0, 2, 6 Regimen)	61	772 2	46	628 9	173	608 0	34	831 9
	9-14-Year Old Females (0, 6 Regimen)	61	1056	30	1130	145	996 9	37	1043
	9-14-Year Old Females and Males (0, 12 Regimen)	44	2109	23	1838	171	2194	31	2684
	9-14-Year Old Males (0, 6 Regimen)	30	856 0	12	962 6	191	1039	38	1251
45	**16-26-Year Old Females (0, 2, 6 Regimen)**	41	317 8	16	236 9	201	172 1	28	326 6
	9-14-Year Old Females (0, 2, 6 Regimen)	61	729 2	46	711 9	173	375 3	34	601 6
	9-14-Year Old Females (0, 6 Regimen)	61	426 2	31	613 2	145	297 8	37	348 9
	9-14-Year Old Females and Males (0, 12 Regimen)	44	482 9	23	650 0	170	353 5	31	611 7
	9-14-Year Old Males (0, 6 Regimen)	30	539 6	13	436 7	191	310 7	39	437 4
52	**16-26-Year Old Females (0, 2, 6 Regimen)**	37	437 8	14	338 4	199	320 8	27	444 7
	9-14-Year Old Females (0, 2, 6 Regimen)	61	890 6	46	850 4	173	598 4	34	842 5
	9-14-Year Old Females (0, 6 Regimen)	61	536 8	31	706 5	144	572 4	36	596 6
	9-14-Year Old Females and Males (0, 12 Regimen)	43	1335	23	1311	171	1007	31	1443
	9-14-Year Old Males (0, 6 Regimen)	30	608 8	13	790 4	191	618 1	39	738 4
58	**16-26-Year Old Females (0, 2, 6 Regimen)**	41	573 6	15	466 2	183	452 5	27	525 7
	9-14-Year Old Females (0, 2, 6 Regimen)	61	1248	46	964 1	170	866 6	34	1420
	9-14-Year Old Females (0, 6 Regimen)	60	1369	29	1430	144	1180	37	1224
	9-14-Year Old Females and Males (0, 12 Regimen)	44	2953	21	2428	169	2261	31	2871
	9-14-Year Old Males (0, 6 Regimen)	30	1260	13	1299	189	1316	38	1440

Source: Reviewer's analysis based on raw data provided by the applicant. Results are confirmed by the applicant's analysis presented in sBLA amendment STN125508/153.2.

Table 11: GMTs at Month 7 by Region between 16-26-Year Old Females (0, 2, 6 Regimen) and 9-14-Year Old Females (0, 6 Regimen)

		Africa	Africa	Asia-Pacific	Asia-Pacific	Europe	Europe	Latin America	Latin America	North America	North America
Serotype	**Group**	**n**	**GMT**	**n**	**GMT**	**n**	**GMT**	**n**	**GMT**	**n**	**GMT**
6	**16-26-Year Old Females (0, 2, 6 Regimen)**	4	821 4	45	673 4	93	762 9	53	894 1	49	718 7
	9-14-Year Old Females (0, 2, 6 Regimen)	34	1472	70	1340	64	1352	65	1065	60	1120
	9-14-Year Old Females (0, 6 Regimen)	23	1705	71	1612	46	1862	46	1479	72	1687
	9-14-Year Old Females and Males (0, 12 Regimen)	17	3492	52	2215	95	2451	30	3688	63	2865
	9-14-Year Old Males (0, 6 Regimen)	8	1782	34	1172	120	1285	25	2364	76	2058
11	**16-26-Year Old Females (0, 2, 6 Regimen)**	4	526 9	45	545 0	93	636 9	53	551 1	49	514 6
	9-14-Year Old Females (0, 2, 6 Regimen)	34	1596	70	1179	64	1199	65	796 1	60	840 7
	9-14-Year Old Females (0, 6 Regimen)	23	1434	71	1315	46	1760	46	1287	72	1309
	9-14-Year Old Females and Males (0, 12 Regimen)	17	3791	52	2403	95	2804	30	3863	63	3065
	9-14-Year Old Males (0, 6 Regimen)	8	1482	35	1034	120	1217	25	1511	76	2063
16	**16-26-Year Old Females (0, 2, 6 Regimen)**	7	4041	51	3211	92	3157	58	3181	51	2732
	9-14-Year Old Females (0, 2, 6 Regimen)	37	7712	75	6278	67	6113	66	5510	63	4854
	9-14-Year Old Females (0, 6 Regimen)	25	9215	74	8100	50	8617	47	6905	76	7887
	9-14-Year Old Females and Males (0, 12 Regimen)	20	14587	52	11192	97	13357	31	21946	64	15760
	9-14-Year Old Males (0, 6 Regimen)	10	11567	38	6875	120	7121	27	10112	78	11087
18	**16-26-Year Old Females (0, 2, 6 Regimen)**	9	996 9	51	720 8	101	735 9	61	752 0	55	718 2
	9-14-Year Old Females (0, 2, 6 Regimen)	37	2394	75	1807	67	1815	66	1265	64	1175
	9-14-Year Old Females (0, 6 Regimen)	24	2073	73	1796	50	2056	49	1777	76	1836
	9-14-Year Old Females and Males (0, 12 Regimen)	20	2608	53	2618	96	2335	31	4625	66	3153
	9-14-Year Old Males (0, 6 Regimen)	10	2772	38	1484	120	1598	27	2381	77	2297
31	**16-26-Year Old Females (0, 2, 6 Regimen)**	8	721 2	52	593 4	99	581 2	59	591 7	56	423 1
	9-14-Year Old Females (0, 2, 6 Regimen)	39	2126	74	1630	68	1497	67	1138	62	1007
	9-14-Year Old Females (0, 6 Regimen)	24	1607	74	1361	50	1422	49	1605	75	1368
	9-14-Year Old Females and Males (0, 12 Regimen)	20	1960	53	1886	97	1958	32	3119	66	2212
	9-14-Year Old Males (0, 6 Regimen)	9	2087	38	1193	119	1329	27	1727	78	1842
33	**16-26-Year Old Females (0, 2, 6 Regimen)**	9	440 8	53	347 4	101	336 7	62	380 3	64	295 8
	9-14-Year Old Females (0, 2, 6 Regimen)	39	647 9	75	744 3	68	760 1	68	592 1	64	569 2
	9-14-Year Old Females (0, 6 Regimen)	24	1015	74	1024	50	1287	49	903 0	76	978 1
	9-14-Year Old Females and Males (0, 12 Regimen)	20	1646	53	1854	97	2223	32	2906	67	2358
	9-14-Year Old Males (0, 6 Regimen)	9	968 1	38	834 9	120	919 0	26	1138	78	1370
45	**16-26-Year Old Females (0, 2, 6 Regimen)**	8	302 0	53	236 1	103	199 9	62	218 0	64	171 4
	9-14-Year Old Females (0, 2, 6 Regimen)	39	883 3	75	665 2	68	541 1	68	363 7	64	306 1
	9-14-Year Old Females (0, 6 Regimen)	25	524 4	74	376 2	50	356 2	49	330 4	76	316 5
	9-14-Year Old Females and Males (0, 12 Regimen)	20	678 6	53	366 0	97	356 4	32	676 4	66	400 9
	9-14-Year Old Males (0, 6 Regimen)	10	445 8	38	361 7	120	274 6	27	451 0	78	454 7
52	**16-26-Year Old Females (0, 2, 6 Regimen)**	7	391 8	49	371 9	102	356 7	60	364 1	63	307 4
	9-14-Year Old Females (0, 2, 6 Regimen)	39	933 8	75	861 9	68	764 2	68	503 4	64	621 8
	9-14-Year Old Females (0, 6 Regimen)	25	605 2	73	523 9	50	663 0	48	566 2	76	590 3
	9-14-Year Old Females and Males (0, 12 Regimen)	20	1227	52	1079	97	1031	32	1290	67	1198
	9-14-Year Old Males (0, 6 Regimen)	10	956 2	38	561 2	120	561 9	27	650 1	78	789 2
58	**16-26-Year Old Females (0, 2, 6 Regimen)**	8	466 6	52	496 0	92	499 4	57	473 5	60	448 3
	9-14-Year Old Females (0, 2, 6 Regimen)	39	1020	75	1146	67	1255	66	852 4	64	776 0
	9-14-Year Old Females (0, 6 Regimen)	23	1211	73	1255	50	1464	49	1147	75	1201
	9-14-Year Old Females and Males (0, 12 Regimen)	18	2292	53	2381	96	2292	32	3175	66	2459
	9-14-Year Old Males (0, 6 Regimen)	10	1215	38	1151	118	1145	26	1382	78	1767

Source: Reviewer's analysis based on raw data provided by the applicant. Results are confirmed by the applicant's analysis presented in sBLA amendment STN125508/153.2.

6.1.11.4 Dropouts and/or Discontinuations

The overall dropout rate in the study was 2.9%, with a slightly higher rate in the younger age groups (9 through 14 years of age) than in the older age group (16 through 26 years of age).

6.1.11.5 Exploratory and Post Hoc Analyses

An additional analysis of cLIA GMTs for time points besides the primary time point (one month post last dose), when applicable, was performed by the applicant per reviewer's request. Table 12 presents a complete tabulation of the GMTs with corresponding lower limits (LLs) and upper limits (ULs) of the 95% CIs based on all available immunogenicity data submitted in the application. It is noted that prior to the last dose in the two dose groups, 0, 6 or 0, 12 regimens, the GMTs for Serotype 45 were low, being 6.1, 4.6, and 4.4, for the 9-14 year-old females 0,6 regimen group, 9-14 year-old males 0,6 regimen group, 9-14 year-old males and females 0,12 regimen group. The GMTs for all other HPV vaccine types remained above the corresponding seropositive cutoffs after the first dose but prior to the second dose in the two-dose regimen groups. The reviewer defers to the medical officer regarding the implication of this finding.

Table 12: Summary of cLIA GMTs (95% CIs) by Group and Time Point (Relative to Day 1)

	Age (Years)	16-26	16-26	16-26	16-26	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14
	Sex	F	F	F	F	F	F	F	F	F	F	F	F	Both	Both	Both	Both	M	M	M	M
	Regimen	(0, 2, 6)	(0, 2, 6)	(0, 2, 6)	(0, 2, 6)	(0, 2, 6)	(0, 2, 6)	(0, 2, 6)	(0, 2, 6)	(0, 6)	(0, 6)	(0, 6)	(0, 6)	(0, 12)	(0, 12)	(0, 12)	(0, 12)	(0, 6)	(0, 6)	(0, 6)	(0, 6)
Analysis Visit	Serotype	n	GMT	95% LL	95% UL	n	GMT	95% LL	95% UL	n	GMT	95% LL	95% UL	n	GMT	95% LL	95% UL	n	GMT	95% LL	95% UL
Day 1	6	238	9 6	9 1	10 1	254	9 0	8 6	9 3	258	8 9	8 6	9 2	257	8 7	8 4	9 0	263	8 4	8 2	8 7
	11	238	3 1	3 0	3 1	254	3 1	3 0	3 1	258	3 1	3 0	3 1	257	3 0	3 0	3 1	264	3 0	3 0	3 1
	16	249	6 1	6 0	6 2	269	6 0	6 0	6 1	272	6 0	6 0	6 1	264	6 0	N/A	N/A	273	6 0	N/A	N/A
	18	267	4 3	4 2	4 5	270	4 3	4 1	4 4	272	4 2	4 1	4 4	266	4 2	4 1	4 3	272	4 1	4 0	4 1
	31	264	2 1	2 0	2 1	271	2 1	2 0	2 1	272	2 0	2 0	2 1	268	2 1	2 0	2 1	271	2 0	N/A	N/A
	33	279	2 1	2 0	2 1	275	2 0	2 0	2 0	273	2 0	2 0	2 0	269	2 0	2 0	2 0	271	2 0	2 0	2 0
	45	280	1 5	1 5	1 5	275	1 5	N/A	N/A	274	1 5	N/A	N/A	268	1 5	1 5	1 6	273	1 5	1 5	1 5
	52	271	1 6	1 5	1 6	275	1 5	1 5	1 5	272	1 5	1 5	1 6	268	1 5	N/A	N/A	273	1 5	1 5	1 5
	58	261	2 2	2 1	2 3	273	2 1	2 0	2 1	270	2 1	2 0	2 1	265	2 0	2 0	2 1	270	2 0	2 0	2 1
Month 1	6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	48	115 1	86 1	153 9	N/A	N/A	N/A	N/A	2	100 4	0 3	37440
	11	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	48	111 5	84 9	146 4	N/A	N/A	N/A	N/A	2	47 4	0 0	162307
	16	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	51	226 0	162 5	314 4	N/A	N/A	N/A	N/A	2	117 2	0 0	1 11E6
	18	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	51	38 1	26 1	55 7	N/A	N/A	N/A	N/A	2	31 6	1 6	626 3
	31	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	51	35 5	25 3	49 9	N/A	N/A	N/A	N/A	2	31 9	0 0	96363
	33	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	51	23 5	17 0	32 6	N/A	N/A	N/A	N/A	2	21 9	0 0	7 94E6
	45	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	51	8 0	5 8	11 1	N/A	N/A	N/A	N/A	2	4 9	0 4	64 4
	52	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	51	42 1	31 7	55 8	N/A	N/A	N/A	N/A	2	80 7	0 1	45928
	58	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	51	37 4	27 1	51 5	N/A	N/A	N/A	N/A	2	10 8	0 0	3 15E6
Month 6	6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	256	76 2	68 5	84 7	N/A	N/A	N/A	N/A	260	67 7	61 4	74 6
	11	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	261	50 7	45 0	57 1	N/A	N/A	N/A	N/A	262	43 2	38 5	48 5
	16	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	274	163 4	145 9	183 1	N/A	N/A	N/A	N/A	271	141 4	124 2	161 1
	18	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	274	37 1	32 5	42 5	N/A	N/A	N/A	N/A	270	29 5	25 9	33 7
	31	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	274	30 3	26 8	34 2	N/A	N/A	N/A	N/A	269	21 8	18 9	25 1
	33	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	275	22 9	20 2	26 0	N/A	N/A	N/A	N/A	269	18 5	16 3	21 0
	45	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**276**	**6.1**	**5.3**	**6.9**	N/A	N/A	N/A	N/A	**271**	**4.6**	**4.0**	**5.2**
	52	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	273	27 2	23 6	31 5	N/A	N/A	N/A	N/A	271	19 3	16 8	22 2
	58	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	272	45 9	41 0	51 4	N/A	N/A	N/A	N/A	268	37 7	33 4	42 7

Table 12 (Cont'd): Summary of cLIA GMTs (95% CIs) by Group and Time Point (Relative to Day 1)

	Age (Years)	16-26	16-26	16-26	16-26	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14	9-14
	Sex	F	F	F	F	F	F	F	F	F	F	F	F	Both	Both	Both	Both	M	M	M	M
	Regimen	(0, 2, 6	(0, 2, 6)	(0, 2, 6)	(0, 2, 6)	(0, 2, 6	(0, 2, 6)	(0, 2, 6)	(0, 2, 6)	(0, 6)	(0, 6)	(0, 6)	(0, 6)	(0, 12)	(0, 12)	(0, 12)	(0, 12)	(0, 6)	(0, 6)	(0, 6)	(0, 6)
Analysis Visit	**Serotype**	**n**	**GMT**	**95% LL**	**95% UL**	**n**	**GMT**	**95% LL**	**95% UL**	**n**	**GMT**	**95% LL**	**95% UL**	**n**	**GMT**	**95% LL**	**95% UL**	**n**	**GMT**	**95% LL**	**95% UL**
Month 7	**6**	244	763 4	681 7	854 8	293	1243 3	1104 0	1400 2	258	1657 9	1480 8	1856 1	N/A	N/A	N/A	N/A	263	1557 4	1401 4	1730 8
	11	244	572 8	509 5	643 9	293	1048 2	923 8	1189 4	258	1388 9	1238 2	1558 1	N/A	N/A	N/A	N/A	264	1423 9	1274 2	1591 1
	16	259	3104 9	2757 0	3496 6	308	5902 7	5291 2	6584 8	272	8004 9	7123 5	8995 3	N/A	N/A	N/A	N/A	273	8474 8	7635 0	9407 1
	18	277	740 3	648 1	845 6	309	1585 8	1382 5	1819 0	272	1872 8	1651 7	2123 4	N/A	N/A	N/A	N/A	272	1860 9	1654 7	2092 9
	31	274	552 4	481 6	633 7	310	1390 1	1220 5	1583 3	272	1436 3	1279 5	1612 3	N/A	N/A	N/A	N/A	271	1498 2	1340 7	1674 1
	33	289	340 6	302 9	383 0	314	662 2	592 4	740 2	273	1030 0	914 1	1160 6	N/A	N/A	N/A	N/A	271	1040 0	935 3	1156 3
	45	290	205 2	177 6	237 1	314	493 6	424 5	573 9	274	357 6	314 4	406 6	N/A	N/A	N/A	N/A	273	352 3	313 2	396 3
	52	281	349 9	310 5	394 2	314	706 3	621 5	802 6	272	581 1	523 0	645 6	N/A	N/A	N/A	N/A	273	640 4	581 3	705 6
	58	269	480 4	424 6	543 6	311	998 1	882 7	1128 6	270	1251 2	1117 6	1400 8	N/A	N/A	N/A	N/A	270	1325 7	1200 3	1464 3
Month 12	**6**	233	295 0	261 4	332 9	251	545 8	488 3	610 1	256	498 8	440 7	564 5	252	57 5	51 1	64 7	260	476 8	428 0	531 1
	11	237	219 4	195 5	246 3	253	443 7	393 2	500 6	257	383 2	339 7	432 2	256	39 0	34 7	43 9	264	368 9	326 8	416 4
	16	247	1100 2	984 2	1229 9	268	2371 2	2132 0	2637 4	270	2204 9	1954 2	2487 8	263	93 9	81 7	107 9	273	2219 3	1982 7	2484 0
	18	266	210 8	183 6	242 0	269	569 2	499 3	648 8	270	416 5	363 3	477 3	265	24 4	21 1	28 3	272	393 0	345 8	446 6
	31	263	175 3	152 6	201 4	270	559 4	491 0	637 3	270	345 2	302 5	394 0	267	22 6	19 6	26 1	271	344 7	302 2	393 1
	33	277	112 4	99 5	126 8	274	262 0	233 4	294 1	271	285 5	250 6	325 3	268	16 6	14 5	19 0	271	285 6	252 1	323 5
	45	278	60 3	52 0	70 0	274	189 2	164 0	218 3	272	72 7	63 4	83 5	267	**4.4**	**3.8**	**5.0**	273	67 7	59 4	77 1
	52	269	121 5	107 4	137 5	274	291 8	259 8	327 7	270	148 6	131 5	167 9	267	15 5	13 3	18 1	273	159 1	142 4	177 8
	58	260	175 3	155 2	198 1	272	442 5	395 0	495 7	268	370 3	330 4	415 0	264	35 1	31 0	39 7	270	395 8	354 5	441 9
Month 13	**6**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	257	2678 8	2367 2	3031 3	N/A	N/A	N/A	N/A
	11	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	257	2941 8	2640 6	3277 4	N/A	N/A	N/A	N/A
	16	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	264	14329	12758	16095	N/A	N/A	N/A	N/A
	18	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	266	2810 4	2468 9	3199 1	N/A	N/A	N/A	N/A
	31	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	268	2117 5	1870 3	2397 4	N/A	N/A	N/A	N/A
	33	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	269	2197 5	1963 2	2459 7	N/A	N/A	N/A	N/A
	45	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	268	417 7	367 4	475 0	N/A	N/A	N/A	N/A
	52	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	268	1123 4	1015 3	1243 0	N/A	N/A	N/A	N/A
	58	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	265	2444 6	2200 0	2716 4	N/A	N/A	N/A	N/A

Source: Reviewer's analysis based on raw data provided by the applicant. Results are similar, with minor differences, to the applicant's analysis presented in sBLA amendment STN125508/153.2.

As shown in Table 13, at 6 months post last vaccination, GMT ratios in 9 to 14 year-old girls in the 0, 6 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen ranged from 1.21 to 2.54. The lower bounds of the 95% CIs for the fold differences were greater than 0.67 for all 9 HPV types. Similar findings were observed when comparing 9 to 14 year-old boys receiving the 0, 6 regimen vs. 16 to 26 year-old women under the 0, 2, 6 regimen.

Table 13: Comparison of HPV cLIA GMT at 6 Months Post Last Dose of 9-14 Year-Old Females (0, 6 Regimen) and 16-26 Year-Old Females (0, 2, 6 Regimen) (Per-Protocol Immunogenicity Population)

Age/Sex	9-14 yo Females	9-14 yo Females	9-14 yo Males	9-14 yo Males	16-26 yo Females	16-26 yo Females		
Regimen	(0, 6)	(0, 6)	(0, 6)	(0, 6)	(0, 2, 6)	(0, 2, 6)		
Group	A	A	B	B	C	C		
Assay (cLIA)	n	GMT (mMU/mL)	n	GMT (mMU/mL)	n	GMT (mMU/mL)	Fold Difference Group A / Group C (95% CI)	Fold Difference Group B / Group C (95% CI)
Anti-HPV 6	256	498.8	260	476.8	233	295.0	1.69 (1.42, 2.01)	1.62 (1.38, 1 90)
Anti-HPV 11	257	383.2	264	368.9	237	219.4	1.75 (1.48, 2.06)	1.68 (1.42, 1 99)
Anti-HPV 16	270	2,204.9	273	2,219.3	247	1,100.2	2.00 (1.70, 2.36)	2.02 (1.72, 2 36)
Anti-HPV 18	270	416.5	272	393.0	266	210.8	1.98 (1.63, 2.40)	1.86 (1.55, 2 25)
Anti-HPV 31	270	345.2	271	344.7	263	175.3	1.97 (1.63, 2.38)	1.97 (1.63, 2 38)
Anti-HPV 33	271	285.5	271	285.6	277	112.4	2.54 (2.13, 3.03)	2.54 (2.14, 3.02)
Anti-HPV 45	272	72.7	273	67.7	278	60.3	1.21 (0.99, 1.48)	1.12 (0.92, 1 37)
Anti-HPV 52	270	148.6	273	159.1	269	121.5	1.22 (1.03, 1.45)	1.31 (1.11, 1 54)
Anti-HPV 58	268	370.3	270	395.8	260	175.3	2.11 (1.79, 2.50)	2.26 (1.92, 2.66)

Source: Tables 56 and 57 in applicant's analysis presented in sBLA amendment STN125508/153.2.

6.1.12 Safety Analyses

Safety data were collected for non-serious adverse events for a total of 15 days (day of vaccination plus 14 calendar days) after each vaccination, and serious adverse events from Day 1 through 6 Months following the last dose, regardless of causality. The safety analysis results are presented in a descriptive manner. The reviewer defers to the medical reviewer with regard to the clinical significance of the observed imbalances in the study. A summary of the safety analysis is provided in Table 14. In general, the proportion of subjects who reported at least one adverse event were higher among subjects who received the 0, 2, 6 regimen compared to the corresponding proportion among subjects who received the 0, 6 or 0, 12 regimen.

Table 14: Adverse Event Summary (Day 1 through Visit Cutoff Date) (All Vaccinated Subjects)

	9-14-Year Old Females (0, 6 Regimen) n (%)	9-14-Year Old Males (0, 6 Regimen) n (%)	9-14-Year Old Females and Males (0, 12 Regimen) n (%)	9-14-Year Old Females (0, 2, 6 Regimen) n (%)	16-26-Year Old Females (0, 2, 6 Regimen) n (%)
Subjects in population with follow-up	294	296	293	300	313
with one or more adverse events	75 (25.5)	48 (16.2)	59 (20.1)	88 (29.3)	127 (40.6)
injection-site	48 (16.3)	24 (8.1)	36 (12.3)	62 (20.7)	87 (27.8)
non-injection-site	40 (13.6)	32 (10.8)	27 (9 2)	43 (14.3)	69 (22.0)
with no adverse event	219 (74.5)	248 (83.8)	234 (79.9)	212 (70.7)	186 (59.4)
with vaccine-related adverse events	58 (19.7)	31 (10.5)	47 (16.0)	75 (25.0)	103 (32.9)
injection-site	48 (16.3)	24 (8.1)	36 (12.3)	62 (20.7)	87 (27.8)
non-injection-site	16 (5.4)	12 (4.1)	12 (4 1)	20 (6.7)	34 (10.9)
with serious adverse events	3 (1.0)	5 (1.7)	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)	0 (0.0)
who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued‡ due to an adverse event	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
discontinued due to a vaccine-related adverse event	0 (0.0)	0 (0.0)	1 (0.3)	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)	0 (0.0)
discontinued due to a serious vaccine-related adverse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 12-2 in the CSR for Study V503-010.

6.1.12.1 Methods

Please refer to the medical officer's review for details.

6.1.12.3 Deaths

There were no deaths as of submission date in the study.

6.1.12.4 Nonfatal Serious Adverse Events

Twenty two (22) subjects reported SAEs during the period from Day 1 through visit cut-off date. There were 3, 5, 3, 3, and 8 subjects who reported an SAE in the 9 to 14 year-old girls 0, 6 regimen, 9 to 14 year-old boys 0, 6 regimen, 9 to 14 year-old girls and boys 0, 12 regimen, 9 to 14 year-old girls 0, 2, 6 regimen, and 16 to 26 year-old women 0, 2, 6 regimen, respectively. None of these SAEs were considered vaccine-related by the reporting investigators.

6.1.12.5 Adverse Events of Special Interest (AESI)

Vaccine-related systemic AEs

A summary of the number and percentage of subjects with systemic clinical adverse experiences by System Organ Class (SOC) from Day 1 to 15 following any vaccination visit considered by the investigator to be vaccine-related is provided in Table 15.
The most frequently reported vaccine-related systemic clinical adverse events across treatment groups were headache and pyrexia. The overall profile of vaccine-related systemic clinical adverse events was generally comparable across all vaccination groups.

Table 15: Subjects with Vaccine-Related Systemic Adverse Events by System Organ Class

	9-14-Year Old Females (0, 6 Regimen) n (%)	9-14-Year Old Males (0, 6 Regimen) n (%)	9-14-Year Old Females and Males (0, 12 Regimen) n (%)	9-14-Year Old Females (0, 2, 6 Regimen) n (%)	16-26-Year Old Females (0, 2, 6 Regimen) n (%)
Subjects in population with follow-up	294	296	293	300	313
with one or more vaccine-related systemic adverse events	16 (5.4)	12 (4.1)	12 (4.1)	19 (6.3)	32 (10.2)
with no vaccine-related systemic adverse events	278 (94.6)	284 (95.9)	281 (95.9)	281 (93.7)	281 (89.8)
Blood and lymphatic system disorders	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)
Ear and labyrinth disorders	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)
Gastrointestinal disorders	3 (1)	1 (0.3)	3 (1)	4 (1.3)	6 (1.9)
General disorders and administration site conditions	4 (1.4)	1 (0.3)	3 (1)	7 (2.3)	8 (2.6)
Infections and infestations	2 (0.7)	0 (0)	0 (0)	3 (1)	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.3)	6 (2)	2 (0.7)	0 (0)	4 (1.3)
Nervous system disorders	5 (1.7)	6 (2)	5 (1.7)	7 (2.3)	15 (4.8)
Respiratory, thoracic and mediastinal disorders	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	0 (0)	1 (0.3)	2 (0.7)	2 (0.6)
Vascular disorders	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Table 14-31 in the CSR for Study V503-010.

Pregnancy Outcomes

Eleven subjects (2 girls in the 0, 12 regimen and 9 young women in the 0, 2, 6 regimen) reported pregnancy in the study. Outcomes were available for 7 of the 11 pregnancies, including 2 pregnancies that resulted in fetal loss (elective abortion) and 5 pregnancies that each resulted in live birth of a normal infant.

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

One subject (0, 12 regimen) discontinued the study or did not complete the assigned treatment regimen due to a clinical adverse event, urticaria. The condition was of moderate intensity and was assessed as vaccine-related by the investigator.

6.1.12.8 Safety Subgroup Analyses

Since the study groups in the trial were gender/sex specific, subgroup analyses by gender and age are presented in the earlier sections in Section 6. Because of the small event rates for adverse events that are of clinical significance, such as vaccine-related serious adverse events and adverse events that led to withdrawals, subgroup analyses by race and region are not performed as they are unlikely to provide meaningful results.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A

8. INTEGRATED OVERVIEW OF SAFETY

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Data from one Phase III GARDASIL®9 clinical study (V503-010) were submitted to support the proposed the label change. In this study, immunogenicity results among preadolescents and adolescents 9 through 14 years of age in 2-dose regimens -- 0, 6 months or 0, 12 months -- were compared with young women 16 through 26 years of age following the approved 3-dose regimen, 0, 2 months, 6 months. The pre-specified noninferiority criteria (> 0.67 fold for geometric mean titer ratios and > -5% for difference in seroconversion rate) regarding the immune responses measured at four weeks post last dose via HPV competitive luminex immunoassay (cLIA) were met.

In addition to the analysis results regarding the primary and secondary immunogenicity objectives, the following additional findings were observed:

- At 6 months post last vaccination, the GMT ratios between 9 to 14 year-old girls/males in the 0, 6 regimen vs. 16 to 26 year-old women in the 0, 2, 6 regimen were lower than the corresponding GMT ratios at 4 weeks post last vaccination. However, the lower bounds of the 95% CIs for the fold differences were greater than 0.67 for all 9 HPV types.

- The 0, 12 regimen generally elicited numerically higher antibody responses than the 0, 6 regimen.

- The study allowed comparison between the 2-dose regimen and 3-dose regimen groups in girls 9 through 14 years of age. The results varied by HPV type.

- Prior to the last dose in the two dose groups, 0, 6 or 0, 12 regimens, the GMTs for Serotype 45 were low, being 6.1, 4.6, and 4.4, for the 9-14 year-old females in the 0,6 regimen group, 9-14 year-old males in the 0,6 regimen group, and 9-14 year-old males and females in the 0,12 regimen group. The GMTs for all other HPV vaccine types remained above the corresponding seropositive cutoffs after the first dose, but prior to the second dose in the two-dose regimen groups.

The reviewer defers to the medical officer on evaluation of the clinical significance of these findings.

With regard to safety, vaccine report cards (VRCs) were not used in this study, given that extensive data on the three-dose regimen had been obtained. Non-serious adverse events (AEs) occurring Day 1 to 15 following any vaccination and serious adverse events (SAEs) through 6 months following the last vaccination were collected in the study. In general, the proportion of subjects who reported at least one adverse event were higher among subjects who received the 0, 2, 6 regimen compared to the corresponding

proportion among subjects who received the 0, 6 or 0, 12 regimen. There were no deaths observed in the study as of the date of the clinical study report. There were 22 subjects reporting an SAE, but none of the SAEs were deemed to be associated with vaccination by the investigators.

Randomization between groups was not possible in this study because subjects cannot be randomized to sex/age. To reduce potential bias in the immunogenicity assessments, the laboratory personnel conducting HPV serology assays were blinded to age and sex of all subjects enrolled in the study. All decisions regarding the inclusion or exclusion of subjects in the per-protocol immunogenicity population based on protocol violations were made while the study team was blinded to immunogenicity results.

10.2 Conclusions and Recommendations

There are no major statistical issues related to this submission. Primary results were confirmed by the reviewer's independent analyses. The primary immunogenicity objective pre-specified in the study was met and, thus, the study results support approval of the license application. The reviewer defers to other members of the review committee regarding implications of the additional observed immunogenicity findings through exploratory analyses noted in this review.