Application Type	sBLA
STN	125508/153
CBER Received Date	February 1, 2016
PDUFA Goal Date	December 1, 2016
Division / Office	DVRPA /OVRR
Priority Review	No
Reviewer Name(s)	Joohee Lee
Review Completion Date / Stamped Date	October 6, 2016
Supervisory Concurrence	Lucia Lee, M.D., Team Leader, CRB1 Jeff Roberts, M.D., Chief, CRB1
Applicant	Merck
Established Name	Human Papillomavirus 9-valent Vaccine, Recombinant
(Proposed) Trade Name	Gardasil 9
Pharmacologic Class	Vaccine

Formulation(s), including Adjuvants, etc	A 0.5 mL dose contains: Recombinant virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58)* adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS) *Amounts of HPV type L1 protein are as follows: 30 mcg/40mcg/60mcg/40mcg/20mcg/20mcg/20mcg/20mcg/20mcg, respectively.
Dosage Form(s) and Route(s) of Administration	0.5-mL suspension for intramuscular injection as a single-dose vial and prefilled syringe
Dosing Regimen	Two-dose regimen: 0 and 6 to 12 months A 3- dose regimen (0, 2 and 6 months) is approved for use in individuals 9 through 26 years of age (STN 125508/0)

Indication(s) and Intended Population(s)	This supplement introduces a 2-dose regimen in addition to the licensed 3-dose regimen. The intended population for the 2-dose regimen is girls and boys 9 through 14 years of age. The previously approved 3-dose regimen is unchanged for girls and young women 15 through 26 years of age and remains indicated for girls 9 through 14 years of age. Gardasil 9 is indicated in girls and women for the prevention of the following diseases: • Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (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. The previously approved 3-dose regimen is unchanged for boys and young men 15 through 26 years of age and remains indicated for boys 9 through 14 years of age. GARDASIL 9 is indicated in boys and men for the prevention of the following diseases: • 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.

Orphan Designated (Yes/No)	No

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GLOSSARY

AAHS	Amorphous Aluminum Hydroxyphosphate Sulfate
AEs	Adverse experiences or events
AHN or All-HN	All-HPV Naive
AIN	Anal intraepithelial neoplasia
AIS	Adenocarcinoma in situ
CFR	Code of Federal Regulations
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
cLIA	Competitive Luminex Immunoassay
CRF	Case report form
CSR	Clinical study report
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECC	Endocervical curettage
eCRF	Electronic case report form
eDMC	External Data Monitoring Committee
EGLs	External genital lesions
(b) (4)	(b) (4)
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMTs	Geometric Mean Titers
hCG	Human chorionic gonadotropin
HN-TS	HPV-Naïve Type-Specific
HPV	Human Papillomavirus
HR	High-risk
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LEEP	Loop Electrosurgical Excision Procedure
LMP	Last menstrual period
LR	Low-risk
LSIL	Low-Grade Squamous Intraepithelial Lesion
LVPP	Labial/vulvar/perineal and perianal
mAbs	Monoclonal antibodies
MARRS	Merck Adverse event Reporting and Review System
mMU/mL	milli-Merck Units per milliliter
MRL	Merck Research Laboratories
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSM	Men-having-sex-with-men
Pap	Papanicolaou
PCR	Polymerase Chain Reaction
PPI	Per Protocol Immunogenicity
RCD	Reverse Cumulative Distribution
RR	Risk reduction
SAEs	Serious Adverse Experiences

SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
SD	Standard deviation
ULN	Upper limit of normal
VaIN	Vaginal Intraepithelial Neoplasia
VE	Vaccine efficacy
VIN	Vulvar Intraepithelial Neoplasia
VLP	Virus-Like Particle
VRC	Vaccination Report Card

1. EXECUTIVE SUMMARY

Human papillomavirus (HPV) vaccines are intended to prevent the development of HPV-associated genital warts and cervical and anal cancers. The HPV vaccine antigens are recombinant HPV L1 capsid proteins, which form HPV virus-like particles (VLPs) devoid of the potentially oncogenic genes, mimicking the structure of HPV virions to induce an immune response. GARDASIL® 9 is a 9-valent (6/11/16/18/31/33/45/52/58) HPV (GARDASIL 9) vaccine that was licensed in 2014 to be given as a 3-dose regimen for girls and women 9 through 26 years of age and for boys 9 through 15 years of age. In 2015, a supplement was approved to expand the indication to include boys and men 16 through 26 years of age. In this supplement Biologics License Application (sBLA), Merck provided safety and immunogenicity data to support use of a 2-dose regimen (Day 1 and Month 6 through 12) of GARDASIL 9 in young adolescent boys and girls 9 to <15 years of age.

This sBLA included safety and immunogenicity data from an open-label Phase 3 study (V503-010) of two 2-dose vaccination regimens of GARDASIL 9 (Day 1 and Month 6; Day 1 and Month 12) in 903 adolescent boys and girls 9 to 14 years of age compared to the 3-dose regimen (Day 1, Month 2, Month 6) in 314 young women 16 to 26 years of age. The comparator group represents the population in which clinical effectiveness of GARDASIL 9 was established prior to initial approval of the GARDASIL 9 vaccine. The study was conducted at 52 sites internationally.

The primary endpoint was the ratio of the 4-week post-vaccination geometric mean titer (GMT) of the 9 different HPV types in the three 2-dose cohorts (P1) against that observed in the 3-dose young women cohort (P2). Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) of the post-vaccination GMT ratio (P1/P2) was >0.67 for all 9 HPV types. The secondary immunogenicity endpoint was the difference in seroconversion at 4 weeks post last dose in the 2-dose cohorts (P1) compared to the 3-dose young women cohort (P2). Non-inferior seroconversion was demonstrated if the lower bound of the 95% confidence intervals of (P1-P2) was > -5% for all 9 HPV types contained in the vaccine.

In V503-010, non-inferiority criteria for the primary and secondary endpoints were met for all 9 HPV types in adolescent boys and girls from both 2-dose regimens (Day 1 and Month 6, Day 1 and Month 12) cohorts relative to the young women vaccinated with 3 doses (Day 1, Month 2, Month 6). Additional immunogenicity data on persistence of antibodies will be collected out to 36 months, which will enable comparison of titers to those from the clinical efficacy population of young women 16 to 26 years of age.

Solicited AEs were not collected due to the existing safety database of over 15,000 subjects who have received GARDASIL 9. Based on the profile of unsolicited AEs and SAEs, there is no indication that a 2-dose regimen is less

safe than the 3-dose regimen. As expected, cumulative rates of local and systemic AEs tended to be lower in the 3 groups receiving 1 less vaccine dose (P1) than in the comparator group (P2).

The 2-dose vaccine regimen of GARDASIL 9 triggered Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). A waiver was granted for the requirement to conduct studies in individuals 0 to < 9 years of age and 15 to <17 years of age, because GARDASIL 9 administered as a 2-dose regimen does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in these age groups and is not likely to be used in a substantial number of pediatric patients in these age groups. Please refer to Section 9.1 for discussion of the differences in “meaningful therapeutic benefit” and “use” in these 2 different age groups. In conclusion, this reviewer recommends approval of the 2-dose regimen of Gardasil 9 in addition to the original 3-dose regimen for females and males 9 through 14 years of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

A total of 1,518 subjects were enrolled in V503-010. Female predominance in the overall study population (70.3%) reflects the two 3-dose regimen arms limited to adolescent girls and young women. Male and female representation was balanced in the three 2-dose arms. Four hundred fifty-one boys (9 to 14 years old) were allocated 2:1 to a Day 1 and Month 6 cohort and to a Day 1 and Month 12 cohort. Seven hundred fifty-three girls (9 to 14 years old) were allocated 2:1:2 to a Day 1 and Month 6 cohort, the Day 1 and Month 12 cohort shared with boys, and a 3-dose regimen cohort, which was not included in the primary and secondary endpoint analyses.

The mean and median ages of the boys and girls in the three 2-dose cohorts ranged from 11.4 to 11.5 years and 11 to 12 years, respectively. The mean and median ages of the 301 girls (9 to 14 years old) allocated to the 3-dose regimen were 11.4 years and 12 years. Age representation in the three 2-dose regimen and one 3-dose regimen arms was evenly distributed across the eligible age range: 32.6 to 33.6% of subjects were 9 to 10 years old, 33.2 to 35.2% of subjects were 11 to 12 years old, and 31.6 to 33.2% of subjects were 13 to 14 years old.

The majority of the young adolescents in the three 2-dose regimen arms were identified as Caucasian (53.2 to 70.1%). The racial demographic profile of the 9 to 14 year-old girls in the three-dose regimen arm was similar, with 154 (51.2%) Caucasians, 63 (20.9%) Asians, 43 (14.3%) Black or African-Americans, and 31 (10.3%) reported as Multi-racial.

The mean and median ages of the 314 young women (16 to 26 years old) of the 3-dose regimen comparator arm were 21.0 and 21.0 years. Racial demographic data were available for 309 of the young women, with 213 (67.8 %) identified as Caucasian, 45 (14.3%) as Asian, 22 (7.0%) as Multi-racial, 21 (6.7%) as Black or African-American, and 8 as American Indian or Alaska native.

A total of 20 different SAEs (from 20 subjects) were observed during the period from Day 1 through visit cut-off date (See Table 16). There was no pattern of SAEs among the GARDASIL 9 recipients and review of the case narratives did not reveal information to

suggest a causal relationship. Given the small number and the diversity of SAEs, no meaningful subgroup analyses can be performed.

Subgroup analyses of the geometric mean titers (GMTs) for the 9 HPV serotypes by sex, race, and by the 5 geographic regions did not reveal any significant differences compared to those reported for the overall per-protocol efficacy population.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

- Genital HPV infection is the most common sexually transmitted infection. In most individuals, these infections are self-limited and are cleared without sequelae.
- A clinical classification of human papillomavirus (HPV), a family of >100 DNA viruses exhibiting tropism for epithelial and mucosal surfaces, categorizes HPV by types:
    - High-risk (HR) cancer-causing types (in descending order of frequency in tumor specimens): HPV 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 39, 51, 73, 66 and 68)
    - Low-risk (LR) types (causing generally benign lesions): e.g., HPV 6, 11, 42, 43, 44)
- Persistent infection with HR oncogenic HPV types is causally linked to the development of almost 100% of cervical cancers, up to 90% of anal cancers, and many vulvar, vaginal, and penile cancers. GARDASIL 9 contains type L1 proteins for 7 oncogenic HPV types. Types 16 and 18 are associated with over 70% of cervical cancers. With the addition of L1 proteins of types 31, 33, 45, 52, and 58 in GARDASIL 9, coverage of oncogenic HPV types increases to over 90%.
- LR HPV types 6 and 11 account for over 90% of genital warts. Coverage against genital warts is unchanged in GARDASIL 9 compared to GARDASIL.

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

2.2.1 Prevention of HPV infection and disease

With the exception of recurrent respiratory papillomatosis, which can be vertically transmitted, abstaining from sexual activity is the only certain way to prevent HPV infection. Consistent use of condoms and limiting the number of sexual partners only reduce the risk of HPV infection.

Screening for cervical cancer is also an important measure for HPV disease prevention. Guidelines for cervical cancer screening are still applicable to female recipients of GARDASIL 9. There is consensus among several clinical practice guidance bodies, such as the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Colposcopy and Cervical Pathology (ASCCP) that cervical cancer screening should begin at 21 years of age, with frequencies changing with age and risk factors. HPV testing is recommended as a reflex or sequential step to evaluate abnormal Pap smear results in women 21 to 29 years of age. For women 30 years and older, HPV testing is recommended to be performed concurrently with Pap smears. Up to 14 oncogenic types can be detected from cervical samples with FDA-approved HPV diagnostic assays.

2.2.2 Treatment of HPV-associated lesions

Although there is no treatment for HPV infection, there are surgical and medical options for HPV-associated lesions. High-grade CIN are managed surgically with excision and/or ablation. Genital warts can be managed by various regimens, which include options that can be applied by the patient (such as topical creams and ointments) and those that require a medical provider (such as cryotherapy, topical treatments, surgical excision).

2.3 Safety and Efficacy of Pharmacologically Related Products

The first licensed HPV vaccine was the quadrivalent HPV (Types 6, 11, 16, and 18) Vaccine, GARDASIL (Merck), which was approved in 2006 as a 3-dose regimen (Day 1, Month 2, Month 6) in girls and women, as well as boys and young men between 9 and 26 years of age. In girls and women, the indication is for prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18, genital warts caused by HPV types 6 and 11, and precancerous or dysplastic cervical, vulvar, vaginal, and anal lesions caused by all 4 HPV types in GARDASIL. In boys and men, the indication is for anal cancer due to types 16 and 18, genital warts due to types 6 and 11, and anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. In addition to the HPV L1 proteins, GARDASIL contains amorphous aluminum hydroxyphosphate sulfate as adjuvant. Clinical trials supporting licensure evaluated GARDASIL against predominantly adjuvant-only as well as saline placebo.

The bivalent (Types 16 and 18) HPV Vaccine, Cervarix (GlaxoSmithKline), was approved in 2009 for use in females between the ages of 9 and 25 years to be administered as a 3-dose regimen (Day 1, Month 1, Month 6). Cervarix is indicated for prevention of cervical cancer, cervical intraepithelial neoplasia (CIN) Grade 1 or worse, and adenocarcinoma *in situ* associated with HPV types 16 and 18. Cervarix contains a proprietary aluminum salt adjuvant, aluminum hydroxide with 3-deacetylated monophosphoryl lipid A (ASO4), which stimulates innate immunity through Toll-like receptor 4 (TLR-4). Clinical trials of Cervarix supporting licensure used the Hepatitis A Vaccine as the control vaccine.

End of study analyses of the Phase III trials of GARDASIL and CERVARIX indicate that both vaccines are safe and immunogenic. Notably, in young women (16 to 26 years of age) naive to the HPV vaccine types, both vaccines provide clinical efficacy against the vaccine-targeted HPV types for endpoints including persistent infection to cervical intraepithelial neoplasia grade 2+. Clinical efficacy studies have not been conducted in adolescent girls and boys, the primary target of vaccination programs, due to ethical reasons. HPV vaccines have been approved based on immunobridging strategies comparing adolescents' immune responses to those of the above-mentioned clinical efficacy population. Duration of antibody levels has been observed to persist out to 10 years. However, even when antibody titers drop to undetectable levels, protection against new infection appears to persist. [1]

(b) (4) . And Merck plans to retire GARDASIL by the end of 2016. (b) (4)

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

2.4.1 Clinical Trials with GARDASIL 9

GARDASIL 9 was studied in 6 clinical trials:

- Study V503-001 was a Phase 2b/3efficacy study that enrolled 15,457 women 16 through 26 years of age and randomized to receive GARDASIL 9 (low-dose, mid-dose, high-dose) or GARDASIL (comparator). The optimal dose for further investigation was defined as the "mid-dose." This study demonstrated efficacy of 96.7% in terms of prevention of combined genital lesions (CIN2+, VIN2+, or VaIN2+) attributed to the 5 additional HPV types not present in GARDASIL.
- Study V503-002 was an– immunobridging study linking clinical efficacy obtained from Study V503-001 to 955 children 9 through 15 years of age. Evaluation of clinical efficacy was not feasible because performing genital examination in this population in the absence of the primary endpoint was not justifiable. Non-inferiority was demonstrated for all 9 vaccine HPV types, and lot consistency criteria were also met for the 9 vaccine HPV types.
- Study V503-009 was an additional immunological bridging study (not conducted under IND) in 600 females 9 through 15 years of age which demonstrated non-inferior GMT ratios for HPV types 6, 11, 16, and 18 between GARDASIL 9 and GARDASIL
- There were 3 studies evaluating vaccine coadministration:
    - V503-005 – assessment of potential interference of Gardasil 9 with concomitant Menactra and Adacel in children 11 through 15 years of age
    - V503-006- safety and immunogenicity study of Gardasil 9 in subjects previously vaccinated with the qHPV vaccine
    - V503-007- concomitant administration study with a non-U.S.-licensed vaccine (Repevax); provided safety data for GARDASIL 9 in adolescents 11 through 15 years of age

An efficacy supplement in December 2015 (STN 125508/15) extended the indication in males through 26 years of age based on immunobridging compared to the clinical efficacy population from V503-001. Clinical data from Protocol V503-003 demonstrated comparable safety and non-inferior immunogenicity in approximately 1,400 young men 16 through 26 years of age compared to that in approximately 1,100 young women 16 through 26 years of age.

2.4.2 Post Licensure Safety Studies of GARDASIL 9

There are 4 ongoing postmarketing studies for the 3-dose regimen (0, 2, and 6 months).

- Ten-year study extension of pre-licensure study V503-002 to evaluate the long-term safety, immunogenicity and effectiveness (NCT00943722) of GARDASIL 9 in males and females who were between 9 and 15 years of age at enrollment
    - Study completion: September 30, 2022
- Ten-year study extension of pre-licensure study V503-001 to evaluate the long-term safety, immunogenicity and effectiveness (NCT02653118) of GARDASIL 9 in women who were 16 to 26 years of age at enrollment
    - Study completion: June 30, 2026
- Observational study to further characterize the safety profile of GARDASIL 9 in approximately 10,000 persons
    - Study completion: December 31, 2018

- Pregnancy registry to continue for at least 5 years from time of establishment, in January 2015, to prospectively collect data on spontaneously reported exposures to GARDASIL 9 occurring within 30 days prior to the last menstrual period or at any time during pregnancy
    - Five-year summary report submission: August 10, 2020

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

2.5.1 Pre-submission Regulatory Activities

- **April 30, 2013:** A Type C meeting was scheduled for this date in response to Merck's request to discuss the licensure approach for an "alternate" 2-dose vaccine regimen for GARDASIL 9. CBER provided preliminary responses to Merck's questions. Subsequently, Merck retracted the request and indicated that they intended to conduct the P3 2-dose trial overseas, not under IND 13447.
- **March 5, 2014:** A Type C teleconference was held to revisit the 2-dose regimen of GARDASIL 9. At this point, over 50% of the total study population was enrolled. Merck sought to establish CBER's agreement on licensing a 2-dose regimen based on immunobridging to the 16 and 26 year-old women in whom clinical effectiveness of the 3-dose regimen was established. The rationale for this immunobridging approach included consideration of the fact that a similar approach was used to bridge efficacy with regard to the original indication from young women 16 to 26 years of age to adolescents 9 to 15 years of age. A long-term clinical effectiveness study of the 2-dose regimen, which was submitted to IND 13447 as an amendment, was also discussed as a potential post-marketing commitment. See Section 11.6 for details on the discussion that led to revision from investigating clinical endpoints to extrapolating effectiveness from immunogenicity data.
- **Jan 2016:** Prior to submitting the efficacy supplement, Merck requested CBER's agreement on inclusion of the 2-dose regimen for 9 to 14 year-old persons *in addition* to the 3-dose regimen. CBER agreed.

2.6 Other Relevant Background Information

- Epidemiological studies indicate that HPV acquisition occurs soon after sexual debut, which tends to occur at 15 years of age and above in most countries. HPV vaccines are intended for prophylaxis, and therefore, initiation and completion of the vaccination regimen before coitarche would be ideal.
- Data on vaccination uptake among adolescents (13 to 17 years old) has been collected by the CDC since 2006. The latest data from 2013 indicate that uptake has been increasing, but remains lower than expected. Initiation rates for an HPV vaccine were estimated at 57.3% for girls and 34.6% for boys. Completion of the 3-dose series lower, with 40% for girls and 15% for boys.[2]
- Interest in a 2-dose regimen for HPV vaccines stems from clinical data and public health-oriented benefits.
    - Immunobridging studies of the 3-dose regimen in pre-adolescents have demonstrated enhanced antibody responses compared to young women between the ages of 16 and 26 years old, in whom vaccine efficacy was established in prelicensure studies of a 3-dose series of HPV vaccine.
        - This suggested the possibility that a dose could be eliminated while maintaining immunogenicity. Subsequently, a published

study comparing 2 doses (Day 1 and Month 6) of the qHPV vaccine in girls 9 to 13 years of age to 3 doses (Day 1, Month 2, Month 6) in young women 16 to 26 years of age showed non-inferior geometric mean titers (GMTs) for all HPV types.[3]

- Experts in the field have speculated that a regimen requiring one less dose and one less healthcare visit could improve acceptability and compliance with HPV vaccination and reduce overall costs of vaccination programs.
  - As of October 2015, at least 55 countries had already implemented a 2-dose regimen of the bivalent and/or quadrivalent HPV vaccine for pre-adolescents and young adolescents.
  - Since 2016, the World Health Organization (WHO) has endorsed a 2-dose regimen.[4]

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

This efficacy supplement includes one study (Protocol V503-010). The study design adhered to good clinical practices.

The BIMO team did not identify any issues relevant to study or data integrity at the three sites inspected (listed below). The sites were selected based on observed outlier AE rates or subject enrollment.

- Site 0011 (Canada)
- Site 0022 (Chile)
- Site 0092 (Norway)

3.3 Financial Disclosures

Covered clinical study (name and/or number): **V503-010**		
Was a list of clinical investigators provided:	**Yes**	No ☐ (Request list from applicant)
Total number of investigators identified: **236** (1 investigator did not return the financial disclosures form)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **1**		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: No Significant payments of other sorts: (b) (4), (b) (6) **for consultant and speaker fees as reported on 2/4/2014** Proprietary interest in the product tested held by investigator: **No. An internal search was performed by Merck;** (b) (4) **This assay was not used in the study of V503.** Significant equity interest held by investigator in sponsor of covered study: **No**		
Is an attachment provided with details of the disclosable financial interests/arrangements:	**Yes** ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **1**		
Is an attachment provided with the reason:	**Yes** ☒	No ☐ (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

The formulation of GARDASIL 9 used in study V503-010 was the same as the formulation reviewed in the BLA (STN 125508/0).

4.2 Assay Validation

CBER requested trend analyses for control samples used in the 9-valent cLIA for the time period of assay testing to V503-010. The results, which were submitted as an amendment (see Section 5.2), were found to be satisfactory by the CMC reviewer.

4.3 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology or toxicology studies of GARDASIL 9 were conducted in support of this efficacy supplement.

4.4 Clinical Pharmacology

No clinical pharmacology studies of GARDASIL 9 were conducted in support of this efficacy supplement.

4.4.1 Mechanism of Action

Preclinical data suggest that a protective effect is mediated through IgG neutralizing antibodies directed against the major capsid L1 protein. Type-specific neutralizing

antibodies to L1 VLPs are measurable, using (b) (4) following vaccination with GARDASIL 9. No correlate of protection has been identified because protection against new HPV infection appears to persist even among subjects for whom type-specific antibody titers are no longer detectable.

4.5 Statistical

Independent analyses of primary and secondary immunogenicity endpoints confirmed the stated conclusions from the Clinical Study Report. Please refer to the statistical review by Lihan Yan for details.

4.6 Pharmacovigilance

The Applicant confirmed that there were no changes to the pre-existing pharmacovigilance plan for GARDASIL 9 specific to this supplement.

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

5.1 Review Strategy

Immunogenicity and safety data from a single study (V503-010) was provided in this sBLA to support a 2-dose regimen of administering GARDASIL 9 in females and males 9 through 14 years of age.

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

The following documents submitted to the BLA, as listed by electronic common technical document (eCTD) module, served as the basis for this review:

- BLA 125508/153.0, Module 1.3.4 (Financial Disclosure)
- BLA 125508/153.0, Module 1.6.2 (Meeting Background Materials)
- BLA 125508/153.0, Module 1.9.4 (Proposed Pediatric Study Plan)
- BLA 125508/153.0, Module 1.12.4 (Request for Comments and Advice on an IND {clinical effectiveness protocol})
- BLA 125508/153.0, Module 1.14.1 (Draft Labeling)
- BLA 125508/153.0, Module 2.5 (Clinical Overview)
- BLA 125508/153.0, Module 2.7.3 (Summary of Clinical Efficacy)
- BLA 125508/153.0, Module 2.7.4 (Summary of Clinical Safety)
- BLA 125508/153.0, Module 2.7.6 (Synopses of Individual Studies)
- BLA 125508/153.0, Module 5.3.5.4 (Protocol and Clinical Study Report for V503-010
- BLA 125508 Amendments
    - 125508/153.1 – Received 3/1/2016; response to IR #1 from February 18, 2016 for list of all study sites used in V503-010
    - 125508/153.2 – Received 5/6/2016; response to IR #2 from April 8, 2016 for [1] subgroup analyses by race and region for primary immunogenicity and safety endpoints; [2] summary of primary immunogenicity endpoints at all time points other than 4 weeks post last dose; [3] submit 6-month safety data for the boys and girls vaccinated at Day 1, Month 12
    - 125508/153.3 – Received 5/16/2016; response to IR #3 from 5/2/2016 for a trend analysis for the control samples used in the 9-valent CLIA for the time period of assay use for V503-010

- 125508/153.5 – Received 9/28/2016; submission of study completion and final study report dates associated with V503-010-01, a post-marketing commitment (PMC), which will follow antibody titers to the nine vaccine-HPV types out to 36 months in the 5 study cohorts of young girls, boys, and young women

- IND amendment with the clinical effectiveness protocol (IND 13447/153)
- BLA 125508/0, Clinical Review

5.3 Table of Studies/Clinical Trials

Table 1: Key features of Protocol V503-010

Study ID	V503-010
IND Number	Not applicable
NCT Number	Not applicable
EudraCT Number	2013-001314-15
Study Phase	3
Study Centers	53 sites, 52 of which enrolled subjects
	Canada (n=4) Chile (n=2) Colombia (n=4) Czech Republic (n=4) Denmark (n=3) Israel (n=4; 1 received supplies but did not enroll) Norway (n=2) Republic of Korea (n=3) Malaysia (n=3) South Africa (n=2)Spain (n=3) Taiwan (n=1) Thailand (n=2) Turkey (n=3) United States (n=12)
Participants Planned	1500
Participants Enrolled	1518
Age Range	8 to 26 years old
Demographics	
GARDASIL 9 2-Dose Regimen [Day 1 and Month 6] [Day 1 and Month 12]	452 girls between 9 and 14 years of age 451 boys between 9 and 14 years of age
GARDASIL 9 3-Dose Regimen [Day 1, Month 2, Month 6]	314 women between 16 and 26 years of age 301 girls between 9 and 14 years of age
Study Duration	37 months
Primary Efficacy Endpoints	Antibody GMTs for all 9 vaccine HPV types
Major Findings	Non-inferior immunogenicity with respect to GMT ratios (primary endpoint) and seroconversion rates (secondary endpoint)

5.4 Consultations

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because review of this submission did not identify concerns or issues which would have benefitted from an advisory committee discussion. There were no issues that required external consults.

5.5 Literature Reviewed

1. Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;305:F123-F138.
2. Stokley S, Jeyarajah J, Yankey D, Cano M, Gee J, Roark J, C. Robinette C, and Markowitz L. MMWR Morb Mortal Wkly Rep 2014; 63(29): 620-4.
3. Dobson SM, McNeil S, Dionne M, et al. Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women: A Randomized Clinical Trial. *JAMA.* 2013;309(17):1793-1802.
4. Human papillomavirus vaccines: WHO position paper, October 2014. Weekly epidemiological record, No.43, 2014, 89, 465-492.
5. Human Papillomavirus Vaccination: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR / August 29, 2014 / Vol. 63 / No. 5

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

[NCT01984697]
V503-010: Phase III Clinical Trial to Study the Immunogenicity and Tolerability of a 2-dose regimen of V503 (9v HPV vaccine, Gardasil 9)

6.1.1 Objectives (Primary, Secondary, etc)

The primary objectives of the trial were to demonstrate that HPV antibody responses, as measured by GMTs for each HPV vaccine type, after administration of a 2-dose regimen of GARDASIL 9 (Day 1 and Month 6, Day 1 and Month 12) among adolescents 9 to 14 years of age (P1) were non-inferior to antibody responses after administration of a 3-dose regimen (Day 1, Month 2, and Month 6) in women 16 to 26 years of age (P2). Non-inferiority was pre-specified as the lower limit of the 95% confidence interval of the GMT ratio (P1/P2) exceeding 0.67 for each HPV type.

Table 2: Study V503-010 Comparison of 2-dose regimens in 3 cohorts of boys and/or girls (P1) with the 3-dose regimen (P2) in young women

P1 (Age range) *Vaccine dose regimen*	**P2** (Age range) *Vaccine dose regimen*	**P3•** (Age range) *Vaccine dose regimen*
Girls (9-14 years old) *Day 1, Month 6*	Young women (16-26 years old) *Day 1, Month 2, Month 6*	Girls (9-14 years old) *Day 1, Month 2, Month 6*
Boys (9-14 years old) *Day 1, Month 6*		
Girls and Boys (9-14 years old) *Day 1, Month 12*		

The group of 9 to 14 year-old girls given the 3-dose regimen of Gardasil 9 was not analyzed as part of the primary or secondary objectives. Immunogenicity data from this group were analyzed relative to the P1 cohorts by sex and to P2 as exploratory endpoints.

The secondary objectives were to demonstrate that HPV antibody responses, as measured by seroconversion rates for each HPV vaccine type, following a 2-dose regimen of GARDASIL 9 in individuals 9 to 14 years of age (P1 cohorts) were non-

inferior to antibody responses following a 3-dose regimen in young women 16 to 26 years old (P1-P2; NI criteria were pre-specified as a lower limit of the 95% CI for P1-P2 exceeding -5%, for each HPV vaccine type).

Exploratory objectives were to describe the:

- Incidence of vaccine or procedure-related SAEs (2-dose cohorts)
- Antibody titers at 4 weeks after the last dose (Month 6 or Month 12) by sex, age and timing of the second dose (2-dose cohorts)
- Durability of antibody titers at Month 24 and Month 36 (2-dose cohorts)
- Peak-time immunogenicity and antibody persistence 9 to 14 year-old girls given the 3-dose regimen (P3)
- B cell memory responses in a subset of subjects from all 5 treatment groups
- Immunogenicity at Month 37 following a booster dose at Month 36 if titers over time are observed to fall below that of the comparator group
    - All subjects in the 2-dose regimen eligible for Dose 3 at Month 36, and subset of girls and young women in 3-dose regimen group eligible for Dose 4 at Month 36)

6.1.2 Design Overview

V503-010 is an open-label, international, multi-center Phase 3 study. This is a 3 year-long study. Enrollment began on December 16, 2013. The cut-off date for safety and immunogenicity analyses submitted to support this efficacy supplement is June 19, 2015. The design of this Phase 3 study was formally reviewed as an amendment submitted to IND 13447. At the time of review, over 50% of the target population of 1500 subjects had been enrolled (see Section 2.5.1). There are five treatment arms. Boys 9 to 14 years of age were randomized to one of the two 2-dose regimens (Day 1 and Month 6, Day 1 and Month 12). Girls 9 to 14 years of age were randomized to one of the two 2-dose regimens (as above) or the 3-dose regimen (Day 1, Month 2, and Month 6). Young women 16 to 26 years of age were limited to the Day 1, Month 2, and Month 6 regimen as a comparator group.

> ***Reviewer comment:*** *Of the 5 vaccination cohorts enrolled in V503-010, four were evaluated for primary and secondary endpoint analyses. Immunobridging was conducted between the three 2-dose regimen cohorts and the comparator arm of young women who received the 3-dose regimen. Data from the fifth cohort of 9 to 14 year-old girls vaccinated at Day 1, Month 2, and Month 6 were limited to exploratory analyses. CBER recommended the addition of this fifth cohort because useful comparisons could be made with this cohort against the young adolescents receiving one of the two 2-dose regimens, as well as against the young women receiving the 3-dose regimen.*

Immunogenicity assessment

Serum samples were obtained at multiple time points. Anti-HPV antibodies to each of vaccine serotypes (6, 11, 16, 18, 31, 33, 45, 52, and 58) were measured using a competitive Luminex Immunoassay (cLIA). Serologic testing was performed by (b) (4) . Study staff conducting the cLIA assays were blinded to the treatment assignment.

Safety assessment
Non-serious adverse events (AEs) were not systematically solicited with the use of a Vaccine Report Card; this was justified by the existence of a large (>15,000 subjects) safety database for GARDASIL 9. Study participants and investigators had the opportunity to report AEs occurring on the day and 14 days after each vaccine dose in the study database. Information about pregnancy outcomes (including subjects who had a positive pregnancy test at Day 1 and were not randomized) and lactation events were collected through Month 37. For all cohorts, serious adverse events (SAEs) were collected for 6 months following the last vaccination. However, since safety follow-up evaluations occurred yearly after the Month 12 visit, SAEs from the Day 1 and Month 12 cohort were collected at Month 24.

> ***Reviewer comment:*** *Although the timing of the SAE collection for the Day 1, Month 12 cohort is not ideal, it is acceptable from a clinical perspective because events defined as SAEs are not likely to be forgotten by subjects and/or their guardians In addition, if they did occur the protocol provided additional ways for SAEs to have been caught sooner than the Month 24 visit. The protocol explicitly states that physician investigators are to immediately report to the Sponsor any cases of subjects discontinuing the trial due to death or any SAE judged to be vaccine related. Given these measures, the 6 month delay in a scheduled collection of SAEs is unlikely to have compromised subject safety or study integrity.*

6.1.3 Population

Eligibility of Boys and Girls 9 to 14 years

- Good physical health, assent and consent
- Has not had coitarche and doesn't plan on becoming sexually active during vaccination period (~13 m)

Eligibility of Women 16 to 26 years

- Good physical health, assent/consent
- No Pap testing or only normal Pap test results
- Lifetime history of up to 4 male and/or female partners at time of enrollment
- No sex since first day of last menstrual cycle through Day 0

Main Exclusion Criteria

- History of positive test to HPV
- Received marketed HPV vaccine
- Known allergy to vaccine components
- Enrolled in other trials
- Thrombocytopenia or coagulopathy
- Immunosuppression, asplenic
- Receipt of inactivated vaccines within 14 days, live vaccines within 21 days, or immune globulin within 3 months
- (Females) - pregnant (as determined by a serum pregnancy test or urine pregnancy test that is sensitive to 25 mIU/mL β-hCG).

6.1.4 Study Treatments or Agents Mandated by the Protocol

GARDASIL 9 is a is a sterile, white cloudy suspension containing recombinant VLPs of HPV types 6, 11, 16, 18, 31, 33,45, 52, and 58 adsorbed on adjuvant amorphous aluminum hydroxyphosphate sulfate (AAHS). Each 0.5 mL dose contained 500 µg of AAHS and the following amount of the above mentioned 9 HPV types: 30/40/60/40/20/20/20/20/20 mcg respectively). The vaccine was administered intramuscularly. Two manufacturing lots of the Vaccine Suspension Injectable Vial V503 were administered in this study: WL00049589 and WL00053191 (Data source: Table "Clinical Supplies Dispensed to Subjects," page 9 of Module 2.7.6, STN 125508/135).

6.1.5 Directions for Use

The study vaccine was to be administered as a 0.5 mL dose from a vial containing about 0.75 mL of vaccine. Inspection to confirm normal appearance – whitish, semi-translucent suspension – was required prior to administration. Needle gauge was required to be 22 to 23 gauge, and needle length to be 1 inch for subjects under 200 pounds, and 1.5 inch for subjects above 200 pounds or for thigh injections. The deltoid region of the non-dominant arm was indicated as the preferred site. Injections were not to be administered in the buttocks or within 2 cm of tattoos, scars, or skin abnormalities. All subjects had to be observed for at least 30 minutes following each study vaccination, with documentation.

> ***Reviewer comment****: None of the protocol deviations listed in 16.2.2 of the Clinical Study Report for V503-010 were related to improper administration or dosing.*

6.1.6 Sites and Centers

V503-010 had 53 study centers, but 1 center (in Israel) did not enroll any subjects. Twelve centers were in the United States, 4 centers were in Canada, 6 centers in South America, 12 centers in Europe, 16 centers in Asia, and 2 centers in Africa. The median number of subjects enrolled at each center was 26 subjects (range 6 to 70).

6.1.7 Surveillance/Monitoring

The following administrative procedures were completed for all subjects at Day 1:

- Informed consent
- Informed consent for future biomedical research
- Informed consent for PBMCs (repeated at Month 24)
- Inclusion/exclusion criteria
- Subject identification card
- Medical history review (Month 6, Month 7, Month 24, Month 36, Month 37)
- Concomitant medication and non-study vaccination review (Month 6, Month 7, Month 24, Month 36, Month 37)
- Assignment of screening/randomization number

Vital signs and pregnancy testing in females were performed prior to each vaccination. Adverse events were reviewed at each vaccination dosing visit, post-dose blood draw visits, and at Months 12, 24, and 36. The clinical regimen varied by treatment cohort. See Table 5 for additional details on the visits per clinical protocol.

Table 3: Serology data timepoints for subjects in V503-010

	Day 1	Month 1	Month 6	Month 7	Month 12	Month 13	Month 24	Month 36*	1 week post Month 36°	Month 37
Serum for anti-HPV	a,b,	a,c	a	a,c	All groups	b	All groups	All groups	All groups	All groups
Blood (DNA) for future biomedical	All groups									
Blood for PBMC testing							All groups	All groups	All groups	All groups

a Girls and Boys [Day 1, Month 6]
b Girls and Boys [Day 1, Month 12]
c Girls and Young Women [Day 1, Month 2, Month 6]
*In a subset of 9 to 14 year-old girls and 16 to 26 year old women, a booster dose of vaccine (Dose #4) will be administered after blood collection.
° Blood from the subset of girls and women who received Dose 4 will be collected at a limited number of selected sites based on proximity to eligible PBMC processing centers. These samples will be used to evaluate HPV type-specific B cells and antibody repertoires after the booster vaccine dose at Month 36.
Source: Table 6.0: Trial Flow Chart from the Protocol/Amendment 010-01 (pp.47-52 of 123) for V503-010 (STN 125508/153)

6.1.8 Endpoints and Criteria for Study Success

The primary immunogenicity endpoints for assessing vaccine-specific immune responses was the geometric mean titer (GMT) from 4 weeks after the last dose (Month 7 or Month 13) to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. Study success was declared if the lower limit of the 95% confidence interval of the GMT ratios (P1/P2) for each of the 9 HPV vaccine types was greater than 0.67.

The secondary immunogenicity endpoint was seroconversion for each HPV vaccine type at 4 weeks post last dose, which refers to the percentages of seronegative subjects (at baseline) who become seropositive, with a cLIA titer at or above the cutoff specific to each HPV type. See Table 12 for the cutoff values. The study was concluded to be a success if the lower limit of the 95% confidence interval for the difference in seroconversion rates (P1-P2) for each of the 9 HPV vaccine type was greater than -5%.

Safety data endpoints were the vaccine-related SAEs rates after a 2-dose regimen.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary analysis
Non-inferiority in terms of geometric mean titer was defined by a lower limit of the two-sided 95% CI of the ratio of the GMTs (2-dose adolescent cohorts (P1) divided by 3-dose young women (P2)) 4 weeks after the final vaccine dose was >0.67 for each of the 9 HPV serotypes in the vaccine. One-sided tests of non-inferiority for each of the 9 HPV types were conducted for the 3 primary hypotheses (the 3 P1 cohorts compared to P2 cohort), with adjustment for multiplicity using a step-wise procedure in which each hypothesis had to reach significance, with a p value of less than 0.025, to move on to the next hypothesis.

Secondary Analysis
Non-inferiority in terms of seroconversion rates was demonstrated if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (2-dose adolescents (P1) minus 3-dose young women (P2)) 4 weeks after the last vaccine dose was > -5% for each of the 9 HPV serotypes within each of the three 2-dose cohorts. One-sided tests (per Miettinen and Nurminen) for non-inferior seroconversion with respect to each of the 9 HPV types were conducted for the 3 P1 cohorts compared to P1, with a p value of 0.025. As with the primary analyses, there was multiplicity adjustment for the secondary analyses.

Observational and safety data analyses were conducted using descriptive statistics.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Immunogenicity Analyses
Primary and secondary efficacy endpoints were assessed in all but 1 of the treatment cohorts, which was the girls (9 to 14 years of age) who received the 3-dose regimen.

Per Protocol Immunogenicity (PPI) population:
- received all planned vaccinations
- were seronegative to the relevant HPV type at Day 0
- serum sample obtained within 21 to 49 days following the last vaccine dose
- had no significant protocol violations

Safety Analyses Population
- All subjects who received at least 1 dose of vaccine

6.1.10.1.1 Demographics

Table 4: Demographics (Region and Countries with Trial Sites) of All Randomized Subjects in V503-010

Cohort	**Girls** (9-14 years old) **Day 1, Month 6** n (%)	**Boys** (9-14 years old) **Day 1, Month 6** n (%)	**Girls & Boys** (9- 14 years old) **Day 1, Month 12** n (%)	**Girls** (9-14 years old) **Day 1, Month 2, Month 6** n (%)	**Young women** (16-26 years old) **Day 1, Month 2, Month 6** n (%)
Africa South Africa	26 (8.6)	11 (3.7)	20 (6.6)	38 (12.6)	12 (3.8)
Asia-Pacific Israel Korea, Republic of Malaysia Taiwan Thailand Turkey	79 (26.2)	39 (13.0)	58 (19.3)	81 (26.9)	63 (20.1)
Europe Czech Republic Denmark Norway Spain	56 (18.6)	132 (43.9)	102 (33.9)	66 (21.9)	114 (36.3)
Latin America Chile Colombia	57 (18.9)	34 (11.3)	44 (14.6)	56 (18.6)	55 (17.5)

Cohort	**Girls** (9-14 years old) **Day 1, Month 6** n (%)	**Boys** (9-14 years old) **Day 1, Month 6** n (%)	**Girls & Boys** (9- 14 years old) **Day 1, Month 12** n (%)	**Girls** (9-14 years old) **Day 1, Month 2, Month 6** n (%)	**Young women** (16-26 years old) **Day 1, Month 2, Month 6** n (%)
North America Canada United States	83 (27.6)	85 (28.2)	77 (25.6)	60 (19.9)	70 (22.3)
Total N (%)	301 (100)	301 (100)	301 (100)	301 (100)	314 (100)

Source: Table 10-6- Subject Characteristics (All Randomized Subjects) of CSR for V503-010 (p. 98 of 372)

Table 5: Demographics of gender, age, race, ethnicity in V503-010

Cohort	**Girls** (9-14 years old) **Day 1, Month 6**	**Boys** (9-14 years old) **Day 1, Month 6**	**Girls & Boys** (9-14 years old) **Day 1, Month 12**	**Girls** (9-14 years old) **Day 1, Month 2, Month 6**	**Young women** (16-26 years old) **Day 1, Month 2, Month 6**
N	301	301	301	301	314
Male	0	301	150 (49.8)	0	0
Female	301	0	151 (50.2)	301	314
Age (yrs)	n(%)	n(%)	n(%)	n(%)	n(%)
≤ 8[a]	1 (0.3)	0	1 (0.3)	0	0
9 to 10	99 (32.9)	98 (32.6)	99 (32.9)	101 (33.6)	0
11 to 12	102 (33.9)	102 (33.9)	106 (35.2)	100 (33.2)	0
13 to 14	99 (32.9)	100 (33.2)	95 (31.6)	98 (32.6)	0
15[b]	0	1 (0.3)	0	2 (0.7)	0
16 to 26	0	0	0	0	314
Mean (SD)	11.4 (1.7)	11.5 (1.7)	11.4 (1.6)	11.4 (1.7)	21.0 (2.7)
Median[Range]	11.0 [8.0,14.0]	12.0 [9.0,15.0]	11.0 [8.0,14.0]	12.0 [9.0,15.0]	21.0 [16.0,26.0]
Race					
American Indian/Alaskan	13 (4.3)	12 (4.0)	8 (2.7)	10 (3.3)	8 (2.5)
Asian	64 (21.3)	30 (10.0)	46 (15.3)	63 (20.9)	45 (14.3)
Black/African-American	32 (10.6)	14 (4.7)	25 (8.3)	43 (14.3)	21 (6.7)
Multiple	32 (10.6)	34 (11.3)	32 (10.6)	31 (10.3)	22 (7.0)
White	160 (53.2)	211 (70.1)	190 (63.1)	154 (51.2)	213 (67.8)
Missing	0	0	0	0	5 (1.6)
Ethnicity					
Hispanic or Latino	68 (22.6)	46 (15.3)	58 (19.3)	64 (21.3)	81 (25.8)
Not Hispanic or Latino	217 (72.1)	249 (82.7)	235 (78.1)	223 (74.1)	228 (72.6)
Not reported	16 (5.3)	6 (2.0)	8 (2.7)	14 (4.7)	5 (1.6)

[a] Per CSR (Section 10.5.1), the sites enrolling the 2 subjects reported as 8 years old were investigated and confirmed to be 9 years old.
[b] Per CSR, the sites enrolling the 3 subjects reported as 15 years old were investigated and it was verified that the subjects were 14 years old at time of enrollment.
Source: Table 10-6- Subject Characteristics (All Randomized Subjects) of CSR for V503-010 (pp. 98-100 of 372)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Per protocol, concomitant medication use was followed from Day 1 through Day 15 following each vaccine dosing visit. Use of at least 1 concomitant medication within 14 days of any vaccination dose was reported in about 28.8% of the study population (436/1516). Concomitant medication use (specifically oral contraceptives) was most prevalent in the young women cohort. Across all groups, the most common medication category was oral antibacterials (0.7 to 6.4%).

6.1.10.1.3 Subject Disposition

Table 6: Study Subject Disposition in V503-010

Cohort	**Girls** (9-14 years old) **Day 1, Month 6**	**Boys** (9-14 years old) **Day 1, Month 6**	**Girls & Boys** (9- 14 years old) **Day 1, Month 12**	**Girls** (9-14 years old) **Day 1, Month 2, Month 6**	**Young women** (16-26 years old) **Day 1, Month 2, Month 6**
Total subjects N	301	301	301	301	314
n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Received Dose 1	301 (100.0)	301 (100.0)	300 (99.7)	300 (99.7)	314 (100.0)
Received Dose 2	293 (97.3)	296 (98.3)	291 (96.7)	298 (99.0)	313 (99.7)
Received Dose 3	N/R	N/R	N/R	293 (97.3)	311 (99.0)
Status in trial					
Discontinued	11 (3.7)	7 (2.3)	9 (3.0)	11 (3.7)	6 (1.9)
Adverse event	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Lost to follow-up	7 (2.3)	2 (0.7)	4 (1.3)	3 (1.0)	4 (1.3)
Physician decision	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Withdrawal by subject	3 (1.0)	5 (1.7)	4 (1.3)	7 (2.3)	2 (0.6)
Status not recorded	290 (96.3)	294 (97.7)	292 (97.0)	290 (96.3)	308 (98.1)
Day 1 Composite HPV serostatus with respect to HPV types 6,11, 16, 18, 31, 33, 45, 52, 58					
N with baseline serology	300	301	299	300	314
Negative	269 (89.7)	283 (94.0)	277 (92.6)	268 (89.3)	215 (68.5)
Positive	31 (10.3)	18 (6.0)	22 (7.4)	32 (10.7)	99 (31.5)

Source: Tables 10-1, 10-2, and 10-8 in the CSR for V503-010 (pp. 82, 83, and 105 of 372)

> ***Reviewer comment:*** *Discontinuation rates ranged from 1.9 to 3.7%, with the most common reason being loss to follow-up. The high retention of study subjects, particularly in these younger age groups, for up to 3 years is notable and is suggestive of a well conducted study.*

6.1.11 Efficacy Analyses

Efficacy endpoints in V503-010 are related to immunogenicity. Clinical effectiveness will be evaluated as a post-marketing commitment.

6.1.11.1 Analyses of Primary Endpoint(s)

Primary endpoint analyses were performed using the Per Protocol Immunogenicity (PPI) population.

Table 7: Per Protocol Immunogenicity Analysis Population in V503-010

	9-14y Girls Day 1, Month 6 N=301[a] (%)	**9-14y Boys** Day 1, Month 6 N=301[a]	**9-14 Boys &Girls** Day 1, Month 12 N=301[a]	**9-14y Girls** Day 1, Month 2, Month 6 N=301[a]	**16-26y Young Women** Day 1, Month 2, Month 6 N=314[a]
HPV 6	258 (85.7)	263 (87.4)	257 (85.4)	254 (84.4)	238 (75.8)
HPV 11	258 (85.7)	264 (87.7)	257 (85.4)	254 (84.4)	238 (75.8)
HPV 16	272 (90.4)	273 (90.7)	264 (87.7)	269 (89.4)	249 (79.3)
HPV 18	272 (90.4)	272 (90.4)	266 (88.4)	270 (89.7)	267 (85.0)
HPV 31	272 (90.4)	271 (90.0)	268 (89.0)	271 (90.0)	264 (84.1)
HPV 33	273 (90.7)	271 (90.0)	269 (89.4)	275 (91.4)	279 (88.9)
HPV 45	274 (91.0)	273 (90.7)	268 (89.0)	275 (91.4)	280 (89.2)
HPV 52	272 (90.4)	273 (90.7)	268 (89.0)	275 (91.4)	271 (86.3)
HPV 58	270 (89.7)	270 (89.7)	265 (88.0)	273 (90.7)	261 (83.1)

[a] N= Number of subjects in cohort (as randomized)
Source: Table 10-3: Immunogenicity Analysis Population from CSR of V503-0101 (p.85 of 372)

Reviewer comment: *The most common reasons for exclusion from the PPI were (in descending order) baseline seropositivity to one of the vaccine HPV types (mostly to either HPV 6 or 11; source: Table 10-10 of CSR for V503-010), missing bloodwork at baseline or at 4 weeks last dose, post-vaccine serology was collected outside the pre-specified range, and the second or third dose of vaccine was given outside the pre-specified range.*

Table 8: HPV GMTs Following a 2-Dose Regimen in Girls Compared to the 3-Dose Regimen in Young Women [Per-protocol population] in V503-010

Anti-HPV response	**P1: 9-14y Girls (Day 1, Month 6)** PPI n	**P1: 9-14y Girls (Day 1, Month 6)** **Estimated GMT (mMU/mL)**	**P2: 16-26y F (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y F (Day 1, Month 2, Month 6)** **Estimated GMT (mMU/mL)**	**GMT ratio (P1/P2) *** (95% CI)
Anti-HPV 6	258	1657.9	238	770.9	**2.15** (1.83, 2.53)
Anti-HPV 11	258	1388.9	238	580.5	**2.39** (2.03, 2.82)
Anti-HPV 16	272	8004.9	249	3154.0	**2.54** (2.14, 3.00)

Anti-HPV response	**P1: 9-14y Girls (Day 1, Month 6)** PPI n	**P1: 9-14y Girls (Day 1, Month 6)** **Estimated GMT (mMU/mL)**	**P2: 16-26y F (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y F (Day 1, Month 2, Month 6)** **Estimated GMT (mMU/mL)**	**GMT ratio (P1/P2) *** (95% CI)
Anti-HPV 18	272	1872.8	267	761.5	**2.46** (2.05, 2.96)
Anti-HPV 31	272	1436.3	264	572.1	**2.51** (2.10, 3.00)
Anti-HPV 33	273	1030.0	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	1251.2	261	491.1	**2.55** (2.15, 3.01)

*Non-inferiority of the GMT ratios for all 9 HPV types was demonstrated (p<0.001).
Source: Table 11-3 from the CSR for V503-010 (p. 142 of 372)

Table 9: Primary Immunogenicity Analysis of a 2-Dose Regimen in Boys Compared to the 3-Dose Regimen in Young Women in V503-010

Anti-HPV response	**P1: 9-14y Boys (Day 1, Month 6)** PPI n	**P1: 9-14y Boys (Day 1, Month 6)** Estimated GMT (mMU/mL)	**P2: 16-26y Females (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Females (Day 1, Month 2, Month 6)** Estimated GMT (mMU/mL)	**GMT ratio (P1/P2) *** (95% CI)
Anti-HPV 6	263	1557.4	238	770.9	**2.02** (1.73, 2.36)
Anti-HPV 11	264	1423.9	238	580.5	**2.45** (2.09, 2.88)
Anti-HPV 16	273	8478.8	249	3154.0	**2.69** (2.29, 3.15)
Anti-HPV 18	272	1860.9	267	761.5	**2.44** (2.04, 2.92)
Anti-HPV 31	271	1498.2	264	572.1	**2.62** (2.20, 3.12)
Anti-HPV 33	271	1040.0	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 response	**P1: 9-14y Boys (Day 1, Month 6)** PPI n	**P1: 9-14y Boys (Day 1, Month 6)** Estimated GMT (mMU/mL)	**P2: 16-26y Females (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Females (Day 1, Month 2, Month 6)** Estimated GMT (mMU/mL)	**GMT ratio (P1/P2) *** (95% CI)
Anti-HPV 52	273	640.4	271	364.2	**1.76** (1.51, 2.05)
Anti-HPV 58	270	1325.7	261	491.1	**2.70** (2.30, 3.16)

*Non-inferiority of the GMT ratios for all 9 HPV types was demonstrated (p<0.001).
Source: Table 11-5 from the CSR for V503-010 (p.145 of 372)

Reviewer comment: *The fold differences and the >0.67 lower bound of the 95% CI of all 9 serotypes indicate non-inferior immunogenicity of the Day 1, Month 6 regimen for both girls and boys compared to the 3-dose regimen in young women. GMT ratios for the 9 vaccine HPV types in GARDASIL 9 in girls and boys were elevated by similar magnitudes, ranging from 1.7 to 3.0 fold.*

Table 10: Primary Immunogenicity Analysis of a 2-Dose Regimen in Girls and Boys Compared to the 3-Dose Regimen in Young Women in V503-010

Anti-HPV response	**P1 9-14y Boys and Girls (Day 1, Month 12)** PPI n	**P1 9-14y Boys and Girls (Day 1, Month 12)** Estimated GMT (mMU/mL)	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** Estimated GMT (mMU/mL)	**GMT ratio (P1/P2) *** (95% CI)
Anti-HPV 6	257	2678.8	238	770.9	**3.47** (2.93, 4.11)
Anti-HPV 11	257	2941.8	238	580.5	**5.07** (4.32, 5.94)
Anti-HPV 16	264	14329.3	249	3154.0	**4.54** (3.84, 5.37)
Anti-HPV 18	266	2810.4	267	761.5	**3.69** (3.06, 4.45)
Anti-HPV 31	268	2117.5	264	572.1	**3.70** (3.08, 4.45)
Anti-HPV 33	269	2197.5	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 response	**P1 9-14y Boys and Girls (Day 1, Month 12)** PPI n	**P1 9-14y Boys and Girls (Day 1, Month 12)** Estimated GMT (mMU/mL)	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** Estimated GMT (mMU/mL)	**GMT ratio (P1/P2) *** (95% CI)
Anti-HPV 52	268	1123.4	271	364.2	**3.08** (2.64, 3.61)
Anti-HPV 58	265	2444.6	261	491.1	**4.98** (4.23, 5.86)

*Non-inferiority of the GMT ratios for all 9 HPV types was demonstrated (p<0.001).
Source: Table 11-7 from the CSR for V503-010 (p.148 of 372)

Reviewer comment: *The GMT ratios for all 9 HPV vaccine serotypes were notably higher in boys and girls 9 to 14 years of age who received the Day 1, Month 12 regimen. The 95% CIs are non-overlapping for all but types 31 and 45. Although we cannot interpret this trend to have clinical significance, it is informative because these data indicate that immune responses are not attenuated, and appear to be actually be enhanced, by increasing the interval between Dose 1 and Dose 2.*

6.1.11.2 Analyses of Secondary Endpoints

Table 11: Non-inferior Seroconversion with a 2-Dose Regimen in Girls Compared to the 3-Dose Regimen in Young Women in V503-010

HPV Type (serostatus cutoff value)	**P1: 9-14y Girls (Day 1, Month 6)** PPI n	**P1: 9-14y Girls (Day 1, Month 6)** **m***	**P1: 9-14y Girls (Day 1, Month 6)** Sero conversion (%)	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** **m***	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** Sero conversion (%)	**Estimated % Point Δ° P1-P2** (95% CI)
HPV 6 (30 mMU/mL)	258	**257**	99.6	238	**237**	99.6	**0.0** (-1.8, 2.0)
HPV 11 (16 mMU/mL)	258	**258**	100	238	**237**	99.6	**0.4** (-1.1, 2.3)
HPV 16 (20 mMU/mL)	272	**272**	100	249	**248**	99.6	**0.4** (-1.0, 2.2)
HPV 18 (24 mMU/mL)	272	**272**	100	267	**263**	98.5	**1.5** (0.1, 3.8)

HPV Type (serostatus cutoff value)	**P1: 9-14y Girls (Day 1, Month 6)** PPI n	**P1: 9-14y Girls (Day 1, Month 6)** **m***	**P1: 9-14y Girls (Day 1, Month 6)** Sero conversion (%)	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** **m***	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** Sero conversion (%)	**Estimated % Point Δ° P1-P2** (95% CI)
HPV 31 (10 mMU/mL)	272	**271**	99.6	264	**263**	99.6	**0.0** (-1.7, 1.8)
HPV 33 (8 mMU/mL)	273	**272**	99.6	279	**278**	99.6	**0.0** (-1.7, 1.7)
HPV 45 (8 mMU/mL)	274	**272**	99.3	280	**274**	97.9	**1.4** (-0.7, 4.0)
HPV 52 (8 mMU/mL)	272	**271**	99.6	271	**270**	99.6	**0.0** (-1.7, 1.7)
HPV 58 (8 mMU/mL)	270	**270**	100	261	**260**	99.6	**0.4** (-1.0, 2.1)

*number of PPI subjects who seroconverted
*Non-inferior seroconversion rates were demonstrated for all 9 HPV types (p<0.001).
Source: Table 11-4 from CSR of V503-010 (p.143 of 372)

Table 12: Non-inferior Seroconversion with a 2-Dose Regimen in Boys Compared to the 3-Dose Regimen in Young Women in V503-010

HPV Type (serostatus cutoff value)	**P1: 9-14y Boys (Day 1, Month 6)** PPI n	**P1: 9-14y Boys (Day 1, Month 6)** **m***	**P1: 9-14y Boys (Day 1, Month 6)** Sero conversion (%)	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** **m***	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** Sero conversion (%)	**Estimated % Point Δ° P1-P2** (95% CI)
HPV 6 (30 mMU/mL)	263	**263**	100	238	**237**	99.6	**0.4** (-1.0. 2.3)
HPV 11 (16 mMU/mL)	264	**264**	100	238	**237**	99.6	**0.4** (-1.0, 2.3)
HPV 16 (20 mMU/mL)	273	**273**	100	249	**248**	99.6	**0.4** (-1.0, 2.2)

HPV Type (serostatus cutoff value)	**P1: 9-14y Boys (Day 1, Month 6)** PPI n	**P1: 9-14y Boys (Day 1, Month 6)** **m***	**P1: 9-14y Boys (Day 1, Month 6)** Sero conversion (%)	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** **m***	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** Sero conversion (%)	**Estimated % Point Δ° P1-P2** (95% CI)
HPV 18 (24 mMU/mL)	272	**272**	100	267	**263**	98.5	**1.5** (0.1, 3.8)
HPV 31 (10 mMU/mL)	271	**271**	100	264	**263**	99.6	**0.4** (-1.0, 2.1)
HPV 33 (8 mMU/mL)	271	**271**	100	279	**278**	99.6	**0.4** (-1.0, 2.0)
HPV 45 (8 mMU/mL)	273	**271**	99.3	280	**274**	97.9	**1.4** (-0.7, 4.0)
HPV 52 (8 mMU/mL)	273	**273**	100	271	**270**	99.6	**0.4** (-1.0, 2.1)
HPV 58 (8 mMU/mL)	270	**270**	100	261	**260**	99.6	**0.4** (-1.0, 2.1)

*number of PPI subjects who seroconverted
° Non-inferior seroconversion rates were demonstrated for all 9 HPV types (p<0.001).
Source: Table 11-6 from the CSR for V503-010 (p.146 of 372)

Table 13: Non-inferior Seroconversion with a 2-Dose Regimen in Boys and Girls Compared to the 3-Dose Regimen in Young Women in V503-010

HPV Type (serostatus cutoff value)	**P1: 9-14y Boys and Girls (Day 1, Month 12)** PPI n	**P1: 9-14y Boys and Girls (Day 1, Month 12)** **m***	**P1: 9-14y Boys and Girls (Day 1, Month 12)** Sero conversion (%)	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** **m***	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** Sero conversion (%)	**Estimated % Point Δ° P1 – P2** (95% CI)
HPV 6 (30 mMU/mL)	257	**257**	100	238	**237**	99.6	**0.4** (-1.1, 2.3)
HPV 11 (16 mMU/mL)	257	**257**	100	238	**237**	99.6	**0.4** (-1.1, 2.3)

HPV Type (serostatus cutoff value)	**P1: 9-14y Boys and Girls (Day 1, Month 12)** PPI n	**P1: 9-14y Boys and Girls (Day 1, Month 12)** **m***	**P1: 9-14y Boys and Girls (Day 1, Month 12)** Sero conversion (%)	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** PPI n	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** **m***	**P2: 16-26y Young Women (Day 1, Month 2, Month 6)** Sero conversion (%)	**Estimated % Point Δ° P1 – P2** (95% CI)
HPV 16 (20 mMU/mL)	264	**264**	100	249	**248**	99.6	**0.4** (-1.1, 2.2)
HPV 18 (24 mMU/mL)	266	**266**	100	267	**263**	98.5	**1.5** (0.1, 3.8)
HPV 31 (10 mMU/mL)	268	**268**	100	264	**263**	99.6	**0.4** (-1.0, 2.1)
HPV 33 (8 mMU/mL)	269	**269**	100	279	**278**	99.6	**0.4** (-1.1, 2.0)
HPV 45 (8 mMU/mL)	268	**268**	100	280	**274**	97.9	**2.1** (0.7, 4.6)
HPV 52 (8 mMU/mL)	268	**268**	100	271	**270**	99.6	**0.4** (-1.0, 2.1)
HPV 58 (8 mMU/mL)	265	**265**	100	261	**260**	99.6	**0.4** (-1.1, 2.1)

*number of PPI subjects who seroconverted
° Non-inferior seroconversion rates were demonstrated for all 9 HPV types (p<0.001).
Source: Table 11-8 from the CSR for V503-010 (p.149 of 372)

Reviewer comment: *The pre-specified noninferiority criteria of >-5% for seroconversion rate differences were met for all 9 HPV types for all three 2-dose cohorts. In fact, all of the estimated points of rate differences were 0.4 or greater.*

6.1.11.3 Subpopulation Analyses

Subpopulation analyses of GMTs at 4 weeks post last dose of GARDASIL 9 were conducted based on the following demographic and baseline characteristics:

- Race: Caucasian, Asian, Black or African-American, Other
- Geographic region: Africa, Asia-Pacific, Europe, Latin America, and North America
- For the three 2-dose cohorts, age strata: 8 to 9 years old, 10 to 11 years old, 12 to 13 years old

Analyses of the GMTs for the 9 HPV serotypes by sex, race, and by the 5 geographic regions did not reveal any significant differences compared to the primary analyses conducted with the overall per-protocol population. Among the boys and girls in the three

2-dose cohorts, numerical GMTs tended to decrease with age for some of the vaccine HPV types, but the significance of these trends is unclear because the 95% confidence intervals generally overlapped. No age-dependent trends in seroconversion were observed among the 9 to 14 year olds.

Solicited AEs were not collected with a VRC in this trial because of the robust safety database that exists for GARDASIL 9. Instead, unsolicited local and systemic AEs were collected based on voluntary reporting from subjects and investigators. Not surprisingly, unsolicited local reactogenicity 15 days following vaccination occurred more frequently in females. About 8% of boys in the Day 1, Month 6 cohort reported local injection site reactions, while about 2 times more girls receiving the same regimen had local AEs. A total of 20 different SAEs (from 20 subjects across all cohorts) were observed during the period from Day 1 through visit cut-off date (See Table 16). There was no pattern of SAEs among the GARDASIL 9 recipients and review of the case narratives did not reveal information to suggest a causal relationship. Given the small number and the diversity of SAEs, no meaningful subgroup analyses can be performed.

6.1.11.5 Exploratory and Post Hoc Analyses

Reverse cumulative distribution (RCD) curves of the cLIA titers to the 9 HPV types contained in GARDASIL 9 were evaluated for each of the treatment groups. For all three of the 2-dose regimen cohorts (Day 1, Month 6 and Day 1, Month 12), the RCDs were all shifted to the right with respect to the comparator young women group for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (See Figure 1).

Figure 1: Reverse Cumulative Distribution Plot of Anti-HPV16 cLIA Titers at 4 Weeks Post Last Dose (Per-Protocol Immunogenicity Population)

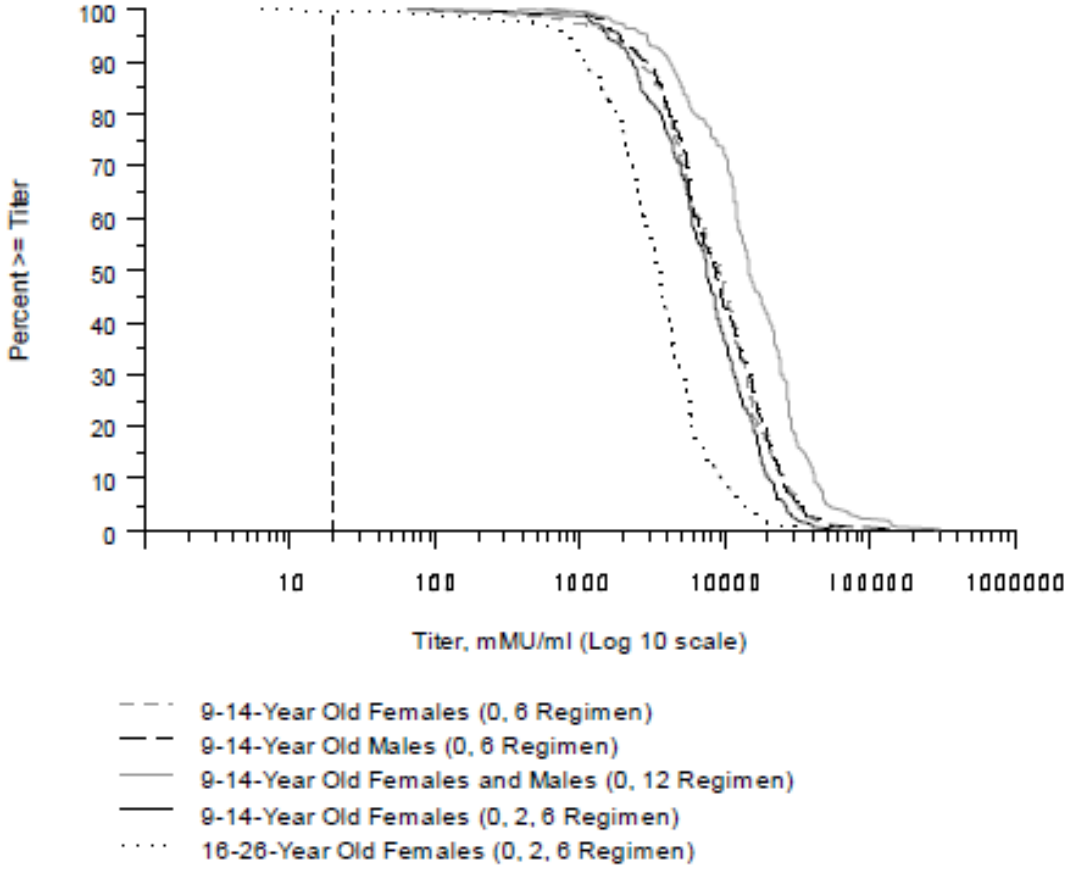

Figure 1 *(Source: Figure 11-4 from the CSR for V503-010 (p. 155 of 372))***:** The reverse cumulative distribution curve (RCD) of anti-HPV 16 is shown above. The horizontal axis represents the percentage of subjects with cLIA titer greater than or equal to a given level. The vertical broken line in the plot represents the cLIA serostatus cut-off for the relevant HPV type. In this RCD plot, the distribution of anti-HPV 16 among the 9 to 14 year old girls and boys for the (0,6) and (0,12) regimens are shifted toward the right compared to the curve for the 16 to 26 year old young women (comparator group). The rightward shift indicates a distributional shift toward higher titer percentiles in the 2-dose regimen groups.
Source: Text in the CSR for V503-010 (p. 150 of 372)

> ***Reviewer comment:*** *The RCD curves for the other HPV vaccine types were fundamentally similar, with right-sided shifts of the 2-dose regimens in boys and girls relative to the comparator group.*

In terms of differences among the two different 2-dose regimens, right-sided shifts in RCD curves of the Day 1, Month 12 cohort of boys and girls were observed for HPV 6, 11, 16, 33, 52, and 58 when compared to those of the Day 1, Month 6 cohorts. A similar trend was observed for the RCD curves for HPV 6, 11, 16, 33, and 58 titers from the Day 1, Month 12 cohort when compared to those from the adolescent girls given the 3-dose regimen.

Reviewer comment: *These trends are inconclusive, but can be interpreted as reassuring because they suggest that a longer interval between the first and second dose does not attenuate immunogenicity.*

Table 14: Exploratory Comparison of Immunogenicity of a 2-Dose to the 3-Dose Regimen in 9 to 14 year-old Girls in V503-10

Anti-HPV response	**P1: 9-14y Girls Day 1, Month 6** PPI n	**P1: 9-14y Girls Day 1, Month 6** Estimated GMT (mMU/mL)	**P3: 9-14yo Girls Day 1, Month 2, Month 6** PPI n	**P3: 9-14yo Girls Day 1, Month 2, Month 6** Estimated GMT (mMU/mL)	**GMT ratio (P1/P3)** (95% CI)
Anti-HPV 6	258	1657.9	254	1491.1	**1.11** (0.94, 1.30)
Anti-HPV 11	258	1388.9	254	1306.3	**1.06** (0.90, 1.25)
Anti-HPV 16	272	8004.9	269	6996.0	**1.14** (0.98, 1.34)
Anti-HPV 18	272	1872.8	270	2049.3	**0.91** (0.77, 1.09)
Anti-HPV 31	272	1436.3	271	1748.3	**0.82** (0.69, 0.97)
Anti-HPV 33	273	1030.0	275	796.4	**1.29** (1.10, 1.52)
Anti-HPV 45	274	357.6	275	661.7	**0.54** (0.45, 0.65)
Anti-HPV 52	272	581.1	275	909.9	**0.64** (0.55, 0.75)
Anti-HPV 58	270	1251.2	273	1229.3	**1.02** (0.87, 1.20)

Source: Table 11-16 from the CSR for V503-010 (p. 181 of 372)

Reviewer comment*: Titers to HPV 45 and 52 are inferior in the girls given the 2-dose regimen compared to the 3 dose regimen. Given the additional dose of GARDASIL 9 in the same 6 month time frame, it is not unexpected that non-inferiority criteria were not met in this exploratory comparison, the clinical significance of the numerical differences in titers has not been confirmed. In general, minimum protective titers of HPV types in vaccines have not been established. There are data from other studies suggesting that some titers below the level of detection, such as to HPV 18, may still provide clinical protection.*

6.1.12 Safety Analyses

6.1.12.1 Methods

A Vaccination Report Card was not used for safety data collection. Therefore, the data represent unsolicited AEs. Severity was graded as mild, moderate, and severe. Serious adverse events were collected for 6 months after the last dose.

6.1.12.2 Overview of Adverse Events

The most common AE of the injection site was pain, and headache was the most common systemic AE reported by subjects.

Table 15: Summary of Safety Outcomes[a] in Subjects from V503-010

Subjects with:	**9-14y Girls** **Day 1, Month 6** **N=294** **n (%)**	**9-14y Boys** **Day 1, Month 6** **N=296** **n (%)**	**9-14 Boys and Girls** **Day 1, Month 12** **N=293** **n (%)**	**9-14y Girls** **Day 1, Month 2, Month 6** **N=300** **n (%)**	**16-26y Young Women** **Day 1, Month 2, Month 6** **N=313** **n (%)**
SAEs; *no fetal loss unless indicated*	3 (1.0)	5 (1.7)	3 (1.0)	3 (1.0)	8 (2.6) Incl. 1 premature delivery and 2 elective abortions
Vaccine-related SAEs	0	0	0	0	0
Deaths	0	0	0	0	0

Source: Tables 12-1 and 12-2 from the CSR for V503-010 (pp. 194-195 of 372)

6.1.12.3 Deaths

No deaths occurred in this trial.

6.1.12.4 Nonfatal Serious Adverse Events

Table 16: Serious Adverse Events[a] Reported in All Vaccinated Subjects in V503-010

	9-14y Girls **(Day 1, Month 6)** N=294	**9-14y Boys** **(Day 1, Month 6)** N=296	**9-14y Boys&Girls** **(Day 1, Month 12)** N=293	**9-14y Girls** **(Day 1, Month 2, Month 6)** N=300	**16-26y Young Women** **(Day 1, Month 2, Month 6)** N=313
Total # subjects with SAEs	3	5	3	3	6
SAEs occurring within Day 15 from Day 1 vaccination	0	0	1	0	1

	9-14y Girls **(Day 1, Month 6)** N=294	**9-14y Boys** **(Day 1, Month 6)** N=296	**9-14y Boys&Girls** **(Day 1, Month 12)** N=293	**9-14y Girls** **(Day 1, Month 2, Month 6)** N=300	**16-26y Young Women** **(Day 1, Month 2, Month 6)** N=313
	-Abd pain -Ovarian cyst -Pharyngitis and dengue fever	-Concussion -Epilepsy -Animal bite -Rotavirus gastroent. -Appendicitis	*-Forearm fracture*[b] -Atopic dermatitis -Appendicitis	-Depression -Appendicitis -Subcutan. Abscess	*-Acute cholecystitis*[b] -Abd pain -Venous thrombosis of limb -Diarrhea -Pharyngotonsillitis -Premature delivery

[a] *Excludes fetal loss*
[b] *Occurrence within Day 15 following vaccination*
Source: Table 12-3 of CSR for V503-010 (pp. 199-204 of 372)

> ***Reviewer comment:*** *Since there was no Month 18 visit, SAEs for the Day 1, Month 12 cohort were collected 12 months after the last vaccination (Month 24 visit). For the other 4 cohorts, SAE data were collected 6 months after the last vaccination (Month 12 visit).. CBER did not identify this as a study flaw when Merck submitted the protocol for V503-010 as an amendment to IND 13447 in February 2014. Of note, by this time the study was ongoing in European countries since December 2013. In light of the existing safety data on GARDASIL 9 and our acceptance of the lack of use of a VRC for safety monitoring for the trial, there is a low baseline suspicion of SAEs occurring with this product. In addition, the protocol provided additional ways for information about SAEs to be obtained than the Month 24 visit. The protocol explicitly states that physician investigators are to immediately report to the Sponsor any cases of subjects discontinuing the trial due to death or any SAE deemed to be vaccine related. Given these measures, the 6 month delay in a scheduled collection of SAEs is unlikely to have compromised subject safety or study integrity.*

6.1.12.5 Adverse Events of Special Interest (AESI)

AEs defined as new medical conditions included HIV, immunological malignancies and medical conditions treated with immunosuppressive therapies.

> ***Reviewer comment:*** *These conditions are possible factors that could contribute to attenuated immunogenicity of GARDASIL 9.*

Most subjects across groups (78.7 to 90.0%) were found to have no new conditions following Day 1. Conditions categorized under “Immune System Disorders” were limited to drug hypersensitivity (2 adolescent girls in the Day 1, Month 6 regimen cohort) and allergy to animal (1 subject in the young women cohort given the 3-dose regimen). According to the tabulated data compiled from Day 1 to the Clinical Study Report cut-off date, none of the subjects in V503-010 have presented with any one of the abovementioned conditions.

6.1.12.6 Clinical Test Results

Clinical laboratory evaluations were not included in this study.

6.1.12.7 Dropouts and/or Discontinuations

Two randomized subjects dropped out prior to vaccination because they voluntarily withdrew consent. One subject discontinued from the study due to an acute episode of urticaria on the day of vaccination. See Section 6.1.12.

6.1.13 Study Summary and Conclusions

- In adolescent boys and girls between the ages of 9 and 14 years, 2-dose the HPV antibody responses following a 2-dose regimen (Day 1 and 6 to 12 months) wtih GARDASIL 9 were non-inferior for all HPV types compared to the 3-dose regimen (Day 1, Month 2, Month 6) in 16 to 26-year-old women, the population in which clinical endpoint effectiveness of GARDASIL 9 has been established.
- Safety with a 2-dose regimen is comparable to the 3-dose regimen, with differences in cumulative numbers of AEs likely attributable to the elimination of one vaccination dose and the associated potential to experience self-limited local and systemic AEs.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Refer to Section 6.1.7 for details on monitoring pregnancy outcomes. A total of 11 subjects (2 girls in the 2-dose (Day 1, Month 12) cohort and 9 young women in the 3-dose regimen cohort) reported pregnancy in the study. Outcomes were available for 7 of the 11 pregnancies, including 2 pregnancies that were electively terminated and 5 pregnancies that each resulted in live birth of a normal infant.

9.1.2 Use During Lactation

There are no lactation data submitted from V503-010. Please refer to Section 11.5 of this review for discussion of the lactation data from pre-licensure studies that supported GARDASIL 9.

9.1.3 Pediatric Use and PREA Considerations

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in the pediatric age group unless this requirement is waived, deferred, or inapplicable. Since the supplement contains data on a new dosing regimen, PREA requirements apply.

A waiver was granted for the requirement to conduct studies in individuals 0 to < 9 years of age and 15 to <17 years of age, because GARDASIL 9 administered as a 2-dose

regimen (0 and 6 to 12 months) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in these age groups and is not likely to be used in a substantial number of pediatric patients in these age groups. For the age group 0 to <9 years of age, GARDASIL 9 is not likely to be used in a substantial number of children because the objective of immunization with this vaccine is to prevent diseases that occur following exposure to HPV during sexual activity and this age group is unlikely to engage in sex. In the age group of 15 to <17 years of age, a 2-dose regimen does not represent a meaningful therapeutic benefit over the 3-dose regimen because of the greater likelihood of HPV exposure through sexual contact in late adolescence compared with younger ages. The risk of HPV exposure during the longer period of time between the first and second dose of the 2-dose regimen may offset any potential therapeutic benefit. For these reasons and because in the U.S., HPV vaccine is recommended to be given routinely at 11 to 12 years of age, the 2-dose regimen is not likely to be used by a substantial number of pediatric patients in the 15 and 16 year-old age group.

The data from V503-010 fulfilled the requirement for ages 9 years to <15 years. Section 8.4 of the PI is appropriately labelled for pediatric use.

9.1.4 Immunocompromised Patients

GARDASIL 9, like all licensed HPV vaccines, is a non-infectious, virus-like particle (VLP) vaccine. As such, there are no scientific or clinical reasons to anticipate that it could not be safely administered to immunocompromised individuals. ACIP, WHO, and other clinical practice advisory bodies recommend that individuals 9 to 26 years of age who are immunocompromised by transplant, medication, or chronic disease should receive the HPV vaccine.[4,5] Safety and effectiveness data with use of GARDASIL 9 in immunocompromised patient populations have not been submitted by the applicant.

9.1.5 Geriatric Use

The safety and effectiveness of GARDASIL 9 have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

10. CONCLUSIONS

The safety and immunogenicity data from V503-010 support the use of GARDASIL 9 administered as a 2-dose regimen in adolescent girls and boys 9 to 14 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See Table 21.

Table 21

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HPV infection is nearly universal in sexually active populations. • In a subset of females infected with oncogenic strains, persistence of infection can lead to cervical dysplasia, and eventually to cervical cancer. • Treatment for cervical dysplasia can result in serious iatrogenic morbidity, such as cervical stenosis, infertility, and preterm birth. • Infection with certain non-oncogenic strains can lead to genital warts. • Genital warts are associated with substantial pain and discomfort, particularly related to treatment. The psychosocial impact can also be debilitating.	• Cervical cancer is a progressive, life-threatening disease. • Cervical dysplasia is a serious condition, based on the chronic morbidity many patients experience. • Genital warts is a serious condition, based on the debilitating impact on physical and psychosocial well-being.
Unmet Medical Need	• Aside from the HPV vaccines, no other drug or biologic is approved for prevention of HPV infection. Prevention is otherwise limited to condom use, which is minimally effective. • Gardasil is one of two HPV vaccines, both of which are licensed for a 3-dose regimen. • The vaccination regimen requires 3 visits within 6 months. Initiation rates for an HPV vaccine were recently estimated at 57.3% for girls and 34.6% for boys. Of note, completion of the 3-dose series is reported to be under 40% for girls and 15% for boys.	• HPV vaccine uptake and completion of the 3-dose series among adolescents is low.
Clinical Benefit	• Efficacy of the 3-dose regimen of HPV9 against high grade histopathology leading to cervical, cancer in 16-26 yo adolescents and women has been demonstrated. • One clinical trial with young adolescents (9 to 14 years of age) vaccinated with 2-dose regimens (Day 1 and Month 6 or Month 12) compared to young women 16 to 26 years of age vaccinated with the licensed 3-dose regimen was submitted. Efficacy was based on demonstrating non-inferior immunogenicity with the young women comparator cohort.	• The 2-dose regimen of HPV9 in 9-14 year olds is non-inferior to the 3-dose regimen in 16-26 year olds which was demonstrated to have clinical efficacy. Thus the 2-dose is likely to be effective as well. • From a public health perspective, a vaccination regimen that includes one less dose to complete HPV primary immunization series could improve acceptability of HPV vaccination among young adolescent population and improve overall uptake of HPV vaccine.
Risk	• The trial did not collect solicited AEs with a Vaccination Report Card based on the rationale that there are robust data indicating that 3 doses of GARDASIL 9 are safe. • Unsolicited local and systemic reactions observed with the 2-dose and 3-dose regimens were comparable • No other safety signals were apparent in young adolescents 9 to 14 years of age. • Delaying a second dose of HPV9 from 2 months to 6 months may increase risk of infection during this window	• Enhanced risk of AE's was not found with a reduced dose regimen of Gardasil 9. • Any increase in risk of HPV infection in the risk window from delayed second dose is unlikely to be significant due to the low level of sexual activity in this young age group.
Risk Management	• Local reactions - erythema, swelling, and pain- are very common with Gardasil 9. However, the most injection site reactions are mild in severity, and they resolve relatively quickly and without sequelae.	• The risks are adequately described in the package insert. The PVP is adequate for the continued assessment of safety in the post-marketing period.

11.2 Risk-Benefit Summary and Assessment

Overall, the benefit risk assessment is favorable for the use of a 2-dose regimen of GARDASIL 9 in the pre-adolescent population.

- Each dose has some associated risks, therefore reduction of an additional dose has advantages in reducing the likelihood of a local or systemic adverse event. The unsolicited safety data from V503-010 support this general statement.
- The data from V503-010 indicate that the elimination of the second dose of the 3-dose regimen of GARDASIL 9 does not compromise the immunogenicity of the vaccine in 9 to 14 year-old boys and girls when compared with the population in whom clinical endpoint efficacy was originally established (16 to 26 year old females). As demonstrated by previous studies of a similar vaccination approach with 4vHPV, in this younger population, the GMTs to the 9 HPV types contained in the vaccine are about 2 to 3-fold greater when compared to those from 16 to 26-year-old women given the 3-dose regimen.

11.3 Discussion of Regulatory Options

As discussed below, the reviewer recommends approval of the 2-dose regimen as an alternative regimen for girls and boys 9 through 14 years of age based on immunobridging data demonstrating non-inferior immune responses measured by HPV serotype titers observed in this age group compared to older adolescents and young women, in whom clinical efficacy is established. Because the 3-dose regimen was previously established as safe and effective, it is appropriate to retain this option in labeling for girls and boys 9 through 14 years of age. In addition, the 3-dose option for this age group provides flexibility that may be preferable in some clinical scenarios. For example, health care providers may recommend the 3-dose regimen for their patients with immunocompromised conditions or therapeutic immunosuppression.

11.4 Recommendations on Regulatory Actions

In the opinion of this reviewer, the immunogenicity and safety data submitted in this application support approval of this supplemental BLA to allow the addition of a 2-dose regimen of GARDASIL 9 in males and females from 9 through 14 years of age.

11.5 Labeling Review and Recommendations

With this supplement, significant changes in content and organization were made to Sections 2 [Dosage and Administration], 8 [Use in Special Populations], and 14 [Clinical Studies] in the PI for GARDASIL 9. Merck submitted revisions to Section 8 to be compliant with the format established by the 2015 Pregnancy and Lactation Labeling Rule (PLLR). Revisions to the Pregnancy and Lactation subsections involved requests for additional analyses of the Gardasil pregnancy registry (data from GARDASIL were considered relevant to GARDASIL 9 for the purpose of labeling pregnancy data because both vaccines are manufactured using the same process and have overlapping compositions). Internal discussion also included colleagues in the Office of Biostatistics and Epidemiology (OBE). The notable changes in the specific subsections are summarized below:

- 2.1 [Dosage]
    - CBER proposed that the regimen for each age group should be presented in a tabular format for clarity and readability. The applicant agreed with this approach.

    - CBER proposed that a footnote be added to the table to provide instructions on when to provide a 3rd dose if Dose 2 was administered in 9 to 14 year olds earlier than six months following the 1st dose. The applicant defined this interval as 4 months after Dose 2; CBER agreed.
- 8.1 [Pregnancy]
    - A risk summary of the human and animal data was drafted in accordance with the PLLR Guidance.
    - With respect to the human data, CBER refined the presentation of pre-existing pre-licensure pregnancy data from the original GARDASIL 9 PI. We requested that the applicant update the data to exclusively report on pregnancies with an estimated onset within 30 days of vaccination.
    - Data from a GARDASIL pregnancy registry study completed after the initial licensure of GARDASIL 9 were incorporated into Section 8. In addition, data from two post-licensure studies of GARDASIL in which pregnancy data were evaluated retrospectively were included in Section 8. These data are not included in the current GARDASIL PI.
    - Discussion of the animal studies was revised for accuracy with respect to the dosing – in terms of human dose equivalent as opposed to mg/kg weight basis - and the formulation of the nonavalent HPV vaccine administered to the animals.
- 8.2 [Lactation]
    - The applicant submitted lactation data obtained from 3 of their pre-licensure trials V503-001, 002, and 003 to be included in this section. Merck collected baseline data, including infant demographics, nutritional information (exclusive breastfeeding vs supplemental), timing of vaccine exposure in the mother, duration of breastfeeding, infant medications and medical history. Every 3 months thereafter, data were collected on infant diet, medical conditions, SAEs, failure to thrive, developmental delays, procedures on mother or infant, and medications. Infants were followed out to Month 7 after breastfeeding. Based on these data, Merck proposed to include in Section 8.2 that adverse experience rates among these 92 breastfeeding women were comparable to the overall population and that none of the infants experienced SAEs.
    - After internal review, CBER concluded that the safety data from these breastfeeding women did not belong in Section 8.2 and that the uncontrolled data from the breastfed infants did not directly inform the risk of vaccine exposure through breastmilk. The applicant agreed to exclude these data.
- 14.5 [Immune Responses to GARDASIL 9 Using the 2-Dose Regimen in Individuals 9 through 14 Years of Age]
    - CBER recommended that the applicant include an additional table to present the primary immunogenicity data endpoints and analyses from V503-010. The applicant agreed.

In addition, the Patient Product Information sheet was revised to reflect the changes in dosing and available pregnancy data in the PI.

11.6 Recommendations on Postmarketing Actions

As stated in the approval letter, Merck agreed to a postmarketing commitment (PMC) to complete the ongoing study V503-010-01 to evaluate the persistence of antibody titers

up to 36 months after vaccination in males and females who received 2-dose and 3-dose regimens of GARDASIL 9.
Merck submitted the commitment dates for study completion and submission of a final report as amendment 5 to STN 125508. The following commitment dates for this PMC are included in the approval letter:

- Study Completion: August 18, 2017
- Final Report Submission: June 30, 2018

Reviewer comment*: The clinical endpoint study protocol that Merck initially submitted to the IND and this efficacy supplement was designed to evaluate cervical dysplasia disease outcomes in a preadolescent female cohort who received the 2-dose regimen. Control data to be used for comparison was to be generated as part of an ecological study of cervical dysplasia disease outcomes in the region in which the study was to be conducted. The value such data was not clear, because background rates of disease will be unpredictable and are likely to be low, no matter what region the study would be conducted because of increasing global vaccine uptake and herd immunity. In addition, such a study would not provide additional certainty with regard to the effectiveness of the 2-dose regimen in comparison to the 3-dose regimen. Therefore, CBER agreed that the applicant should consider alternative study designs. CBER and the applicant agreed that the ongoing study V503-010-01 will adequately address how the 2-dose regimen compares to the 3-dose regimen in terms of persistence of antibody titers up to 36 months after vaccination with GARDASIL 9.*