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Reviewer Name	Sixun Yang, MD, PhD
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Supervisory Concurrence	Nancy Miller, MD, Secondary Reviewer Doran Fink, MD, PhD, Team Leader Andrea Hulse, MD, Branch Chief
Applicant	Merck Sharp & Dohme Corp.
Established Name	Human Papillomavirus 9-valent Vaccine, Recombinant
Trade Name	Gardasil 9
Pharmacologic Class	Prophylactic Vaccine
Formulation	Sterile suspension of Recombinant Virus Like Particles of HPV 6/11/16/18/31/33/45/52/58 absorbed on 500 µg of AAHS
Dosage Form and Route of Administration	0.5 ml, Intramuscular Injection
Dosing Regimen	3-doses at Day 1, Month 2 and Month 6
Indication(s) and Intended Population(s)	Prevention of HPV 6/11/16/18/31/33/45/52/58-Related Anogenital Lesions in Females 9 through 26 years of age and males 9 through 15 years of age
Orphan Designated (Yes/No)	No

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GLOSSARY

9vHPV	Nine-valent Human Papillomavirus vaccine
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
AN	Allocation number
ASC-H	Atypical squamous cells cannot rule out HSIL
ASC-US	Atypical squamous cells of undetermined significance
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
EEC	Endo/ectocervical
EGLs	External genital lesions
ELISA	Enzyme-linked immunosorbent assay
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
HSIL	High-Grade Squamous Intraepithelial Lesion
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
(b)(4)	---(b)(4)--- 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
(b)(4)	----------(b)(4)----------
PCR	Polymerase Chain Reaction
PPE	Per Protocol Efficacy
PPI	Per Protocol Immunogenicity
qHPV	Quadrivalent Human Papillomavirus vaccine
RR	Risk reduction
SAEs	Serious Adverse Experiences
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
SD	Standard deviation
SEM	Standard error of the mean
siDMC	Standing Internal Data Monitoring Committee
ULN	Upper limit of normal
VaIN	Vaginal Intraepithelial Neoplasia
VE	Vaccine efficacy
VIN	Vulvar Intraepithelial Neoplasia
VLP	Virus-Like Particle
VRC	Vaccination Report Card
WBC	White blood (cell) count

1. EXECUTIVE SUMMARY

Human Papillomavirus (HPV) infection causes benign and malignant dysplastic disease, localized primarily in the anogenital area, in both men and women. Chronic HPV infection significantly increases the risk of cervical and other anogenital cancers. Cervical cancer is the second most common cancer in women worldwide, with approximately 530,000 new cases diagnosed each year and 275,000 deaths annually. Overall, HPV is responsible for approximately 5% of the global cancer burden. Nearly 100% of cervical cancers and 90% anal cancers are caused by oncogenic HPV types. Approximately 70% cervical cancers and 90% of anal cancers are caused by HPV types 16 and 18, both of which are targeted by the currently licensed HPV vaccines, Gardasil (also referred to as qHPV) and Cervarix. However, neither Gardasil nor Cervarix provides effective cross-protection against other oncogenic HPV types.

Gardasil 9, also referred to as 9vHPV, is an aluminum adjuvanted 9-valent HPV vaccine manufactured by Merck & Co., Inc. The 9vHPV vaccine targets the five additional oncogenic HPV types (31, 33, 45, 52 and 58) that cause approximately 20% of cervical cancers and that are not covered by currently licensed HPV vaccines. Overall, the 9vHPV vaccine has a potential to prevent 90% anogential cancers. Gardasil 9 is prepared from highly purified virus like particles (VLP) of the recombinant major capsid (L1) protein of the vaccine containing HPV types. The VLPs are adsorbed on amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant. Each 0.5-ml dose is formulated to contain 500 µg of AAHS and L1 protein content of 30 µg for HPV 6, 40 µg for HPV 11, 60 µg for HPV 16, 40 µg for HPV 18, and 20 µg each for HPV 31, 33, 45, 52 and 58. The final container is a sterile suspension for injection in a single-dose vial or a prefilled syringe. Hereafter, HPV types 6, 11, 16 and 18 will be referred to as the "original types" because they are included in qHPV, while HPV types 31, 33, 45, 52 and 58 will be referred to as the "new types" included in 9vHPV.

The Applicant, Merck & Co., Inc., seeks licensure of Gardasil 9 for prevention of the following diseases:

For females aged 9 to 26 years:

- 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 1, 2 and 3 and cervical adenocarcinoma *in situ* (AIS).
- Vulvar intraepithelial neoplasia (VIN) grade 2 and 3.
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and 3.
- Anal intraepithelial neoplasia (AIN) grades 1, 2 and 3.

For males aged 9 through 15 years:

- 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.
- AIN grades 1, 2 and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

To support the above indication, the Applicant submitted six final study reports of clinical trials with 9vHPV. Study V503-001 was an efficacy study conducted in women 16 through 26 years of age. Study V503-002 was an immunobridging study to bridge clinical efficacy obtained from Study V503-001 to children 9 through 15 years of age because of the inadvisability to perform genital examination in this population and the likely absence of the primary endpoint. Study V503-009 provided additional immunological bridging from qHPV vaccine to 9vHPV vaccine in females 9 through 15 years of age, by demonstrating that both vaccines have similar immunogenicity with respect to HPV types 6, 11, 16, and 18. Study V503-005 evaluated potential interference of Gardasil 9 with Menactra and Adacel when administered concomitantly to children 11 through 15 years of age. Study V503-006 evaluated the safety profile of Gardasil 9 in subjects who were previously vaccinated with the qHPV vaccine, as well as immunogenicity of Gardasil 9 in this population. Study V503-007 was a concomitant administration study with a non-U.S.-licensed vaccine (Repevax) and provided safety data for 9vHPV in adolescents 11 through 15 years of age. The major findings and of these studies are summarized below.

Study V503-001 was a randomized, double-blinded, qHPV-controlled, adaptively–designed, phase 2b/3 trial to evaluate the efficacy, immunogenicity, and safety of Gardasil 9 in women 16 through 26 years of age. Part A (phase 2b) was a dose finding study, and Part B (phase 3) was an efficacy and safety study. Part B also included those subjects enrolled under Part A who received the dose formulation of 9vHPV vaccine selected for Part B or the qHPV vaccine control. The study randomized 14,215 females 16 through 26 years of age from 5 continents and 18 countries into two treatment groups: 7,106 9vHPV recipients and 7,109 qHPV recipients. Both vaccines were administered intramuscularly (IM) at Day 1, Month 2, and Month 6. The median duration of follow-up post-Day 1 was approximately 40 months. As agreed to in pre-licensure discussions with CBER, effectiveness of 9vHPV with respect to the original HPV types was inferred by immunobridging from qHPV to 9vHPV via non-inferior immunogenicity comparison, and the efficacy for the new HPV types was determined by combined proportion of subjects with CIN2/3-, VIN 2/3- and VaIN 2/3-or worse related to HPV types 31, 33, 45, 52 and 58. Since efficacy evaluation for anal lesions associated with the five new HPV types was not feasible due to low incidence, CBER agreed that effectiveness with respect to this endpoint could be inferred from efficacy against genital lesions (due to highly similar pathophysiology), immunogenicity, and prevention of persistent infection. Safety endpoints included injection site

and systemic reactions, new onset of medical conditions including potential autoimmune disorders, and serious adverse events (SAEs).

The immunogenicity results showed that GMT responses for each of the original HPV types induced by the 9vHPV vaccine in females 16 through 26 years of age were non-inferior as compared with the qHPV vaccine group at 4 weeks post-dose 3 in the per protocol immunogenicity (PPI) population. Numerically, the GMT ratios (9vHPV/qHPV) for HPV types 6, 11, 16, and 18 ranged from 0.80 to 1.19 with lower bounds of 95% CIs all above 0.67, the pre-specified success criterion. The proportion of subjects who became seropositive to HPV 6, 11, 16, and 18 by Month 7 in the 9vHPV group was also non-inferior to that in the qHPV group. Therefore, non-inferior immunogenicity of 9vHPV vaccine compared with qHPV vaccine supports bridging prior efficacy findings for qHPV vaccine with respect to HPV 6/11/16/18-related persistent infection and cervical, vulvar, vaginal, external genital, and anal disease to 9vHPV vaccine.

The primary efficacy endpoint for the new HPV types was assessed in the per protocol efficacy (PPE) population. The overall observed efficacy against HPV 31/33/45/52/58-related high-grade cervical, vulvar and vaginal lesions in females 16 through 26 years of age in the PPE population was 96.7% (95% CI: 80.9, 99.8; $p<0.0001$). The results met the success criterion for this efficacy endpoint, the lower bound of the two-sided 95% CI for the vaccine efficacy being greater than 25%. The efficacy of the 9vHPV in preventing high grade genital lesions was consistent (ranging from approximately 87% to 100%) among different subgroups in terms of age, race, geographic region, ethnicity, hormone contraception use, and lifetime number of sexual partners. The 9vHPV vaccine also prevented HPV 31/33/45/52/58-related persistent infection assessed at Month 6 and Month 12. In addition, the 9vHPV vaccine reduced the proportion of subjects with HPV 31/33/45/52/58-related genital biopsy and definitive therapy by 31.3% and 46.5%, respectively.

Subpopulation analyses across different ages, races, ethnicities, and geographic regions did not reveal any substantial differences in estimates of vaccine efficacy against HPV 31/33/45/52/58-related genital lesions, though this is not surprising given that only one primary endpoint case was observed in the entire per-protocol efficacy population. Vaccine efficacy against HPV 31/33/45/52/58-related persistent infection was also similar across subpopulations stratified by age, race, ethnicity, or geographic region. For example, in the per-protocol efficacy population the point estimates for efficacy against HPV 31/33/45/52/58-related persistent infection were 97.4% for Whites, 97.3% for Blacks, 95.8% for Asians, and 93.7% for Others.

Study V503-002 was an open label multi-centered clinical trial to assess immunogenicity, safety, and manufacturing consistency of the 9vHPV vaccine. The study enrolled 2534 children 9 through 15 years of age (1890 girls and 644 boys) and 465 young women 16 through 26 years of age. The results showed that antibody GMTs for each of the 9vHPV vaccine types were non-inferior in children compared with young women, with GMT ratios (children/women) at 4 weeks post-dose 3 ranging from 1.83 to 3.35 for the 9 HPV types. These results support the bridging of efficacy findings in 16- to 26-year-old women to 9- to 15-year-old children. The GMT responses for each of the 9 HPV types at 4 weeks post-dose 3 were similar among girls (9 through 15 years of age) randomized to 1 of 3 final manufacturing process vaccine lots and met the success criteria for clinical demonstration of lot consistency.

The immunogenicity of the 9vHPV vaccine was non-inferior to the qHPV vaccine with respect to the original HPV types in girls 9 through 15 years of age as shown in Study V503-009, further supporting the bridging of efficacy of the qHPV vaccine to the 9vHPV vaccine in this age group.

Concomitant administration of the 9vHPV with the pediatric vaccines Menactra and Adacel did not show any adverse impact on immune responses to any antigen component in the 9vHPV vaccine, Menactra and Adacel (Study V503-005).

When 9vHPV was administered to subjects who were previously vaccinated with a 3-dose regimen of the qHPV (Study V503-006), seroconversion rates for all the 9 HPV types were greater than 98% at 4 weeks after the third dose. Antibody GMTs for the five new HPV types were lower than those in HPV vaccine naïve subjects in the other studies, though the clinical significance is unclear.

Safety findings for 9vHPV vaccine were consistent across the six studies and generally similar to those observed with qHPV. Vaccine-related systemic adverse reactions reported in the 9vHPV treatment group were similar to the qHPV treatment group, while rates of injection-site reactions were slightly higher in the 9vHPV treatment group (90.2%) compared with the qHPV treatment group (84.0%). The most common injection-site reactions were injection-site pain, swelling and erythema. The rates of injection-site reactions in children 9 through 15 years of age were numerically lower compared with those in females 16 through 26 years of age.

Subpopulation analyses of systemic and injection-site adverse reactions revealed no substantial differences by race, ethnicity, age, or gender.

Concomitant administration of the 9vHPV with the pediatric vaccines Menactra and Adacel did not negatively impact the safety profile of the 9vHPV. The safety profile of the 9vHPV vaccine in subjects who were previously vaccinated with qHPV vaccine was similar to that of the vaccine in HPV vaccine naive subjects except for numerically higher rates of injection-site swelling and erythema.

New onset clinical conditions of potential autoimmune etiology were well-balanced between the 9vHPV and qHPV treatment groups except for a small numerical imbalance in reports of multiple sclerosis (MS): 5 cases in the 9vHPV group and 2 cases in the qHPV group. The cases appeared to be randomly distributed with regard to geographic region and ethnicity. Because the number of the cases in each group is small, the clinical relevance is unknown.

Overall pregnancy outcomes among females who became pregnant during the studies, including rates of spontaneous abortions, were well-balanced between the two treatment groups. However, *post hoc* analyses showed that spontaneous abortion rate in subjects who received the 9vHPV vaccine and became pregnant within 30 days of any vaccination was higher than those who received the 9vHPV vaccine and became pregnant outside of the 30-day vaccination window [19.1% (17/89) vs. 9.6% (105/1089)]. In addition, the spontaneous abortion rate in subjects who received the 9vHPV vaccine and became pregnant within 30 days of any vaccination was higher than the corresponding rate in subjects in the qHPV treatment group [19.1% (17/89) vs. 8.0% (7/88)].

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups. The Applicant has fulfilled the pediatric study requirement for children 9 through 16 years of age in this application. The Applicant requested a partial waiver from the requirements of PREA for children 0 through 8 years of age. CBER granted the waiver request for this age group because initiating vaccination prior to age 9 does not represent a

meaningful therapeutic benefit over initiating vaccination at 9 years of age and older, and Gardasil 9 is not likely to be used in a substantial number of children in this age group.

Taken together, the submitted data support the effectiveness of 9vHPV in males 9 through 15 years of age and females 9 through 26 years of age in preventing benign and malignant anogenital lesions caused by the vaccine HPV types as described in the proposed indication. The safety profile of 9vHPV observed in the clinical trials was favorable and similar to the licensed qHPV vaccine.

The numerical imbalances described above in cases of MS and spontaneous abortions will be further assessed through FDA-sponsored post-marketing studies. Rates of selected autoimmunity-associated diagnoses, including MS, will be assessed through a Mini-Sentinel study, while FDA and CDC are collaborating to design a post-marketing study utilizing Vaccine Safety Datalink (VSD) to further evaluate rates of spontaneous abortions. Additionally, Merck will sponsor a pregnancy registry to further evaluate pregnancy outcomes among females who are exposed to 9vHPV around the time of conception.

In conclusion, this reviewer recommends approval of the proposed indication and dose regimen of Gardasil 9 for females 9 through 26 years of age and males 9 through 15 years of age.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Human papillomavirus (HPV) infection causes benign and malignant dysplastic anogenital disease including cervical, vulvar, vaginal, and anal cancers and their precursors, as well as anogenital warts[1,2].

Cervical cancer is the second most common cancer in women worldwide, and nearly 100% of cervical cancers are associated with HPV infection[3,4]. Of the 470,000 new cases per year diagnosed worldwide, half will die from this malignancy[5]. Eighty percent of these occur in developing countries. Implementation of cervical cancer screening programs using the Pap test and/or HPV testing has reduced the incidence of cervical cancer by 75% in developed countries. These programs have largely shifted the burden of HPV disease from the morbidity and mortality associated with cervical cancer to the detection, follow-up, and treatment of a large number of premalignant lesions. For example, every year in the United States, screening detects approximately 3.5 million cases of Pap test abnormalities, 300,000 cases of high-grade cervical dysplasia (CIN 2/3), and 10,000 cases of cervical cancer. Approximately 3,000 cervical cancer deaths occur annually in the United States[5]. In 2010 (the most recent year numbers are available), 1,818 women in the United States were diagnosed with cervical cancer, and 3,939 women in the United States died from cervical cancer[6]. The total yearly cost of diagnostic screening and treatment of cervical cancer in the U.S. is approximately $6 billion[5].

Most anal cancers (90%), and approximately 50% of vulvar and vaginal cancers, are caused by HPV. Each year, about 5,500 Americans are diagnosed with these cancers. All three cancers arise from pre-malignant precursor lesions. Anal cancer rates among men-having-sex-with-men (MSM) have increased greatly in the past 30 years. Rates of HPV-related vulvar and vaginal cancers have also increased. These cancers share epidemiologic features with cervical cancer, and they are often found in women with cervical pre-cancer and cancer[3,7].

Anogenital warts are generally benign, exophytic, hyperkeratotic lesions. In women, the lesions may appear over the vulva, urethra, vagina, perineum, and anus. Most patients with anogenital warts are asymptomatic[8]. Treatment consists of chemical or physical ablation. However, therapy is often unsuccessful and recurrence rates are high[9].

Though most HPV infections are self-limited, persistent infection may occur and lead to dysplastic disease. Cervical cancer pathopysiology typifies the process by which HPV infection causes anogenital diseases in general. In most cases, low-grade cervical intraepithelial neoplasia (CIN 1) resolves without clinical sequelae, but in some cases CIN persists and develops further into CIN 2/3 (moderate and high grade cervical dysplasia and cervical carcinoma *in situ)* and cancer[10]. Rates of progression of CIN 2/3 to cervical cancer are high, and rates of regression to normal are low. The determinants of progression versus clearance of HPV disease have not been well defined. However, persistent detection of HR HPV DNA is a predictor for progression to cervical cancer[10-12].

HPV viruses are small, non-enveloped icosahedral capsid viruses containing double stranded deoxyribonucleic acid (DNA). The Late (L) genes encode the two capsid proteins (L1, major capsid protein) and L2 (minor capsid protein). Proteins encoded on the early (E) portion of the genome are involved in viral DNA synthesis. The E6 and E7 proteins induce epithelial cell hyperproliferation by inhibiting cell cycle regulatory proteins.

The HPV family of viruses represents nearly 100 related epitheliotropic DNA viruses that have been classified by types and species[13]. Clinically, HPV types are classified into 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) and low-risk (LR) types (causing generally benign lesions: e.g., HPV 6, 11, 42, 43, 44)[14]. Phylogenetically, HPV are classified into several species. Species A7 and A9 contain most of the HR types. The A7 Species includes HPV types 18, 39, 45, 59, and 68. The A9 Species includes HPV types 16, 31, 33, 35, 52, and 58. HPV types 16 and 18 are responsible for most (over 70%) cases of cervical cancer[5,15-18]. Species A10 contains LR HPV Types 6 and 11, which are responsible for over 90% of anogenital warts.

HPV types 16, 18 and 45 are associated with the highest propensity to progress to invasive cervical cancer as evidenced by the relatively lower proportion of women with normal cytology who are infected with HPV types 16, 18 or 45 compared to the percentage with cervical cancers related to those same types[19]. HPV types 31, 33, 52, and 58 (the additional high-risk HPV types included in the 9vHPV vaccine) are also associated with higher rates of detection in invasive cervical cancer as compared to detection in normal cytology specimens.

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

2.2.1 Prevention

Several studies in men have reported that condom use is associated with fewer genital HPV infections and a shorter duration of infection in these men who were infected[20]. However, HPV can infect genital areas that are not covered by condoms. For women, a meta-analysis found no consistent evidence that condom use in their sexual partners reduced the risk of acquisition of cervical HPV infection, but it was associated with some protection against genital warts, CIN 2/3 and cervical cancer[21]. The success of Pap screening in reducing the incidence of cervical cancer has been attributed to excision of CIN 2/3 lesions prior to the development of cancer[22].

2.2.2 Treatment

The mainstays of treatment of high-grade CIN (i.e., CIN 2 or worse) are excision or ablation of the transformation zone of the cervix (an anatomic area that contains the transition from the squamous epithelium of the ectocervix to the glandular epithelium of the endocervix). Hysterectomy is an option for women who are incompletely treated with excision or ablation or who have recurrent CIN. The efficacy rate for both ablation and excision is approximately 90% to 95%. Overall, the rate of recurrent or persistent CIN is 5-17% despite therapy with any of the excision or ablative techniques[23]. However, both excision and ablation have been associated with an increased risk of adverse obstetric outcomes (pregnancy loss, cervical incompetence, premature rupture of membranes, preterm delivery), and morbidity (hemorrhage, pain, dysmenorrhea, discharge, cervical stenosis)[23].

Both medical and surgical options are available for treatment of genital warts. Treatment effectiveness studies show highly variable results. There is no definitive evidence that any of the available treatments are superior to any other, and no single treatment is ideal for all patients or all warts. All therapies are associated with localized discomfort including itching, burning, erosions, and pain since the epithelium is disrupted, and complications resulting from treatment include scarring and chronic genital area pain[24, 25]

Treatment options for invasive cancers are surgery, radiation therapy and chemotherapy. Prognosis following treatments is largely dependent on disease stage. Cervical cancer treatment is associated with pelvic pain, sexual dysfunction, bowel dysfunction, urinary incontinence, and ovarian failure including infertility and premature menopause, which can persist for years or lifelong following treatment.

2.3 Safety and Efficacy of Pharmacologically Related Products

Two HPV vaccines, Gardasil and Cervarix, are licensed in the United States and numerous countries worldwide. Both Gardasil and Cervarix contain recombinant VLPs of HPV types 16 and 18 and provide varying degrees of cross-protection against persistent infection and cervical dysplasias associated with HPV 31, 33 and 45. However, the cross-protection seems to wane over time. Gardasil also protects against HPV types 6 and 11, which cause 90% genital warts. Both vaccines are formulated in a sterile suspension for intramuscular injection (IM). Each dose of Gardasil (in 0.5 ml) contains 20 µg, 40 µg, 40 µg and 20 µg, of L1 proteins of HPV types 6, 11, 16 and 18, respectively, and approximately 225 µg of the proprietary adjuvant AAHS. Each dose of Cervarix (in 0.5m) contains 20 µg each of HPV types 16 and 18 L1 proteins, and the adjuvant AS04, which contains 50 µg of monophosphoryl lipid A and 0.5 mg of aluminum hydroxide.

Gardasil was registered in 127 countries, with an estimated >95 million doses distributed worldwide, and Cervarix was registered in >115 countries, with an estimated >33 million doses distributed worldwide[26]. Both Gardasil and Cervarix[27] have demonstrated similar efficacy against the vaccine-targeted types for a range of cervical endpoints from persistent infection to CIN 3 in women naïve to the corresponding type at the time of vaccination. However, protection from incident infection or disease from non-vaccine types is restricted, and the vaccines have no effect on prevalent infection or disease. Gardasil has demonstrated strong protection against genital warts, VIN and VaIN associated with the vaccine types in women, and also protected men for incident infection, genital warts and AIN by the vaccine types. For practical reasons, efficacy studies have not been conducted in preadolescent and adolescent girls and boys. Efficacy in this population was inferred from clinical trials in adults by immunogenicity bridging.

The safety profile of both vaccines was assessed extensively in randomized controlled clinical trials conducted prior to licensure and has been further elucidated following licensure from surveillance and specific studies in large populations. In summary, both vaccines are associated with relatively high rates of injection site reactions, particularly pain, but this is usually of short duration and resolves spontaneously. Systemic reactions (headache, fever, nausea, dizziness, and vomiting) have generally been mild and self-limited. Post vaccination syncope has occurred, but can be avoided with appropriate care. Serious vaccine-attributable adverse events, such as anaphylaxis, are rare. Post marketing case reports have linked vaccination with a range of new onset chronic conditions, including autoimmune diseases. However, well-conducted population-based studies show no association between the HPV vaccines and such conditions(26).

One observer-blinded randomized head-to-head study compared Cervarix and Gardasil directly(28). In the approximately 1,100 women aged 18–45 years, solicited AEs were significantly more common following Cervarix [95.1% (95 % CI 92.8–96.7)] compared with Gardasil [85.1% (95% CI 81.8–88.1)]. Severe injection site reactions (pain, redness and swelling) were more common in Cervarix recipients [17.4% (95% CI 14.2–20.9)] compared with Gardasil recipients [3.4% (95 % CI 2.0–5.4)]. At 24-month follow-up, the proportions reporting serious adverse events (SAEs), significant medical conditions, new onset chronic diseases or autoimmune diseases were similar between the two groups. The safety results of this single head-to-head study are generally consistent with those from separate studies of both vaccines reported in their package inserts (PIs). The safety and efficacy of Gardasil are discussed in further detail in the next section.

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

Gardasil 9 (also designated as 9vHPV in this review) is a non-infectious recombinant 9-valent HPV vaccine prepared from the purified VLPs of L1 protein HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. The L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. There is no previous human experience with 9vHPV and it has not been approved for marketing in any country. However, previous human experience with qHPV is relevant to 9vHPV since the vaccines are similar in composition and contain four common HPV types (6, 11, 16 and 18).

2.4.1 Clinical Trials with qHPV

Administration of a 3-dose regimen (Month 0, 2 and 6) of qHPV to women naïve to the relevant vaccine HPV types at Day 1 through completion of the vaccination regimen was over 94% efficacious in preventing the development of HPV 16- and 18-related CIN 2/3, adenocarcinoma in situ (AIS), VIN 2/3 and VaIN 2/3; HPV 6- and 11-related external genital lesions (including condyloma acuminata); HPV 6-, 11-, 16-, and 18-related AIN; and HPV 6-, 11-, 16-, and 18-related persistent infection. Efficacy was maintained for ≥5 years post-vaccination(29). The qHPV vaccine affords some cross-protection against other oncogenic HPV types. However, this cross-protection is incomplete and limited to only a few types(30).

A pooled analysis of clinical trials showed that injection site reactions were significantly more common in qHPV recipients compared with recipients of aluminum containing placebo(31). Injection site pain was most common (83% vs. 77%), with severe pain reported in 4% of qHPV recipients compared with 2% of aluminum-containing placebo recipients. Erythema (24% vs. 18%) and swelling (24 vs. 16%) were also more common in vaccine recipients. Common systemic adverse experiences did not differ markedly between groups, with headache most common (26%), followed by fever (13%) and nausea (6%). There was no significant difference

in the frequency of SAEs overall or by system organ class over a median follow-up period of 3.6 years and >34,000 person-years-at-risk. Six vaccine-related SAEs were experienced by five qHPV recipients: recurrent vaginal hemorrhage, bronchospasm, gastroenteritis, ulcerative colitis, and a combination of hypertension and headache. Deaths occurred in 0.1% of both vaccine and control recipients, respectively, with no death assessed as related to the vaccine. The overall proportions of subjects reporting new onset autoimmune conditions were not different between the qHPV and placebo groups (2.4 % in each); specific conditions that were nominally higher among qHPV recipients included thyroiditis, rheumatoid arthritis and proteinuria. Analysis of pooled data from many clinical trials has still not provided enough participants to detect meaningful differences in these low-incidence events.

2.4.2 Post Licensure Safety of qHPV

The qHPV vaccine was initially approved by the FDA in June 2006. As reported by CDC's Morbidity and Mortality Weekly Report on July 26, 2013[(32)], from June 2006 through March 2013, approximately 56 million doses of qHPV were distributed in the United States. During this period, the Vaccine Adverse Event Reporting System (VAERS) received a total of 21,194 adverse event reports occurring in females after receipt of qHPV; 92.1% were classified as non-serious. Among non-serious adverse events, the most commonly reported generalized symptoms were syncope, dizziness, nausea, headache, fever, and urticaria; the most commonly reported local symptoms were injection-site pain, redness, and swelling. Among the 7.9% of qHPV-related VAERS reports classified as serious, headache, nausea, vomiting, fatigue, dizziness, syncope, and generalized weakness were the most frequently reported symptoms. Overall reporting of adverse events to VAERS is consistent with pre-licensure clinical trial data.

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

2.5.1 Pre-submission Regulatory Activities

- August 3, 2007, Original IND Submission
- September 22, 2008, End of Phase 2 (EOP2) Meetings
  The Applicant proposed a co-primary endpoint assessment of persistent infection related to the new HPV types (31, 33, 45, 52 and 58) and immune responses to the original HPV types (6, 11, 16 and 18). The Applicant requested a seamless phase 2/3 adaptive trial design. The following agreements were reached between CBER and the Applicant:
  - The primary efficacy endpoint in the clinical trial to support licensure of 9vHPV for prevention of HPV 31, 33, 45, 52 and 58 would be limited to the combined histopathological endpoints of HPV 31, 33, 45, 52 and 58-related CIN 2/3 or worse and VIN 2/3- and VaIN 2/3- or worse in the PPE population. The success criterion would be a lower bound (LB) of vaccine efficacy (VE) of the two-sided 95% CI being greater than 25%. Persistent infection would be a secondary endpoint.
  - The clinical benefit of 9vHPV against the original HPV types would be demonstrated by non-inferiority comparison between qHPV and 9vHPV as assessed by antibody responses to the original HPV types. The success criterion would be a LB of the two-sided 95% CI for the geometric mean titer (GMT) ratio (9vHPV/qHPV) being greater than 0.67 for each HPV type.
  - Transfer of label claims for qHPV would be granted for 9vHPV if and only if the efficacy were demonstrated for the combined histopathological endpoints mentioned above, non-inferior immunogenicity of 9vHPV were obtained as compared to qHPV in regards to the original HPV types, and no safety issues were identified.

  - The proposed seamless adaptive trial design was acceptable.
- November 21, 2008, the Applicant submitted a revised clinical protocol based on the EOP2 meeting agreements.
- December 23, 2009 Fast Track Designation requested
- February 19, 2010 Fast Track Designation granted
- June 28, 2011, Type C Meeting to discuss the study(ies) design(s) to support use in males 9 through 26 years of age.
  - The Applicant proposed to conduct a safety and immunogenicity study in males 9 through 15 years of age (to be submitted as part of the original BLA submission).
  - CBER requested a safety and immunogenicity study in males 16 through 26 years of age in order to bridge efficacy to this population to be submitted as a supplemental.

***Reviewer's comments**: Efficacy of qHPV against anal disease due to vaccine HPV types was assessed in males 16 through 26 years of age, but not in females. The efficacy of qHPV against anal disease due to HPV 6, 11, 16 and 18 in females and boys 9 through 15 years of age was inferred by immunological bridging from males 16 through 26 years of age.*

In contrast to HPV associated cervical cancers, HPV associated anal cancer is predominately caused by HPV types 16 and 18. For example, among HPV-positive anal cancerous lesions, 87% were HPV 16 positive and 9% were HPV 18 positive[(33)]. It is not feasible to assess efficacy of 9vHPV against anal disease due to HPV types 31, 33, 45, 52 and 58 using qHPV as a comparator because very few cases of anal lesions are caused by the new HPV types in 9vHPV. In addition, it is ethically problematic to conduct a placebo controlled study to evaluate the efficacy of 9vHPV in prevention of HPV related anal lesions. Inferring efficacy in males from the core efficacy study in females 16 through 26 years of age by immunological bridging is therefore acceptable.

- December 6, 2011 Pre-BLA Meeting

2.5.2 Post-BLA Submission Regulatory Activities

- May 20, 2014 CBER requested that the Applicant conduct an internal audit of Study Site ----(b)(4)(b)(6)-- under Study V503-001 for potential issues of non-compliance with Good Clinical Practices (GCP).
- July 31, 2014 CBER requested that the Applicant provide additional information regarding public allegations of non-compliance with GCP at clinical sites (b)(3)(b)(4)(b)(7) in (b)(3)(b)(4)(b)(7) in Study V503-002.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission in general 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 application contains six studies (Protocol V503-001, -002, -005, -006, -007 and -009). All studies except for V503-009 were at least partially conducted under IND 13447. The designs of studies under IND13447 adhered to good clinical practices, including elements of informed consent as required by 21 CFR 50.25 and pediatric ethical considerations as outlined in 21 CFR 50.51-54. Study V503-009 was requested by the European Medicines Agency to provide additional supporting data to bridge immunogenicity from qHPV to 9vHPV vaccines in girls 9 through 15 years of age. This study was not conducted under IND. The clinical protocol states that the investigator and the sponsor agreed to conduct the study in an efficient and diligent manner in accordance with this protocol, International Conference of Hominization (ICH) GCP standards, Declaration of Helsinki and applicable regulatory requirements, as well as any European and/or local applicable laws and regulations relating to the conduct of the study.

***Reviewer's comments**: Under Module 5.2, the Applicant indicated that the studies under Protocols* V503-001, -002, -005, -006, and -007 *conducted at non-U.S. sites were not conducted under IND13447. In response to IRs dated February 14, 2014 and April 23, 2014 requesting clarification on these hybrid IND/non-IND studies, Merck submitted a response under STN 125508/0.13 on May 12, 2014 indicating that non-U.S. sites followed all FDA requirements except for signing Form 1572.*

BIMO inspected four U.S. study sites and two foreign country sites, and no concerns were identified in the course of these inspections. The four U.S. study sites included Georgia Regents University Research and Medical college of Georgia Research (enrolled 105 subjects for V503-001 and 26 subjections for V503-002), H. Lee Moffitt Cancer Center and Research Institute (enrolled 113 subjects for V503-001), University of Washington (enrolled 139 subjects for V503-001), and Primary Physicians Research Inc. in Pennsylvania (enrolled 55 for V503-002). The two foreign sites included Vaccine Trial Center of Mahido University in Bangkok, Thailand (enrolled 135 subjects for V503-001, and 130 subjects for V503-002), and Frederiksberg Hospital in Frederiksberg, Denmark (enrolled 953 subjects for V503-001).

During the review of this application, CBER became aware that another vaccine manufacturer was closing a site ----(b)(4)(b)(6)----- for multiple violations including:

- Violations of GCP with regard to obtaining informed consent
- Backdating, copy and pasting clinical assessments/visit notes, medical charts completed days after subject visits
- Lack of evidence that PI was providing adequate oversight or even directly involved in the conduct of the study

The investigator at site (b)(4)(b)(6) was also involved in Study V503-001, which enrolled 247 subjects who received 9vHPV vaccine and 248 subjects who received qHPV vaccine. An Information Request was sent to Merck on May 20, 2014, to inquire if Merck had conducted (or was planning to conduct) an internal audit of this site. Merck then conducted an internal audit of this site. Merck submitted the audit to CBER under STN 125508/0.31 on September 2, 2014. The preliminary audit showed deviations in the informed consent process and deviations from the clinical protocol.

Further investigation conducted by the Applicant showed that all 580 subjects entering the study provided primary informed consent upon enrollment. The Applicant also confirmed that all 580 subjects except 3 signed the final, revised informed consent. As mentioned in the submission of STN 125508/0.31, there were gaps in the process of obtaining certain applicable re-consents

from some study subjects at this site. The results regarding this investigation were submitted to STN 125508/0.40 on October 6, 2014.

Reviewer's comments: *Based on the additional information provided by the Applicant, the non-compliance with GCP was limited to the re-consent process. The clinical and statistical reviewers thoroughly assessed the adverse events, immunogenicity results, and gynecological results (PCR, cytology and pathology). The rates and intensities of adverse events, antibody responses to the vaccine HPV types, and gynecological data collected from the site were similar to those observed in other sites under Study V503-001. Two subjects contributed to the cases of primary efficacy analysis: one in the 9vHPV group (the only one primary efficacy case in Study V503-001), and one in the qHPV group. The data collected from this site appears to be consistent with other sites in this study. Consequently, the review team determined that the data collected from this study site should be included in the clinical assessment. Please also refer to the BIMO review by Ms. Erin Mcdowell.*

In addition, the review team became aware of allegations of non-compliance of GCP at two clinical sites ---(b)(3)(b)(4)(b)(7)--- in Study V503-002. CBER requested that the Applicant provide additional information regarding the allegations and medical monitor reports of these sites on July 31, 2014. The Applicant submitted the requested information to STN 125508/0.30 on August 8, 2014.

Site ----------(b)(3)(b)(4)(b)(7)---------- of all subjects in Study V503-002. The review team assessed copies of informed consent documents and Medical Monitor reports for these two sites submitted by the Applicant and determined that these documents do potentially corroborate some of the allegations. The proportion of subjects with injection-site reactions reported in Site (b)(3)(b)(4)(b)(7), much lower compared with the overall rate reported in Study V503-002 (80.6%), (b)(3)(b)(4)(b)(7) reported an oral temperature ≥37.8ºC in Site (b)(3)(b)(4)(b)(7) (compared with 8.8% in Study V503-002), suggesting that adverse events may have been under-reported at these sites.

Reviewer comments: *Based on the above findings, especially the problems with the informed consent process, the review team determined that data collected from these study sites should be excluded from the clinical assessment and package insert. Please also refer to the BIMO review by Ms. Erin Mcdowell. On October 31, 2014 CBER asked the Applicant to re-analyze data excluding Study Sites* (b)(3)(b)(4)(b)(7) *and to revise the package insert accordingly. The re-analysis data were submitted to STN 125508/0.43, and were reviewed and incorporated into this review (please refer to Sections 6.2, 7 and 8) and the PI. The data reviewed in Sections 6.2, 7, and 8 of this document reflect the exclusion of the two* (b)(3)(b)(4)(b)(7) *sites from the dataset of study V503-002. Sensitivity analyses showed that exclusion of these data resulted in no changes greater than 1% for rates of any adverse events, no changes in seroconversion rate for any vaccine HPV type, and no changes greater than 2% for GMTs for any vaccine HPV type.*

3.3 Financial Disclosures

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators under Studies V503-001, -002, -005, -006 and -007 as recommended in the *Guidance for Industry Financial Disclosure by Clinical Investigators*. All investigators in these five studies except one investigator under Study V503-002 have provided financial disclosure information. Five investigators from 3 studies (Study V503-001, -002 and -006) received significant payments from the Applicant.

Financial disclosure information for Study V503-009 was not included in the original submission but was submitted to STN 125508/0.4_Module 1.11.3 on March 14, 2014, following a CBER request on February 14, 2014.

Potential issues with financial disclosure for the six clinical studies submitted to this BLA are summarized below.

Five investigators in the three studies had disclosable financial interests/arrangements.

- One Investigator who participated in Studies V503-001, -002 and -006 received Significant Payments of Other Sorts of -------(b)(6)------ (internal search by the Applicant). The payments reported by this investigator to the Applicant were -----(b)(6)-----.
- Two investigators who participated in Study V503-001 received Significant Payments of Other Sorts (internal search by the Applicant) of ----------(b)(6)----------, respectively. The corresponding payments reported by the investigators to the Applicant were ----------(b)(6)----------, respectively.
- Two investigators who participated in Study V503-002 received Significant Payments of Other Sorts (internal search by the Applicant) of ----------(b)(6)---------- reported by investigator) and ----------(b)(6)---------- reported by investigator), respectively.

CBER requested the following information from the Applicant on February 14, 2014:

- Please provide a description of the steps taken to minimize potential bias.
- Please provide details as to the nature of the payments to the five investigators and specify the Merck product involved for each payment.
- Please explain why the payments to the five investigators reported by Merck via internal search are different from those reported by the investigators to Merck.
- Please provide the number of primary efficacy cases in Study V503-001 (tabulated by qHPV and 9vHPV treatment arms) reported by the investigators with disclosable financial interests.

On March 14, 2014, the Applicant submitted its responses to STN 125508/0.4. The Applicant explained that for Studies V503-001 and V503-009, potential bias would be minimized by the study design (randomized and double blind). For V503-002, all subjects received 9vHPV, subjects were randomized in equal numbers to three manufacturing product lots, and laboratory personnel were blinded. Therefore, the risks of bias in immunogenicity evaluation were mitigated. However, potential bias for safety evaluation still exists. The payments to the investigators were for symposia, consultant fees, medical education and research, speaker fees and participation on an advisory board. The discrepancies in payments reported by the Applicant and the investigators were caused by different reporting periods used by the investigators and the Applicant.

Reviewer's Comments*: Only one primary endpoint case (in the qHPV group from study site 0005) was reported from study sites involving the investigators discussed above. The Applicant's explanations and clarifications are acceptable. As for the potential bias for safety evaluation, it is a limitation of the study design and is discussed further in Section 8 of this review.*

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

4.1 Chemistry, Manufacturing, and Controls

The manufacturing process for the five new HPV types in 9vHPV vaccine remains unchanged for the HPV types contained in the licensed qHPV vaccine. The CMC reviewer states that there are no substantive issues that will impact approval of the application. Please refer to the CMC review by Dr. Haruhiko Murata for details.

4.2 Assay Validation

The assay reviewers identified issues in the validations for the assays to assess responses to pertussis and meningococcal antigens used in the concomitant vaccination study (V503-005). The reviewers determined that the issues may be addressed by assessing the performance of the assays during the time in which samples were tested. If the assays can be shown to have been well controlled during sample analysis, and since the data from the study do not indicate any unusual results, the assays may be deemed appropriate for use. However, these issues should be addressed before the assays are used for future studies. Please refer to the Assay Validation Review by Ms. Freyja Lynn for details.

4.3 Nonclinical Pharmacology/Toxicology

Based on the nonclinical toxicity assessments of the V503 vaccine submitted in this BLA, there are no significant safety issues to preclude the BLA from being approved. Please refer to the toxicology review by Dr. Nabil Al-Humadi for details.

4.4 Clinical Pharmacology

No clinical pharmacology studies of the 9vHPV vaccine were conducted in support of this application

4.4.1 Mechanism of Action

Animal studies suggest that the protective effect of L1 VLP vaccines may be mediated by the development of IgG neutralizing antibodies directed against HPV L1 capsid proteins generated as a result of vaccination.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data. Please refer to the statistical review by Dr. Lihan Yan for details.

4.6 Pharmacovigilance

The pharmacovigilance medical reviewer recommends a post-marketing safety study to assess risk of spontaneous abortion following vaccination, with particular attention to pregnancies that occur within 30 days of vaccination with 9vHPV. A study of this type may require a computerized database of linked anonymized longitudinal medical records, in which medical record data for pregnant women is available for at least one year prior to their last menstrual period, and can be linked to the administration of vaccines. No REMS is warranted at this time. Please refer to the pharmacovigilance review by Dr. Adamma Mba-Jonas for the integrated risk assessment.

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

5.1 Review Strategy

The results of six clinical studies are included in this BLA submission. Study V503-001 provides major clinical efficacy, immunogenicity and safety data to support licensure of 9vHPV in females 16 through 26 years of age. Study V503-002 provides immunogenicity data to infer clinical effectiveness in boys and girls 9 through 15 years of age because clinical efficacy studies were not feasible in this population. Study V503-002 also includes a lot consistency study. The review efforts focused on these two studies, which are reviewed and documented separately under Section 6. Study V503-009 is a non-inferiority immunogenicity study of antibody responses to HPV types 6, 11, 16 and 18 comparing qHPV and 9vHPV in girls 9 through 15 years of age. Because the immunogenicity and safety data for this study are listed separately in the draft package insert, this study is also reviewed individually under Section 6.

The remaining three supportive studies are included in the review analyses under Sections 7 [Integrated Summary of Efficacy (ISE)] and 8 [Integrated Summary of Safety (ISS)]. Studies V503-005 and V503-007 provide immunogenicity and safety data in children 11 through 15 years of age who received 9vHPV concomitantly administered with Menactra/Adacel and Repevax, respectively. Study V503-006 provides immunogenicity and safety data on 9vHPV administered to females 12 through 26 years of age who previously received Gardasil vaccination. Immunogenicity data for Studies V503-005 and V503-006 are reviewed under Section 7, and the safety data are reviewed under Section 8. Because Repevax is not licensed in the U.S., immunogenicity data from subjects vaccinated concomitantly with 9vHPV and Repevax (Study V503-007) are briefly summarized and documented in the ISE. The remaining pooled safety and immunogenicity data from all the 6 studies (including Study V503-007) are analyzed in Sections 7 and 8.

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

This clinical review considered the following documents submitted to the BLA, as listed by electronic common technical document (eCTD) module:

- BLA 125508/0.0, Module 1.3.4 (Financial Disclosure)
- BLA 125508/0.0, Module 1.6.2 (Meeting Background Materials)
- BLA 125508/0.0, Module 1.7.1 (Fast Track Designation Request)
- BLA 125508/0.0, Module 1.9.1 (Request for Waive of Pediatric Studies)
- BLA 125508/0.0, Module 1.14.1.1 (Draft Carton and Container Labels)
- BLA 125508/0.0, Module 1.14.1.3 (Draft Labeling Text)
- BLA 125508/0.0, Module 1.16 (Risk Management Plans)
- BLA 125508/0.0, Module 2.5 (Clinical overview)
- BLA 125508/0.0, Module 2.7.3 (Summary of clinical efficacy, i.e., Integrated Summary of Efficacy)
- BLA 125508/0.0, Module 2.7.4 (Summary of clinical safety, i.e., Integrated Summary of Safety)
- BLA 125508/0.0, Module 5.2 (Summary Level of Clinical Site Information)
- BLA 125508/0.0, Module 5.3.5.1.p001 [Clinical Study Report for P001 (V503-001)]
- BLA 125508/0.0, Module 5.3.5.1.p009 [Clinical Study Report for P009 (V503-009)]
- BLA 125508/0.0, Module 5.3.5.1.p002 [Clinical Study Report for P002 (V503-002)]
- BLA 125508/0.0, Module 5.3.5.1.p005 [Clinical Study Report for P005 (V503-005)]

- BLA 125508/0.0, Module 5.3.5.1.p007 [Clinical Study Report for P007 (V503-007)]
- BLA 125508/0.0, Module 5.3.5.1.p006 [Clinical Study Report for P006 (V503-006)]
- BLA 125508/0.0, Module 5.3.5.1.NA [Gardasil Historical Studies]
- BLA 125508/0.0, Module 5.3.5.3 (Statistical Analysis Plan)
- BLA 125508/0.0, Module 5.3.6 (Post-marketing Studies of Gardasil)
- BLA 125508/0.3, Module 1.14.1.2 Annotated Draft Labeling Text (revised)
- BLA 125508/0.4, Module 1.11.3 Efficacy Information Amendment (Response to CBER Information Request #1)
- BLA 125508/0.6, Module 1.11.3 Efficacy Information Amendment (Response to CBER Information Request #2)
- BLA 125508/0.8, Module 1.11.3 Safety Update Report (4 months)
- BLA 125508/0.13, Module 1.11.3 Efficacy Information Amendment (Response to CBER Information Request #5: Spontaneous abortions)
- BLA 125508/0.22, Module 1.11.3 Response to CBER Information Request #13 Regarding Multiple Sclerosis
- BLA 125508/0.25, Module 1.11.3 Efficacy Information Amendment (Response to CBER Information Request #13: Spontaneous abortions)
- BLA 125508/0.30, Module 1.11.3 Efficacy Information Amendment (Response to CBER Information Request #16: (b)(3)(b)(4)(b)(7) Sites Non-compliance with GCP)
- BLA 125508/0.31, Module 1.11.3 Efficacy Information Amendment (Response to CBER Information Request #10: (b)(3)(b)(4)(b)(7) Site Non-compliance with GCP)
- BLA 125508/0.34, Module 1.11.3 Response to Information Request (IR) on Site (b)(3)(b)(4)(b)(7)
- BLA 125508/0.35, Module 1.11.3 Response to IR for Post-marketing Assessment of Spontaneous Abortions
- BLA 125508/0.38, Module 1.11.3 Sensitivity Analyses (Excluding Study Sites -------- (b)(3)(b)(4)(b)(7) and Study Sites (b)(3)(b)(4)(b)(7))
- BLA 125508/0.39, Module 1.11.3 Response to IR#18 for Causality Assessment of the Case of Pulmonary Vasculitis
- BLA 125508/0.41, Module 1.11.3 Response to IR#18 for Causality Assessment of the Case of Pulmonary Vasculitis-Follow-up Response
- BLA 125508/0.43, Module 1.11.3 Response to IR#19 for Re-analyses of Excluding (b)(3)(b)(4)(b)(7) Sites (b)(3)(b)(4)(b)(7)

5.3 Table of Studies/Clinical Trials

The clinical studies reviewed in this BLA are summarized in Table 1 and Table 2 below.

Table 1: Overview of Clinical Studies V503-001, -002 and -009.

Study ID	**V503-001**	**V503-002**	**V503-009**
IND Number	13447	13447	Not Under IND
NCT Number	00543543	00943722	01304498
Study Phase	2b/3	3	3
Study Centers	105 international	70 international	24 centers in Europe
Participants Planned	14620	2800	600
Participants Enrolled	Phase 2b: 1242; Phase 3: 14215	2999	600
Age Range	16 to 26	9-26	9 to 15

Study ID	**V503-001**	**V503-002**	**V503-009**
Demographics	Females only	63.0% 9-15 year-old females; 21.5% 9-15 year-old males; 15.5% 16-26 year-old females	Females only
9vHPV Recipients	8020 (7099 received Mid-dose)	2991	300
9vHPV Dose	Low-dose, Mid-dose and High-dose	Mid-dose	Mid-dose
9vHPV Regimen	3 doses IM at Day 1, Month 2 & Month 6	3 doses IM at Day 1, Month 2 & Month 6	3 doses IM at Day 1, Month 2 & Month 6
Comparator	qHPV, 3 doses IM at Day 1, Month 2 & Month 6	NA	qHPV, 3 doses IM at Day 1, Month 2 & Month 6
Randomization Ratio	Phase 2b: 1:1:1:1; Phase 3: 1:1	1:1:1 (Lot consistency)	1:1 with two age strata (9 to 12 and 13 to 15 years of age)
Study Duration	Phase 2b: 7 months; Phase 3: ≥42 months	12 months	7 months
Primary Efficacy Endpoints	Combined proportion of subjects with HPV type 31, 33, 45, 52 and 58-related CIN2 or VIN2/3 or VaIN2/3 or worse; Antibody GMTs for HPV types 6, 11, 16 and 18	Antibody GMTs for all 9 vaccine HPV types	Antibody GMTs for HPV types 6, 11, 16 and 18
Major Findings	Efficacy: 96.7% (95%CI: 80.9, 99.8) in prevention of combined genital lesions associated with the five new HPV types. Immunogenicity: Non-inferiority -demonstrated between 9vHPV and qHPV for HPV types 6, 11, 16, and 18.	Non-inferiority demonstrated between 9 through 15 year-olds and 16 through 26 year old females for all 9 vaccine HPV types. Lot consistency criteria were met for all 9 vaccine HPV types.	Non-inferiority demonstrated between 9vHPV and qHPV for HPV types 6, 11, 16, and 18.

Table 2: Overview of Clinical Studies V503-005, -006, and -007

Study ID	**V503-005**	**V503-006**	**V503-007**
IND Number	13447	13447	13447
NCT Number	00988884	01047345	01073293
Study Phase	3	3	3
Study Centers	Multi-centers	Multi-centers	Multi-centers
Participants Enrolled	1241	924	1054
Age Range	11 to 15 years	12 to 26 years	11 t0 15 years
Demographics	620 males, 621 females	Females previously vaccinated with qHPV	526 males, 528 females
9vHPV Recipients	1241	618	1054
9vHPV Dose	Mid dose	Mid dose	Mid dose
9vHPV Regimen	3 doses IM at Day 1, Month 2 & Month 6, with concomitant administration of the first dose of 9vHPV with Menactra and Adacel	3 doses IM at Day 1, Month 2 & Month 6	3 doses IM at Day 1, Month 2 & Month 6, with concomitant administration of the first dose of 9vHPV with Repevax.
Comparator	Administration of 9vHPV	Placebo	Administration of 9vHPV

Study ID	V503-005	V503-006	V503-007
	without concomitant administration of Menactra and Adacel		without concomitant administration of Repevax
Randomization Ratio	1: 1	2: 1	1: 1
Study Duration	7 months	7 months	7 months
Primary Efficacy Endpoints	Antibody GMTs for all 9 vaccine HPV types and antigens in Menactra and Adacel	Antibody GMTs and seroconversion rates for all 9 vaccine HPV types	Antibody GMTs for all 9 vaccine HPV types and antigens in Repevax
Major Findings	Concomitant administration of the first dose of 9vHPV with Menactra and Adacel does not impact the immune responses to any of the vaccines.	Seroconversion rates for all 9 vaccine HPV types were similar among prior qHPV recipients compared to HPV vaccine-naïve subjects in other studies, though antibody GMTs were reduced for HPV types 31, 33, 45, 52 and 58.	Concomitant administration of the first dose of 9vHPV with Repevax does not impact the immune responses to 9vHPV and Repevax.

5.4 Consultations

No Advisory Committee meeting was held and no external consults were sought.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL CLINICAL TRIALS

6.1 Trial #1: V503-001 (Designated as Study 1 in the Draft Package Insert)

Title: A Randomized, International, Double-Blinded (With In-House Blinding), Controlled with Gardasil, Dose-Ranging, Tolerability, Immunogenicity, and Efficacy Study of 9vHPV Vaccine Administered to 16- to 26-Year-Old Women

Reviewer's comment*: In-house blinding was defined as blinding of the sponsor's research personnel except the statistician creating the schedule.*

6.1.1 Objectives

Protocol V503-001 was a phase 2b/3 pivotal, adaptively designed, qHPV-controlled, dose ranging, efficacy, immunogenicity and safety study of 9vHPV in females 16 through 26 years of age.

6.1.1.1 Objectives of Part A (Phase 2b)

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

6.1.1.2 Objectives of Part B (Phase 3) Efficacy Study

Primary Objectives:

1. To evaluate the tolerability of 9vHPV vaccine when administered to 16- to 26-year-old women.
2. To demonstrate that administration of 9vHPV vaccine will reduce the combined proportion of subjects with HPV 31-, 33-, 45-, 52-, and 58-related high grade cervical abnormalities (CIN 2/3), Adenocarcinoma *In Situ* (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer, compared with GARDASIL™ in 16- to 26-year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.

   Reviewer's comment: *The composite clinical endpoint of the five new HPV type related high grade cervical, vulvar and vaginal disease described above constitutes the primary efficacy cases.*

3. To demonstrate that the 9vHPV vaccine induces non-inferior GMTs for anti-HPV 6, 11, 16, and 18 compared to qHPV.

Secondary Objectives

1. To demonstrate that 9vHPV will reduce the combined proportion of subjects with HPV 31-, 33-, 45-, 52-, and 58-related persistent infection (6 months or longer) compared with qHPV in 16- to 26-year-old females in PPE population.
2. To demonstrate that 9vHPV induces non-inferior immune responses with respect to seroconversion percentages for HPV 6, 11, 16, and 18 compared to qHPV.
3. To quantify the amount by which the administration of 9vHPV reduced the combined proportion of subjects with HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar and

vaginal disease compared with qHPV in 16- to 26-year-old females who were seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type(s).
4. To evaluate the persistence of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 immune responses generated by 9vHPV.
5. To evaluate the impact of administration of 9vHPV on the proportion of subjects with Pap test abnormalities [ASC-US (Positive for High Risk HPV) or worse].

Exploratory Objectives

1. To demonstrate that 9vHPV reduces the combined proportion of subjects with HPV 31-, 33-, 45-, 52-, and 58-related persistent infection for a duration 12 months or longer compared with qHPV in 16- to 26-year old females who were seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type(s).
2. To evaluate the impact of 9vHPV on the combined proportion of subjects with CIN, AIS, and cervical cancer caused by any HPV type.
3. To evaluate the impact of 9vHPV on the combined proportion of subjects with vulvar and vaginal disease caused by any HPV type.
4. To evaluate the impact of 9vHPV on the proportion of subjects with Pap test abnormalities (ASC-US [Positive for High Risk HPV] or worse) related to HPV Types 31, 33, 45, 52, & 58.
5. To evaluate the impact of 9vHPV on the proportion of subjects with cervical biopsy and cervical definitive therapy treatments.

6.1.2 Design Overview

This was a phase 2b/3 adaptively designed, randomized, double-blind (operating under in-house blinding procedures), qHPV controlled, multinational, dose-ranging, safety, immunogenicity and efficacy study with a target enrollment of 14,620 subjects. The study was enrolled in two parts. Approximately 1240 subjects were enrolled in Part A and were equally randomized to 3 dose formulations of 9vHPV or qHPV. One dose formulation of 9vHPV was selected for Part B based on interim immunogenicity results. Approximately 13,380 subjects were enrolled in Part B and were equally randomized to the selected dose formulation of 9vHPV or qHPV. Each subject was scheduled to receive 3 doses of the assigned study vaccine intramuscularly at Day 1, Month 2 and Month 6. Three substudies were conducted:

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

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

Reviewer's comments**:** *The optimal dose for Part B was selected by a Merck committee based on immunogenicity data. The selected dose formulation was communicated to the Data Safety Monitoring Board (DSMB) to ensure there was no safety concern identified for the dose. After*

the dose formulation was selected, the unblinded statistician generated a list of subjects who received the formulations that were not chosen for further evaluation in Part B. These subjects completed their regimens and were followed for safety and immunogenicity through Month 7.

6.1.3 Population

6.1.3.1 Main Inclusion Criteria

- Female between the ages of 16 and 26 years inclusive on the day of randomization.
- Never had Pap testing or only had normal Pap test results.
- Subject (or, for minor subjects, parent/legal guardian and subject) fully understood study procedures, alternative treatments available, the risks involved with the study, and voluntarily agreed to participate by giving written informed consent.
- Able to read, understand, and complete the vaccination report card.
- Judged to be in good physical health on the basis of medical history, physical examination, and laboratory results.
- The subject had the following lifetime sexual history at the time of enrollment:
    - One to 4 male and/or female sexual partners; or
    - No male and/or female sexual partners, was 18 years of age or older, and planned to become sexually active within the first 3-6 months of the study.
    - Male partner was defined as someone with whom the subject had penile penetrative sexual intercourse. Female partner was defined as someone who had contacted, either by penetrative (with fingers or other objects) or non-penetrative means, the subject's genitalia during sexual activity.

6.1.3.2 Main Exclusion Criteria

- A history of an abnormal cervical biopsy result (CIN or worse).
- A history of a positive test for HPV.
- Current user of recreational or illicit drugs or had a recent history (within the last year) of drug or alcohol abuse or dependence. Alcohol abusers were defined as those who drank despite recurrent social, interpersonal, and/or legal problems as a result of alcohol use.
- History of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension or shock) that required medical intervention.
- Subject had known allergy to any vaccine component, including aluminum, yeast, or BENZONASE (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).
- Currently immunocompromised or was diagnosed as having a congenital or acquired immunodeficiency, HIV infection, lymphoma, leukemia, systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), inflammatory bowel disease, or other autoimmune condition.
- History of splenectomy.
- Receiving or had received in the year prior to enrollment chemotherapy, immunosuppressive therapies, or radiation therapy.
- Received any immune globulin product or blood-derived product within the 3 months prior to the Day 1 vaccination, or planned to receive any such product during Day 1 through Month 7 of the study.
- History of thrombocytopenia or other coagulation disorder that would contraindicate intramuscular injections.
- Expecting to donate eggs during Day 1 through Month 7 of the study.

- Concurrently enrolled in clinical studies of investigational agents or studies involving collection of cervical specimens.
- Received a marketed HPV vaccine, or had participated in an HPV vaccine clinical trial and had received either active agent or placebo.
- History or current evidence of any condition, therapy, lab abnormality or other circumstance that might confound the results of the study, or interfere with the subject's participation for the full duration of the study, such that it was not in the best interest of the subject to participate.
- History of or clinical evidence at the Day 1 pelvic examination of HPV related external genital lesions (e.g., condyloma acuminata or VIN) or external genital cancer, HPV-related vaginal lesions (e.g., condyloma acuminata or VaIN) or vaginal cancer.

6.1.4 Study Treatments or Agents Mandated by the Protocol

6.1.4.1 Study Product Description

Gardasil 9 is a sterile, white cloudy liquid suspension containing recombinant VLPs of HPV types 6, 11, 16, 18, 31, 33,45, 52, and 58 absorbed on 500 µg of adjuvant amorphous aluminum hydroxyphosphate sulfate (AAHS). The vaccine was filled into single-dose vials to ensure a minimum recoverable volume of 0.5 mL for injection. The product formulations used for this study were Lots WL00025085, WL00025087, WL00025088, WL00027320, WL00030772, WL00030851, WL00030920 and WL00034579 (Data source: Table 2, page 5 of Module 3.2.P.5.4, STN 125508/0, and Table 9-4, STN 125508/0, Module 5.3.5.1.p001-CSR of V503-001, p131).

Three dose formulations of 9vHPV were assessed in this study:

- Low dose formulation: Each 0.5 ml dose contains 20µg of VLP for each HPV type (except for 40 µg for types 11 and 16) absorbed on 500 µg AAHS. The total dose of VLPs is 220 µg.
- Mid dose formulation: Each 0.5 ml dose contains 30 µg of VLP for types 6 and 18, 40 µg for type 11, 60 µg of for type 16, and 20 µg for the other HPV types absorbed on 500 µg of AAHS. The total dose of VLPs is 270 µg.
- High dose formulation: Each 0.5 dose contains 30 µg of VLP for each HPV type (except 40 µg for type 11, 80 µg for type 16, and 55 µg for type 18) adsorbed on 500 µg AAHS. The total dose of VLPs is 355 µg.

Gardasil is a quadrivalent HPV vaccine manufactured and marketed by Merck. Each 0.5 ml dose contains 20 µg of VLP for HPV types 6 and 18 and 40 µg for types 11 and 16 absorbed on 225 µg of AAHS. The total dose of VLPs is 120 µg. The product formulations used for this study were Lots WL00024099, WL00027324, WL00029942, and WL00040674 (Data source: Table 9-4, STN 125508/0, Module 5.3.5.1.p001-CSR of V503-001, p131).

Reviewer's comments*: The amount of AAHS adjuvant used for all 3 dose formulations of 9vHPV was 500 µg, more than twice that used in qHPV. The higher amount of AAHS is the same as that used in Recombivax HB™, a recombinant protein-based vaccine licensed in many countries including the U.S. to prevent infection with hepatitis B virus. Recombivax HB™ has been administered to millions of infants, adolescents, and adults, and no significant safety issue has been identified.*

6.1.4.2 Randomization, Dose Schedule and Route of Administration

Part A (Phase 2b): Study participants were randomized at 1: 1: 1: 1 to receive a dose of either qHPV or one of 3 formulations of 9vHPV vaccine (V503-low, V503-mid and V503-high) administered intramuscularly at Day 1 and Months 2 and 6.

Part B (Phase 3): Participants were randomized at 1:1 to receive a dose of either qHPV or 9vHPV (V503-mid selected from Part A) administered intramuscularly at Day 1 and Months 2 and 6.

6.1.4.3 Concomitant medications

Use of medicines and non-study vaccines was documented in the data collection system. Unless medically necessary, subjects and investigators were advised to avoid use of immunosuppressive drugs and blood products from 3 days prior to Day 1 through Month 7, non-study inactivated vaccines for 14 days prior to each study vaccination through 14 days after each vaccination, or attenuated vaccines for 21 days prior to each study vaccination through 14 days after each vaccination. Subjects were allowed to receive allergen desensitization therapy and tuberculin skin testing while participating in the study.

6.1.5 Directions for Use

The vaccines (qHPV or 9vHPV) were withdrawn from vials and administered intramuscularly using a 1.0-mL syringe. The deltoid muscle of the non-dominant arm was the preferred site of vaccination. Injections were avoided within 2 cm of a tattoo, scar, or skin deformity.

Reviewer's comment: *A total of 15 subjects who received injectable contraceptives (e.g., DEPO-PROVERA) or implanted contraceptives (e.g., NORPLANT) in both arms in the previous 9 months, were given the injection in the thigh rather than in an arm.*

6.1.6 Sites and Centers

The study was an international clinical trial conducted at 105 study centers: 28 centers in the United States (US) and 77 centers internationally. The median number of subjects enrolled at each center was 100 (ranging 14 – 1105).

6.1.7 Surveillance/Monitoring

Table 3 summarizes the surveillance and monitoring for Study V503-001. All scheduled visits were conducted at study sites. Collection of medical history and physical examination was conducted at Day 1 for all subjects. Vital signs were taken prior to each vaccination. In order to assess HPV status at baseline, study participants underwent the following protocol-mandated testing on Day 1: (1) gynecological history and examination; (2) testing of serum for anti-HPV antibodies; (3) PCR testing of cervical and external genital samples for HPV DNA; and (4) ThinPrep™ Pap test. All Pap tests were performed within the context of the study and were read by a central laboratory designated by the Applicant.

Table 3: Surveillance and Monitoring for Study V503-001

Visit (Day or Month)	Day 1	D16	M2	M3	M6	M7	M12	M18	M24	M30	M36	M42	M48	M54
Visit Window			±3wk	±1wk	±4wk	-1wk to ±3wk	±4wk	±4wk	±4wk	±4wk	±4wk	±4wk	±4wk	±4wk
Informed Consent, Allocation Number	X													
Inclusion/Exclusion Criteria	X													
Medical / Gynecologic History	X													
New conditions or Adverse Experiences			X	X	X	X	X	X	X	X	X	X	X	X
Medications and Non-Study Vaccines	X	X	X	X	X	X								
Pregnancy Test§	X		X	X	X	X								
Anti-HPV (including Retention Serum) †	X			X		X	X*		X*		X*	X*		
Vital Signs	X		X		X									
Gynecologic Physical Examination	X					X		X		X		X		X
LVPP and EEC Swabs for HPV PCR	X					X	X	X	X	X	X	X	X	X
Pap Test (ThinPrep™)	X					X	X	X	X	X	X	X	X	X
STI Testing	X		X	X	X	X	X	X	X	X	X	X	X	X
External Genital Wart Inspection	X					X	X	X	X	X	X	X	X	X
Vaccination (IM)	X		X		X									
Provide Vaccination Report Card	X		X		X									
Review and Collect VRC data‡		X	X	X		X								
Adverse Experiences, Clinical Follow-up for Safety‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: Adapted from Table 9-2, STN 125508/0, Module 5.3.5.1-Clinical Study Report of Study V503-001 (page 112-114).
† Serum for anti-HPV measurements may be collected after the pelvic examination, but must be collected before vaccination.
‡Observe subjects for 30 minutes after each vaccination for immediate untoward effects. The subject should use the Vaccination Report card (VRC) to document this safety information: oral temperature in the evening after each study vaccination and daily, at the same time of day, for 4 days after each study vaccination; injection-site or systemic adverse experience(s) starting after each study vaccination for a total of 15 days. Serious adverse experiences (SAEs), pregnancy events, and lactation events should be reported to the sponsor as instructed in the protocol.
* These samples were taken from a randomized subset of 20% of subjects in PPI population.

6.1.7.1 Immunogenicity Assessment

Serum was collected from all subjects at visits specified in Table 3 for analysis of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses by HPV-9 competitive Luminex Immunoassay (cLIA). All subjects in Part A were included in the Part A primary immunogenicity analysis for dose selection for Part B. All subjects enrolled in Part B were included in the Part B immunogenicity hypothesis testing at Month 7. For the purpose of demonstrating vaccine-induced anti-HPV antibody persistence at Months 12, 24, 36, and 42, a random sample of approximately 20% of Part B subjects was tested and analyzed.

6.1.7.2 Efficacy Assessment

Pelvic samples, including external genital and cervicovaginal swabs and Pap test samples, were collected as scheduled in Table 3. All subjects were followed for efficacy through at least Month 42. Labial/vulvar/perineal/perianal (LVPP) and endo/ectocervical (EEC) swabs were tested for detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 by PCR assay to assess persistent HPV infection endpoints.

Any subject with an abnormal Pap test was referred for colposcopy using a protocol mandated triage algorithm. The colposcopist obtained cervical biopsies of areas of the most severe abnormalities and could choose to perform an endocervical curettage (ECC) if no cervical dysplasia was observed. A subject might need subsequent cervical definitive therapy per the protocol-mandated cervical definitive therapy guidelines. Vaginal lesions were biopsied if they were observed during a Pap test, colposcopy, or at any other time. A thorough external genital wart/lesion inspection was performed at routine visits. External genital warts/lesions noted after Day 1 were biopsied. In addition, subjects with histologically confirmed HPV-related external genital lesions (e.g., condyloma acuminata, VIN, cancer) or vaginal warts (e.g., condyloma acuminata, VaIN, cancer) were referred to colposcopy if the biopsies were not obtained during a colposcopy.

Tissue obtained from biopsy and cervical definitive therapy procedures was analyzed by MRL HPV Thinsection PCR assay (for detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and by a consensus diagnosis from the HPV Vaccine Program Pathology Panel to assess clinical disease efficacy endpoints. The panel consisted of four pathologists who reviewed all biopsy slides and adjudicated all pathology specimens for the purpose of providing the official pathologic diagnosis-Each Pathology Panel member independently reviewed the slides, blinded to vaccination group and the subject's HPV PCR status, to formulate a consensus. Consensus Diagnosis Process: The two panelists within each pair reviewed the slides from a given subject independently, blinded to the HPV status of the tissue specimen, the Central Laboratory's diagnosis, other panelist's diagnosis, and other demographic and clinical data of the study subjects. If the diagnoses made by the initial two panelists agreed, that diagnosis was considered the final consensus diagnosis. If the two diagnoses were discrepant, the slide would be sent to a third pathologist for diagnosis. The third panelist was not aware he/she was a "tie-breaker". On rare occasions in which all three diagnoses disagreed, a fourth pathologist reviewed the slides. The final diagnosis was the one rendered by two pathologists. If each of the pathologists provided a different diagnosis for a given biopsy, a panel meeting consisting of all four pathologists would

take place to reach the final consensus. The consensus diagnosis of the panel represented the final diagnosis for study purposes.

The analysis of LVPP/EEC swabs and tissue specimens included PCR analysis for non-vaccine HPV types (35, 39, 51, 56, 59, and potentially others) to document rates of disease associated with non-vaccine HPV types and to assess cross-protection.

6.1.7.3 Safety Assessment

All subjects were monitored for safety for the duration of the study as outlined below:

- All subjects received a vaccination report card (VRC) after each vaccination. On the VRC, the subject or the parent/guardian of the subject was asked to record the subject's oral temperature in the evening after each study vaccination and daily for 4 days after each vaccination to identify febrile events. Also, the subject was asked to record injection-site and systemic adverse experiences, concomitant medications, and concomitant vaccinations on the VRC for 15 days after each vaccination including the day of vaccination.
- SAEs were collected regardless of causality from Day 1 through 6 months following the last vaccination. Events of fetal loss were reported as SAEs if the last menstrual period (LMP) was between Day 1 and 6 months following the last vaccination.
- Deaths, vaccine-related SAEs, and study procedure-related SAEs were collected throughout the study.
- New medical conditions not present at baseline and not reported as an adverse experience were collected throughout the study.
- Any overdose of test vaccine (9vHPV or qHPV), defined as a subject receiving more than 3 doses of vaccine (0.5 mL each dose) or receiving ≥0.75 mL of vaccine in any one dose, was recorded.

Pregnancy and lactation information was also collected. Any female subject with a positive pregnancy test at Day 1 was not vaccinated and was not allowed to participate in the study. Female subjects with a positive pregnancy test after Day 1 who had received fewer than 3 vaccinations were offered the option to complete the vaccination series but were not given further vaccinations until after the final pregnancy outcome was determined. Pregnancy and associated adverse experiences, lactation (if a subject received study vaccine while breastfeeding during the Day 1 through Month 7 period), and SAEs in study subjects and infants were followed to final outcome.

6.1.8 Endpoints and Criteria for Study Success

6.1.8.1 Primary Safety and Tolerability Endpoints

- Occurrence of injection site adverse experiences prompted for on the VRC (such as redness, swelling, and pain/tenderness/soreness occurring Day 1 through Day 5 following any vaccination) and elevated temperature (≥100.0°F or ≥37.8ºC), from Day 1 to Day 5 following any vaccination.
- Severe injection-site adverse experiences and the rates of any vaccine-related SAEs.

Hypothesis: 9vHPV would be generally well tolerated in 16 through 26 year-old women.

6.1.8.2 Primary Efficacy Endpoint

The primary efficacy endpoint was combined cases of HPV 31-, 33-, 45-, 52-, and 58-related CIN 2/3- or VIN 2/3- or VaIN 2/3- or worse. To be classified as an endpoint case for the primary analysis, a subject must have developed at least one of the following after the completion of the Month 7 visit:

- CIN 2/3, AIS, or invasive cervical carcinoma related to HPV types 31, 33, 45, 52 or 58. This endpoint was defined to have occurred if on a single cervical biopsy, endocervical curettage (ECC), Loop Electrosurgical Excision Procedure (LEEP), or conization (cold knife/laser) specimen, there was: (a) a HPV Vaccine Program Pathology Panel consensus diagnosis of CIN 2/3, AIS, or cervical cancer; AND (b) detection of at least one of HPV types 31, 33, 45, 52 or 58 by Thinsection PCR in an adjacent section from the same tissue block.
- VIN 2/3, VaIN 2/3, vulvar cancer, or vaginal cancer related to HPV types 31, 33, 45, 52 or 58. This endpoint was defined to have occurred if on a single biopsy or excised tissue, there was: (a) a HPV Vaccine Program Pathology Panel consensus diagnosis of VIN 2/3, VaIN 2/3, vulvar cancer, or vaginal cancer; AND (b) detection of at least one of HPV types 31, 33, 45, 52 or 58 by thin section PCR in an adjacent section from the same tissue block.

An additional efficacy endpoint evaluated in a sensitivity analysis defined a case of disease as requiring a consensus diagnosis of HPV disease by the pathology panel, the appropriate HPV type detected in an adjacent section of the same tissue block AND at least one specimen acquired immediately prior to or subsequent to the biopsy or definitive therapy sample that was positive for the same HPV type that was found in the biopsy.

The statistical criterion for success for the primary efficacy endpoint required that the LB of the two-sided 95% CI for 9vHPV vaccine efficacy (relative to qHPV) be greater than 25%.

6.1.8.3 Primary Immunogenicity Endpoints

The primary immunogenicity endpoints were anti-HPV type 6, 11, 16, and 18 antibody GMTs 4 weeks post dose 3 assessed among subjects who were seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type(s). The GMTs for each of HPV types 6, 11, 16, and 18 were tested separately.

The criterion for success for each type-specific non-inferiority comparison of GMTs was that the LB of the two-sided 95% CI for the geometric mean ratio of 9vHPV versus qHPV be greater than 0.67.

Reviewer's comments*: The immunoassay used in this study was the HPV-9 cLIA. During Phase 2b evaluation, a pre-validated assay was used. For the Phase 3 immunogenicity which included all subjects who received mid dose formulation of 9vHPV or qHPV, the sera were re-assessed using the validated assay.*

6.1.8.4 Secondary Efficacy Endpoints

HPV 31-, 33-, 45-, 52-, and 58-related persistent infection detected in samples from two or more consecutive visits at least 6 or 12 months apart: This endpoint was defined to have occurred if a subject who, after completion of the Month 7 visit, was positive for the same HPV type by PCR assay in two or more consecutive cervicovaginal/external

genital swab, biopsy, or definitive therapy samples obtained at two or more consecutive visits at least 6 or 12 months apart.

The statistical criterion for success was that the LB of the two-sided 95% CI for 9vHPV vaccine efficacy (relative to qHPV) be greater than 25%.

Reviewer's Comments: *In the original submission, the documented duration of persistent infection could be affected by visit windows of up to one month before or after the scheduled visit. CBER requested in the first requested information letter dated February 14, 2014, that only subjects with duration of persistent infection equal to or greater than 6 or 12 months be included in the analyses of persistent infection. The Applicant agreed to do so and the revised data were submitted to STN 125508/0.4, Module 1.11.3. The revised data are assessed and incorporated in this review.*

HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar and vaginal disease: This endpoint was defined as a subject who, after completion of the Month 7 visit, was found to have a biopsy or excised tissue specimen with (a) a HPV Vaccine Program Pathology Panel consensus diagnosis of CIN (any grade), AIS, cervical cancer, genital wart, VIN(any grade), VaIN (any grade), vulvar cancer, or vaginal cancer, AND (b) detection of at least one of HPV types 31, 33, 45, 52, or 58 by Thinsection PCR in an adjacent section from the same tissue block.

Pap test abnormalities: A case was defined as a subject who, after completion of the Day 1 visit, was found to have a Pap test result of atypical squamous cells of undetermined significance (ASC-US) with positive HPV probe or worse [ASC-US positive for High Risk HPV, LSIL, atypical squamous cells suggestive of a high-grade intraepithelial lesion (ASC-H), HSIL, atypical glandular cells, or AIS].

Seroconversion: A subject with a cLIA titer at or above the serostatus cutoff for a given HPV type was defined as seropositive for that HPV type (or seroconverted if below the cutoff pre-vaccination). The seropositivity cutoffs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 were 30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/mL, respectively.

6.1.8.5 Criterion for Study Success

The evaluation of primary safety and efficacy objectives for the 9vHPV vaccine included combined data from subjects enrolled in Part A who received qHPV or the 9vHPV dose selected for Part B (mid dose formulation) and subjects enrolled in Part B. The evaluation of the primary immunogenicity objective included the subjects enrolled in Part B only. The study was considered successful if success was achieved on all primary endpoints or hypotheses (safety, efficacy and immunogenicity). Success on the secondary efficacy endpoints was not necessary to declare the study successful.

6.1.9 Statistical Considerations and Statistical Analysis Plan

6.1.9.1 Study Hypotheses, and Sample Size and Power Calculations

Primary Efficacy Endpoint

Efficacy evaluations were conducted on subjects who received either the 9vHPV (mid-dose formulation) or qHPV. The null hypothesis of the study was that the vaccine efficacy (VE) was ≤ 25%, and the alternative hypothesis was that VE was >25%.

The study was powered to demonstrate statistically significant efficacy against the primary efficacy endpoint using a fixed event design. Assuming that the efficacy of 9vHPV relative to qHPV against the primary efficacy endpoint would be approximately 83%, then a total of 30 primary efficacy endpoint cases would be needed to provide at least 90% power to achieve a LB of the 95% CI of VE >25% at a one-sided α=0.025 level of significance. To ensure that at least 30 cases of primary efficacy endpoint were accrued, approximately 14,000 subjects (9vHPV and qHPV groups combined) were enrolled. The assumptions below were used for the sample size calculation:

- Seropositivity at Day 1 and/or PCR positivity at Day 1 through Month 7 to HPV types 31, 33, 45, 52 and 58 would not be greater than 23%.
- Attrition rate between Day 1 and Month 7 would not be greater than 10%
- Annual attrition rate post-Month 7 would not be greater than 5%.
- Annual incidence rates for the primary efficacy endpoint would be 0.35 per 100 person-years.
- Median follow-up time would be 30 month post randomization.

No interim analyses were planned relating to the testing of the primary efficacy hypotheses. Therefore, no multiplicity adjustment was done in the testing of the primary efficacy hypotheses. No type 1 error inflation was expected from this study design.

Primary Immunogenicity Endpoint

The overall sample size in the study was determined by the efficacy analysis. With approximately 13,380 subjects in Part B, this study had over 99% power for the primary immunogenicity hypothesis of non-inferiority with respect to antibody GMTs for HPV types 6, 11, 16 and 18. The calculations were based on the following assumptions:

- 15%, 15%, 18% and 10% of the subjects would be initially seropositive or PCR positive to HPV types 6, 11, 16 and 18, respectively.
- The expected attrition rate through Month 7 time point would be 10%
- The percentage of subjects excluded due to vaccinations or serology samples out of range would be no more than 8%.
- The standard deviations of the natural logarithms of the Month 7 titers would be no more than 1.2 mMU/ml for each HPV type.

6.1.9.2 Handling of Missing Data

In the analysis of vaccine efficacy with respect to HPV 31/33/45/522/58-related persistent infection and disease endpoints, subjects with missing data were handled as described in Table 4.

Table 4: Disposition of Handling of Missing Data in Efficacy Populations (Study V503-001)

Type of Missing Data	Subject Included or Excluded in Analysis	Subject Eligible to Be Case Based on Missing Data
Subject lost-to-follow-up before becoming an endpoint case and before the end of the study	Included	No
Incomplete data with respect to persistent infection endpoint. Subject not previously classified as an endpoint case, and detected with vaccine HPV type-related infection at the subject's last study visit	Included	No
Missing Day 1 serology result for relevant HPV type	Excluded	N/A
Missing one or both Day 1 PCR swab results for relevant HPV type	Excluded	N/A
Missing Month 7 EEC or LVPP swab PCR results for relevant HPV type	Excluded	N/A
Missing post-Month 7 EEC or LVPP swab PCR result for relevant HPV type	Included	Only if the other swab is positive
Missing post-Month 7 Thinsection PCR result for relevant HPV type for a biopsy specimen.	Included	No
Missing post-Month 7 Pathology Panel diagnosis for a biopsy specimen	Included	Yes-Infection endpoints No- Disease endpoints

Source: Adapted from STN 125508/0_Module 5.3.5.1.p001, CSR, Section 16.1.9.4, Table 10 (p302).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Efficacy Analyses Populations

Per-Protocol Efficacy (PPE) Population: This population was used for the primary efficacy analysis and included all subjects who:

- Received all 3 vaccinations with the correct clinical material within one year
- Had one or more follow-up visits following Month 7.
- Had Month 7 PCR swab samples collected within 14 to 72 days post-dose 3
- Were seronegative for the relevant HPV type(s) at Day 1 and PCR negative for the relevant HPV type(s) on all cervicovaginal swabs and biopsies from Day 1 through Month 7. HPV types 6 and 11 L1 proteins are highly homologous, resulting in strong cross-reactivity between the two types. Therefore, evaluations of efficacy with respect to either HPV type 6 or HPV type 11 required that subjects be negative at the aforementioned time points for both HPV 6 and 11. For evaluations of efficacy with respect to any other vaccine HPV type, subjects needed only to be negative at the aforementioned time points for the HPV type under evaluation.
- Did not violate the protocol in ways that could interfere with the evaluation of immune response to injections of the 9vHPV or qHPV vaccines.

Modified Intent-to-Treat (MITT) Analyses

Three MITT populations were analyzed to support the analyses in the PPE population, to explore the robustness of the vaccine efficacy, and to evaluate the secondary and exploratory efficacy objectives. The definitions of the MITT populations used in the 9vHPV clinical development program were similar to those used in the qHPV clinical development program. Subjects who received at least one vaccination and had any follow-up visit following the first vaccination could be included in all three populations. In all three populations, events occurring any time after Day 1 were eligible to be counted as endpoint cases if they met the appropriate case definitions. The populations were defined as follows:

1. HPV-Naïve, Type-Specific Population (HN-TS): This population included only subjects who were seronegative and PCR-negative at enrollment for the relevant HPV types, as defined in the Primary Per-Protocol Analysis. The numbers of subjects in this population ranged from 5953 to 6704 depending on clinical endpoints.
2. Full Analysis Set (FAS): This population included all randomized subject who received at least one dose of the 9vHPV or qHPV vaccines and had at least one follow-up visit after Day 1. The number of subjects in this population for 9vHPV and qHPV groups was 7099 and 7105, respectively.
3. All-HPV Naïve Population (All-HN): This population included only subjects who (a) were seronegative and PCR-negative at enrollment for all 9 vaccine HPV types; (b) were PCR-negative at enrollment for all other non-vaccine HPV types for which PCR assays were available; and (c) had a normal Pap test result at enrollment. The numbers of subjects in this population ranged from 2865 to 3032 depending on clinical endpoints, Pap tests and relevant HPV types.

Immunogenicity Analyses Population

Per-Protocol Immunogenicity (PPI) Population: The PPI population was used for the primary immunogenicity analysis and included all subjects who:

1. Had received all three vaccinations with the correct dose of the correct clinical material, with each vaccination visit within acceptable windows as specified in the protocol.
2. Had provided a Month 7 serology sample with a valid result within 21 to 49 days post-dose 3.
3. Were seronegative for the relevant HPV type at Day 1 and PCR negative for the relevant HPV type on all swabs and biopsies from Day 1 through Month 7.
4. Had no other protocol violations that could interfere with the evaluation of the subject's immune response to the study vaccine.

Safety Analysis Population

All safety analyses were performed on the All-Subjects-as-Treated (ASaT) population. The ASaT population included all randomized subjects who received at least one injection of 9vHPV or qHPV and had follow-up data. For subjects who received injection series that did not correspond to any of the protocol-defined vaccination groups (i.e., cross-treated subjects), a safety profile listing was created separately from the safety reports that were provided for the protocol-defined vaccination groups.

6.1.10.1.1 Demographics
Table 5 displays the demographic characteristics of subjects randomized into this efficacy study, by vaccination group. The two vaccination groups were balanced with

respect to these demographic characteristics. The mean age of randomized subjects was 21.9 years. All subjects were between 16 and 26 years of age as specified in the protocol. The distribution of age at enrollment into the study was generally similar between the vaccination groups. Approximately 12.8%, 33.9%, 33.4%, and 20.0% of the subjects were from the Asia-Pacific region, Europe, Latin America, and North America, respectively. The largest race category was White (55.2%) followed by Multi-racial (26.8%), Asian (14.3%), and Black or African American (3.3%). The remaining subjects were American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or did not report their race (Unknown).

Table 5: Subject Characteristics (Study V503-001, All Randomized Subjects, Efficacy Substudy)

Characteristics	**9vHPV N (%)**	**qHPV N (%)**
Gender		
Female	7,106 (100.0)	7,109 (100.0)
Age (Years)		
16 to 18	674 (9.5)	747 (10.5)
19 to 21	2,489 (35.0)	2,437 (34.3)
22 to 24	2,666 (37.5)	2,701 (38.0)
25 to 26	1,277 (18.0)	1,224 (17.2)
Mean	21.9	21.8
SD	2.5	2.5
Median	22.0	22.0
Race		
American Indian Or Alaska Native	6 (0.1)	10 (0.1)
Asian	1,022 (14.4)	1,006 (14.2)
Black	243 (3.4)	233 (3.3)
Multi-Racial	1,897 (26.7)	1,909 (26.9)
Native Hawaiian or other Pacific Islander	5 (0.1)	10 (0.1)
White	3,923 (55.2)	3,928 (55.3)
Unknown	10 (0.1)	13 (0.2)
Ethnicity		
Hispanic Or Latino	2,525 (35.5)	2,510 (35.3)
Not Hispanic Or Latino	4,580 (64.5)	4,599 (64.7)
Null	1 (0.0)	0 (0.0)
Region		
Asia-Pacific	905 (12.7)	909 (12.8)
Europe	2,406 (33.9)	2,409 (33.9)
Latin America	2,372 (33.4)	2,372 (33.4)
North America	1,423 (20.0)	1,419 (20.0)

Source: Adapted from STN 125508/0_Module 5.3.5.1.p001, CSR, Table 10-13 (p223)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Summary of Sexual History, Gynecological and Pregnancy History, and Contraceptive Use

Table 6 presents the sexual history, gynecological and pregnancy history, and contraceptive use at enrollment for all randomized subjects by vaccination group. Overall, the two vaccine groups were well balanced in terms of number of sexual

partners, gynecological procedures, genital tract infections, number of pregnancies, number of live births and abortions, and contraceptive use.

Table 6: Sexual History, Gynecological and Pregnancy History and Contraceptive Use at Enrollment by Vaccine Group (All Randomized Subjects, Study V503-001, Efficacy Substudy)

Sexual and Pregnancy History	**9vHPV (N=7,106) n (%)**	**qHPV (N=7,109) n (%)**
Subjects With Sexual History Data	**7,102 (99.9)**	**7,108 (100.0)**
Virgins		
Non-Virgins	169 (2.4)	199 (2.8)
Lifetime Number of Sexual	6,933 (97.6)2,063 (29.0)	6,909 (97.2)
Partners Among Non-Virgins	1,691 (23.8)	2,023 (28.5)
1	3,179 (44.8)	1,698 (23.9)
2	2	3,188 (44.9)
≥3		2
Median		
Gynecological History		
Cervical, Vaginal, and Vulvar Surgical Procedures	14 (0.2)	19 (0.3)
Genital Tract Infections or Sexually Transmitted Diseases	1,007 (14.2)	1,002 (14.)
Pregnancy History		
Number of Past Pregnancy		
0	5,797 (81.6)	5,896 (82.9)
1	924 (13.0)	838 (11.8)
≥2	380 (5.3)	372 (5.2)
Number of Full Term Live Births[1]		
1	589 (45.2)	581 (48.0)
≥2	189 (14.5)	182 (15.0)
Number of Premature Live Births[1]		
1	58 (4.4)	59(4.9)
≥2	11 (0.8)	8 (0.7)
Number of Spontaneous Abortions[1]		
1	254 (19.5)	254 (21.0)
≥2	32 (2.5)	30 (2.5)
Number of Electric Abortions[1]		
1	20 (1.5)	12 (1.0)
≥2	0 (0.0)	2 (0.2)
Number of Fetal Deaths[1]		
1	10 (0.8)	11 (0.9)
2	3 (0.2)	0 (0.0)
Subjects with Congenital Abomalies[1]		
Unknown	5 (0.4)	2 (0.2)
Yes	16 (1.2)	16 (1.3)
No	1,109 (85.0)	1,033 (85.4)
NA	174 (13.3)	159 (13.1)
Contraceptive Use		
Barrier	2,318 (32.6)	2,303 (32.4)
Behavior	1,014 (14.3)	1,035 (14.6)
Hormonal	4,273 (60.2)	4,292 (60.4)
Others	216 (3.0)	182 (2.6)

Source: Generated by CBER reviewer from STN 125508/0_Module 5.3.5.1.p001_CSR, Table 10-15 (p226), Table 10-16 (228), Table 10-18 (p237-8), and Table 10-19 (p240)
N=Number of subjects randomized.

n=Number of subjects in the respective category.
[1]Percentages calculated as 100*(n/number of subjects with ≥ 1 past pregnancy).

Summary of HPV-Related Laboratory Tests Performed at Day 1

Table 7 displays Pap test results at Day 1 for all randomized subjects by vaccination group. Among the 14,072 total subjects with a satisfactory Pap test result, 11.9% (n=1,673) of subjects had either borderline abnormal or abnormal Pap results, with LSIL being the most common single abnormal Pap test result and occurring in 7.1% (n=999) of subjects. The proportion of subjects reporting an abnormal Pap test result was generally comparable across the two vaccination group. Two subjects (both in 9vHPV group) had high grade lesions (one case of atypical glandular cells and one case of squamous cell carcinoma) at Day 1.

Table 7: Summary of Pap Test Results at Day 1 by Vaccination Group (All Randomized Subjects, Study V503-001, Efficacy Substudy)

Pap Tests	**9vHPV (N=7,106) n (%)**	**qHPV (N=7,109) n (%)**	**Total (N=14,215) n (%)**
Subjects with Satisfactory Day 1 Pap Test Results	**7,033**	**7,039**	**14,072**
Day 1 Pap Test Diagnosis[1]			
Negative for SIL	**6,198 (88.1)**	**6,202 (88.1)**	**12,400 (88.1)**
Borderline Abnormal Pap	**124 (1.8)**	**115 (1.6)**	**239 (1.7)**
Abnormal Pap	**712 (10.1)**	**722 (10.3)**	**1,434 (10.2)**
ASC-US (HR positive)	163 (2.3)	193 (2.7)	356 (2.5)
LSIL	509 (7.2)	490 (7.0)	999 (7.1)
ASC-H	7 (0.1)	18 (0.3)	25 (0.2)
HSIL	31 (0.4)	21 (0.3)	52 (0.4)
Atypical glandular cells	1 (<0.1)	0 (0.0)	1 (<0.1)
Squamous cell carcinoma	1 (<0.1)	0 (0.0)	1 (<0.1)

Source: Adapted from STN 125508/0_Module 5.3.5.1.p001_CSR, Table 10-20 (p243).
[1]Percentages for Pap test diagnoses calculated as 100*(n/number of subjects with satisfactory Pap test result).
N=Number of subjects randomized.
n=Number of subjects who have the indicated diagnosis or Pap test result.
ASC-H=Atypical squamous cells, cannot exclude HSIL; ASC-US=Atypical squamous cells of undetermined significance; HPV=Human papillomavirus; HR=High risk HPV probe result; HSIL=High-grade squamous intraepithelial lesion; LSIL=Low-grade squamous intraepithelial lesion; Pap=Papanicolaou's test; SIL=Squamous intraepithelial lesion.

Table 8 summarizes the composite proportions of subjects with positive PCR or serology for HPV types 6, 11, 16, 18, 31, 33, 45, 52, or 58 at Day 1 by vaccination group in the efficacy substudy. A total of 38.3% and 27.5% of subjects were positive for at least one vaccine HPV type by serology or by PCR, respectively. The proportions of subjects positive for at least one HPV type were similar between the two treatment groups and were similar to those of subjects in the immunogenicity substudy.

The propositions of subjects with positive PCR or serology for any of the individual 14 HPV types assessed at Day 1 (i.e., HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, or 59) were also similar between the two treatment groups (data not shown). [Data Source: STN 125508/0_Module 5.3.5.1.p001, Table 10-23 (p251) and Table 10-24 (p252)]

Table 8: Summary of Composite Proportions of Subjects with Positive PCR or Serology for HPV Types 6, 11, 16, 18, 31, 33, 45, 52, or 58 at Day 1 by Vaccination Group (All Randomized Subjects, Study V503-001, Efficacy Substudy

Day 1 PCR and Serology	**9vHPV (N=7,106) m/n (%)**	**qHPV (N=7,109) m/n (%)**
Negative to HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58		
By Serology	4,311/7,082 (60.9)	4,431/7,078 (62.6)
By PCR	5,032/6,919 (72.7)	5,023/6,943 (72.3)
By Serology or PCR	3,605/6,970 (51.7)	3,638/6,983 (52.1)
Positive to HPV types 6, 11, 16, 18, 31, 33, 45, 52 or 58		
By Serology	2,771/7,082 (39.1)	2,647/7,078 (37.4)
By PCR	1,887/6,919 (27.3)	1,920/6,943 (27.7)
By Serology or PCR	3,365/6,970 (48.3)	3,345/6,983 (47.9)

Source: Adapted from STN 125508/0_Module 5.3.5.1.p001_CSR, Table 10-21 (p248).
N=Number of subjects randomized.
m=Number of subjects positive for at least one HPV type by the indicated test.
n=Number of subjects with non-missing data (serology, PCR, or both) at Day 1 for HPV-types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

6.1.10.1.3 Subject Disposition

Part A subjects who received either the selected dose formulation of 9vHPV (mid-dose formulation) or qHPV were enrolled in both the dose-ranging substudy and the efficacy substudy. Therefore, baseline data for these subjects was included in reports for both the dose-ranging substudy cohorts and the efficacy substudy cohorts.

The immunogenicity substudy represented a subset of the efficacy substudy that included approximately 95% of the subjects enrolled in the efficacy substudy. Therefore, only selected immunogenicity substudy baseline data are reported in this section. These include basic information about the immunogenicity substudy cohorts (i.e., subject characteristics and accounting of subjects in the per protocol immunogenicity population) and information about HPV serostatus at baseline.

Disposition of Subjects in the Study

A total of 15,334 subjects were screened to participate in V503-001. Of these, approximately 97% (n=14,840) were randomized.

Dose-ranging substudy: A total of 1,242 subjects were enrolled in the dose-ranging substudy under Part A. Overall, 99.8% of subjects received at least one dose, and 95.7% of subjects received all three dose. In total, 5.2% of subjects discontinued the study, 0.2% of subjects due to adverse events, 2.9% of subjects due to lost to follow up, 2.0% of subjects due to withdrawal by subjects and 0.1% of subjects due to protocol violation. Of these, 617 subjects (Mid-dose 9vHPV and qHPV cohorts) were also included in the efficacy substudy. Subject disposition is provided in Table 9.

Table 9: Disposition of Subjects (Study V503-001, Dose-Ranging Study, Day 1 to Month 7)

Disposition	Low-Dose 9vHPV N (%)	Mid-Dose 9vHPV N (%)	High-Dose 9vHPV N (%)	qHPV N (%)	Total N (%)
Randomized	**315**	**307**	**310**	**310**	**1242**
Vaccinated at					
Dose 1	312 (99.0)	307 (100.0)	310 (100.0)	310 (100.0)	1239 (99.8)
Dose 2	305 (96.8)	300 (97.7)	306 (98.7)	305 (98.4)	1216 (97.9)
Dose 3	300 (95.2)	291 (94.8)	297 (95.8)	300 (96.8)	1188 (95.7)
Completed	**295 (93.7)**	**290 (94.5)**	**296 (95.5)**	**297 (95.8)**	**1178 (94.8)**
Discontinued	**20 (6.3)**	**17 (5.5)**	**14 (4.5)**	**13 (4.2)**	**64 (5.2)**
Adverse Event	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.2)
Lost to Follow-up	12 (3.8)	8 (2.6)	9 (2.9)	7 (2.3)	36 (2.9)
Protocol Violation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Withdrawal by Subject	7 (2.2)	8 (2.6)	5 (1.6)	5 (1.6)	25 (2.0)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p001_CSR, Table 10-1 (p196)

Efficacy substudy cohorts – A total of 14,215 subjects were enrolled in the efficacy substudy. Overall, 99.9% of subjects received at least one dose, and 97.5% of subjects received all three doses. In total, 14.0% of subjects discontinued the study, 0.1% of subjects due to adverse events, 7.1% of subjects due to lost to follow up, 6.6% of subjects due to withdrawal by subjects and 0.2% of subjects due to other reasons. Summary of subject disposition by vaccination group is provided in Table 10.

Table 10: Subject Disposition (Day 1 through Visit Cut-off Date April 10, 2013, Study V503-001)

Disposition	9vHPV N (%)	qHPV N (%)	Total N (%)
Subjects Screened			15,334
Subjects Randomized			14,840
Excluded from efficacy substudy (Low- and High-dose 9vHPV)			625
Included in efficacy substudy (Mid-dose 9vHPV, qHPV)	7,106 (100)	7,109 (100)	14,215 (100)
Received at least one vaccination	7,099 (99.9)	7,105 (99.9)	14,204 (99.9)
Completed 3-dose vaccination regimen	6,928 (97.5)	6,934 (97.5)	13,862 (97.5)
Completed the study	838 (11.8)	863 (12.1)	1,701 (12.0)
On active study follow-up	5,250 (73.9)	5,273 (74.2)	10,523 (74.0)
Discontinued from the study	1,018 (14.3)	973 (13.7)	1,991 (14.0)
Adverse Event	11 (0.2)	6 (0.1)	17 (0.1)
Lost-to-follow-up	528 (7.4)	487 (6.9)	1,015 (7.1)
Physician decision	4 (0.1)	5 (0.1)	9 (0.1)
Pregnancy	0 (0.0)	1 (<0.1)	1 (<0.1)
Protocol violation	6 (0.1)	6 (0.1)	12 (0.1)
Withdrawal by subject	469 (6.6)	468 (6.6)	937 (6.6)

Source: Adapted from STN 125508/0.13, Module 1.11.3_Table 1 (p2, Requested information).
Percent was calculated relative to the number of subjects randomized in the vaccination groups included in the efficacy substudy.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Immunogenicity Bridging - Results Supporting Vaccine Prophylactic Effectiveness for the Original qHPV Types (6/11/16/18)

The efficacy findings for qHPV with respect to the original types were bridged to 9vHPV based on the demonstration of non-inferior immunogenicity. As show in Table 11, non-inferiority of GMT antibody responses in the 9vHPV group was demonstrated for each of HPV types 6, 11, 16, and 18 in 9vHPV group relative to GMT antibody responses in the qHPV group at four weeks post-dose 3 in the PPI population. The GMT ratios ranged from 0.80 to 1.19 with the LB of 95% CIs all above 0.67, the success criterion for non-inferiority.

Table 11: Non-Inferiority Comparison of Month 7 Anti-HPV 6, 11, 16 and 18 Antibody Geometric Mean Titers (GMTs) between 9vHPV and qHPV Recipients (Study V503-001, Per Protocol Immunogenicity Population)

Antibody Assay	9vHPV (N=6,792)		qHPV (N=6,795)		9vHPV/qHPV (95%CI)
	n	GMT (mMU/ml)	N	GMT (mMU/ml)	
Anti-HPV6	3,993	893.1	3,975	875.2	1.02 (0.99, 1.06)
Anti-HPV11	3,995	666.3	3,982	830.0	0.80 (0.77, 0.83)
Anti-HPV16	4,032	3,131.1	4,062	3,156.6	0.99 (0.96, 1.03)
Anti-HPV18	4,539	804.6	4,541	678.7	1.19 (1.14, 1.23)

Source: Adapted from STN 125508/0_Module 2.7.3, Table 2.7.3 hpvdiesease:13 (p115).
Note: PPI population included all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV types, and had a Month 7 serum sample collected within an acceptable day range.
N=Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n=Number of subjects contributing to the analysis

In the PPI population, the seroconversion rates for each of HPV types 6, 11, 16, and 18 at 4 weeks post dose 3 of 9vHPV were also non-inferior to the seroconversion rates following qHPV (Table 12). The LB exceeded -5.0 percentage points, the non-inferiority success criterion, for all HPV types.

Table 12: Statistical Comparison of Month 7 Anti-HPV Antibody Seroconversion Rates Between 9vHPV and qHPV Recipients for HPV types 6, 11, 16, and 18 (Study V503-001, PPI Population)

Antibody Assay	9vHPV (N=6,792)		qHPV (N=6,795)		9vHPV - qHPV (95%CI)
	n	Seroconversion	N	Seroconversion	
Anti-HPV6	3,993	99.8%	3,975	99.8%	0.0 (-0.3, 0.2)
Anti-HPV11	3,995	100.0%	3,982	99.9%	0.0 (-0.1, 0.2)
Anti-HPV16	4,032	100.0%	4,062	100.0%	0.0 (-0.1, 0.2)
Anti-HPV18	4,539	99.8%	4,541	99.7%	0.0 (-0.1, 0.4)

Source: Adapted from STN 125508/0_Module 2.7.3, Appendix 2.7.3 hpvdiesease: 8 (p424).
Note: PPI population included all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

N=Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n=Number of subjects contributing to the analysis

Efficacy of 9vHPV against HPV 31/33/45/52/58-Related High Grade Cervical, Vulvar, or Vaginal Lesions

Table 13 presents the results of the primary efficacy analysis of high grade cervical, vulvar, and vaginal disease related to HPV types 31, 33, 45, 52, and 58 in the PPE population. No cases of AIS, cervical cancer, vulvar cancer or vaginal cancer occurred in either group. As shown in the table, the overall observed efficacy of the 9vHPV vaccine against HPV 31/33/45/52/58-related high-grade cervical, vulvar and vaginal lesions was 96.7% (95% CI: 80.9, 99.8; p<0.0001) among subjects who were naïve to the relevant HPV type during the vaccination period. The observed LB of the 95% CI was greater than 25%, the statistical success criterion for the primary efficacy endpoint.

Table 13: Analysis of Efficacy against HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer (Study V503-001, Per-Protocol Efficacy Analysis Population)

Endpoints	9vHPV (N=7,099) No. of cases/n	qHPV (N=7,105) No. of cases/n	% Efficacy of 9vHPV (95% CI)
HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	**1/6,016**	**30/6,017**	**96.7 (80.9, 99.8)**
By HPV Type			
HPV 31-Related	0/5,308	7/5,252	100 (40.1, 100)
HPV 33-Related	0/5,624	7/5,628	100 (39.3, 100)
HPV 45-Related	0/5,724	2/5,724	100 (-246.8, 100)
HPV 52-Related	0/5,320	11/5,216	100 (67.3, 100)
HPV 58-Related	1/5,361	6/5,340	83.4 (- 23.9, 99.3)
By Lesion Type			
CIN 2 or worse	1/5,948	27/5,943	96.3 (79.5, 99.8)
CIN 2/3 or AIS	1/5,948	27/5,943	96.3 (79.5, 99.8)
CIN 2/3	1/5,948	27/5,943	96.3 (79.5, 99.8)
CIN 2	1/5,948	23/5,943	95.6 (76.3, 99.8)
CIN 3	0/5,948	5/5,943	100 (-0.2, 100)
VIN 2/3 or VaIN 2/3 or worse	0/6,009	3/6,012	100 (-71.5, 100)
VIN 2/3 or worse	0/6,009	0/6,012	NA
VaIN 2/3 or worse	0/6,009	3/6,012	100 (-71.5, 100)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p0011_CSR, Table 11-1 (p282-3).
PPE population consisted of individuals who received all 3 vaccinations within one year of enrollment, did not have major protocol deviations, and were PCR negative and seronegative to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1 and PCR negative from Day 1 through one month post-dose 3 (Month 7).
Subjects were counted once in each applicable endpoint category. A subject might appear in more than one category.
N=Number of subjects who were randomized to the respective group and received at least one injection.
n=Number of subjects who had at least one follow-up visit after Month 7.
AIS=Adenocarcinoma in situ; CIN=Cervical intraepithelial neoplasia; NA=Not applicable; VaIN=Vaginal intraepithelial neoplasia; VIN=Vulvar intraepithelial neoplasia

Reviewer's comments: *Although efficacy was statistically significant for the combined efficacy endpoint (HPV 31/33/45/52/58-related CIN2/3-, VIN 2/3-, VaIN 2/3- or worse), the vast majority of the cases contributing to the combined endpoint were cervical lesions (i.e., CIN). With a lower bound on the 95%CI of -71.5%, efficacy against VIN2+ or VaIN2+ has not been demonstrated. However, the study was not powered to demonstrate efficacy by each lesion grade.*

The single case of the primary efficacy endpoint in the 9vHPV group was a subject (SUBJID=18149) who was PCR-negative from Day 1 through the Month 7 study visit for HPV 58 and was eligible for inclusion in the HPV 58 PPE analysis. This subject had LSIL at the Day 1 and Month 7 visits and was PCR-positive for HPV 56 at Day 1 through Month 42. The subject had a definitive therapy procedure at four months after the scheduled Month 7 visit. One of four quadrants of the tissue sample obtained during the definitive therapy procedure was diagnosed as a case of CIN 2 by the Pathology Panel and was also PCR-positive for HPV 56 and 58. Per case definition, the subject was counted as a case of the primary efficacy endpoint for HPV 58 at approximately 11 months after dose 1. Except for the single-time PCR-positive for HPV 58 at Month 11, the subject was PCR-negative for HPV 58 at all other time points through Month 42.

For the 30 primary endpoint cases observed in qHPV group, 11 cases showed co-infection in the lesion biopsy tissues with HPV types other than 31, 33, 45, 52 or 58. These non-vaccine HPV types were present in the specimens obtained at baseline (Day 1 and/or Month 7) and were present together with vaccine HPV types (31, 33, 45, 52 or 58) in the biopsy tissues when the diagnoses were made in 4 (AN 71340, AN 21049, AN 69544 and AN72985) out of the 11 cases with co-infections. In addition, 18 primary endpoint cases were associated with co-infection with HPV types other than 31, 33, 45, 52 or 58 as determined by PCR in specimens of cervicoviginal/external-genital swabs taken prior to biopsies used for to diagnose the primary endpoint cases. These circumstances complicated the definitive diagnoses of the primary endpoint cases.

According to the per-protocol definition of a primary endpoint case, the diagnosis of a primary endpoint case in the PPE population required the presence of both a high grade intraepithelial lesion and at least one of the HPV types 31, 33, 45, 52 or 58, regardless of the presence of other HPV types in the same lesion. If these lesions were attributed to HPV types detected in the lesion other than the 5 new vaccine types in 9vHPV, the efficacy point estimate would be lower (with wider 95% CI). However, only 2 lesions in the qHPV group were positive for a higher-risk oncogenic HPV type (16) in addition to one of the 9vHPV new vaccine types, so the remainders of cases were most likely due to the 9vHPV vaccine types identified in the lesions.

Consistent with the results in the PPE population, 9vHPV reduced the primary efficacy endpoint cases in the HN-TS population with an LB of 95% CI >68% (Table 14). No cases of AIS, cervical cancer, vulvar cancer or vaginal cancer occurred in either group in this population. All endpoint cases in the 9vHPV group occurred on or before 18 months after vaccination dose 1. Among the six cases of HPV 31/33/45/52/58-related high grade cervical, vulvar, and vaginal disease in the 9vHPV group in the HN-TS population:

- Five subjects (SUBJID=18149; 18828; 19890; 67888; 70988) were PCR-positive at Day 1 for at least one oncogenic HPV type other than the HPV type associated with the endpoint case
- One subject (SUBJID=75402) was PCR-negative at Day 1 for all the oncogenic HPV types tested, was then PCR-positive for multiple oncogenic HPV types at 8

months post Day 1, and was diagnosed as a case of HPV 31-related CIN 3 at 10 months post Day 1.

Reviewer's comment: *Subject 75402 was seropositive for HPV types 18 and 58, but seronegative for other HPV types including HPV 31 and 56 at baseline. She was reported PCR positive for HPV 56 (E7) before study. On Day 1 (prior to Dose 1), all genital and cervical swabs were PCR negative for all the HPV types and her Pap smear was negative. At Month 7, her swabs showed PCR positive for HPV types 18, 31, 51, 52 and 56, and her Pap smear showed LSIL. At Month 10, her cervical specimen showed CIN3 and PCR positive for HPV 31 (L1, E6 and E7); all other HPV types (6, 11, 16, 18, 33, 35, 39, 45, 52, 56, 58 and 59) were negative. It appears that this subject was infected with at least HPV 18, 56 and 58 prior to participating in the clinical trial. Because of the limited information, it was unknown if this patient had pre-existing cervical lesions although Pap smear at baseline was negative. Since the specimen with a CIN3 lesion also showed PCR positive for HPV 31 but no other HPV types, the CIN 3 lesion was diagnosed as a case of HPV 31-related CIN 3 per protocol primary case definition.*

Table 14: Analysis of Efficacy against HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer (Study V503-001, HPV-Naive Type-Specific Analysis Population)

Endpoints	9vHPV (N=7,099) No. of cases/n	qHPV (N=7,105) No. of cases/n	% Efficacy of 9vHPV (95% CI)
HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	**6/6,873**	**42/6,866**	**85.7 (68.4, 94.1)**
By HPV Type			
HPV 31-Related	2/6,110	12/6,104	83.3 (28.0, 97.3)
HPV 33-Related	1/6,444	8/6,467	87.4 (19.7, 99.4)
HPV 45-Related	0/6,562	3/6,571	100 (-72.3, 100)
HPV 52-Related	2/6,140	17/6,129	88.2 (53.7, 98.1)
HPV 58-Related	1/6,173	9/6,193	88.8 (19.6, 99.5)
By Lesion Type			
CIN 2 or worse	5/6,735	39/6,718	87.2 (67.8, 95.2)
CIN 2/3 or AIS	5/6,735	39/6,718	87.2 (67.8, 95.2)
CIN 2/3	5/6,735	39/6,718	87.2 (67.8, 95.2)
CIN 2	4/6,735	33/6,718	87.9 (67.1, 96.1)
CIN 3	3/6,735	9/6,718	66.6 (-22.5, 92.2)
VIN 2/3 or VaIN 2/3 or worse	1/6,870	3/6,865	66.6 (-203.1, 98.7)
VIN 2/3 or worse	1/6,870	0/6,865	NA
VaIN 2/3 or worse	0/6,870	3/6,865	100 (-71.9, 100)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p0011_CSR, Table 11-2 (p285-6).
HPV Naïve Type-Specific (HN-TS) population included only subjects who were seronegative and PCR negative at Day 1 to the relevant HPV types.
Subjects were counted once in each applicable endpoint category. A subject might appear in more than one category.
N=Number of subjects who were randomized to the respective group and received at least one injection.
n=Number of subjects who had at least one follow-up visit after Month 7.
AIS=Adenocarcinoma in situ; CIN=Cervical intraepithelial neoplasia; NA=Not applicable; VaIN=Vaginal intraepithelial neoplasia; VIN=Vulvar intraepithelial neoplasia.

***Reviewer's comments**: The efficacy estimates for the HN-TS population were generally lower compared with PPE population because the HN-TS population included subjects who were infected with relevant HPV types prior to completion of the vaccination series*.

Sensitivity Analyses Relating to the Primary Efficacy Endpoint

Sensitivity analyses were conducted to evaluate the robustness of primary endpoint efficacy estimates. These analyses assessed the impacts of losses-to-follow-up, the rigor of the endpoint case definition, and the rigor of the endpoint case ascertainment. These sensitivity analyses did not change the overall conclusion that 9vHPV prevented high-grade cervical disease related HPV 31/33/445/52/58.

Impact of Losses-to-Follow-up on the Estimate of Efficacy

A proportion of subjects lost-to-follow-up were imputed as primary endpoint cases under the assumption of no vaccine efficacy. Therefore, the cumulative incidence probability of HPV 31/33/45/52/58-related primary cases in qHPV group (excluding subjects who were lost-to-follow-up) was estimated for both 9vHPV and qHPV groups. In the qHPV group, the cumulative incidence probability of becoming a primary efficacy endpoint case was 0.0057. Thus 0.57% of subjects lost to follow-up in each of the 9vHPV and qHPV groups were imputed as endpoint cases.

A total of 596 and 581 subjects in PPE population were lost-to-follow-up in the 9vHPV and qHPV groups, respectively, through 60 months of follow-up (The cumulative incidence was presented in Table 14.3-26, p1714 of the CSR, not shown in this review). Thus, 3.4 and 3.3 additional cases were imputed in the 9vHPV and qHPV vaccine groups, respectively. The total numbers of cases in the adjusted PPE analysis were 4.4 (out of 6,016) for 9vHPV and 33.3 (out of 6017) for qHPV, and the adjusted efficacy estimate was 87.9% (95% CI 67.2, 96.1).

In the HN-TS population, the cumulative incidence probability of becoming a case of the primary efficacy endpoints in HN-TS population was 0.008. A total of 917 and 895 subjects were lost-to-follow-up in 9vHPV and qHPV groups, respectively, through 60 months of follow-up. Thus, 7.3 and 7.1 additional cases were imputed in the 9vHPV and qHPV groups, respectively. The total numbers of cases in the adjusted HN-TS analysis were 13.3 (out of 6,873) for 9vHPV and 49.1 (out of 6,866) for qHPV, and the adjusted efficacy estimate was 73.5% (95% CI 51.6, 86.0).

Impact of Primary Endpoint Case Definition on the Estimate of Efficacy

The first sensitivity analysis performed to evaluate the impact of the endpoint case definition was intended to add rigor to the HPV type-attribution on the tissue samples on which diagnosis of high-grade disease were adjudicated. To this end, in addition to meeting all the protocol-defined criteria for a primary efficacy endpoint case (HPV 31/33/45/52/58-related high grade cervical, vulvar, or vaginal disease endpoint case), subjects were also required to be PCR-positive to the same HPV type on a study visit immediately before or immediately after the study visit when the subject became a primary efficacy endpoint case. Results of this sensitivity analysis by analysis populations and efficacy endpoints are shown in Table 15.

Table 15: Analysis of Efficacy against HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer with Preceding or Succeeding Infection with the Same HPV Type (Study V503-001, PPE, HN-TS, and FAS Analysis Populations)

Analysis Population and Endpoints	**9vHPV (N=7099) No. of cases/n**	**qHPV (N=7105) No. of cases/n**	**Observed Efficacy of 9vHPV % (95% CI)**
PPE			
High Grade Cervical, Vulvar and Vaginal Disease	0/6016	29/6017	100 (88.5, 100)
CIN 2/3 or worse	0/5948	26/5942	100 (86.9, 100)
VIN 2/3 or VaIN 2/3 or worse	0/6009	3/6012	100 (-71.5, 100)
HN-TS			
High Grade Cervical, Vulvar and Vaginal Disease	3/6876	40/6870	92.5 (77.3, 98.0)
CIN 2/3 or worse	2/6735	37/6718	94.6 (79.5, 99.1)
VIN 2/3 or VaIN 2/3 or worse	1/6873	3/6869	66.6 (-203.1, 98.7)
FAS			
High Grade Cervical, Vulvar and Vaginal Disease	118/7027	148/7027	20.1 (-1.7, 37.8)
CIN 2/3 or worse	114/6882	142/6871	19.4 (-3.8, 37.6)
VIN 2/3 or VaIN 2/3 or worse	5/7027	6/7026	16.3 (-201.9, 75.0)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p0011_CSR, Table11-87 (p642).
N = Number of randomized subjects who received at least 1 injection.
n = Number of subjects in the given population who had at least one follow-up visit after Month 7 in the PPE population; after Day 1 in all other analysis populations.
AIS=Adenocarcinoma in situ; CI=Confidence interval; CIN=Cervical intraepithelial neoplasia; HPV=Human papillomavirus; VaIN=Vaginal intraepithelial neoplasia; VIN=Vulvar intraepithelial neoplasia

***Reviewer's comments**: This population included subjects who were infected with relevant HPV types before study initiation or completion of the vaccination series. The efficacy of the 9vHPV was not demonstrated in the FAS population because the FAS population included subjects who were infected with relevant HPV types prior to initiation or completion of the vaccination series, and the sample size was not powered to demonstrate efficacy in this population.*

The second sensitivity analysis performed to evaluate the impact of the endpoint case definition was intended to evaluate the impact of the adjudication approach (Pathology Panel diagnosis vs. Central Pathology Laboratory diagnosis). To this end, in addition to meeting all the protocol-defined criteria for a primary efficacy endpoint case, the diagnosis attributed to tissue samples was the most histopathologically advanced of the diagnoses rendered by the Pathology Panel and the Central Pathology Laboratory. Results of this sensitivity analysis were similar to those obtained in the first sensitivity analysis in the PPE, HN-TS, and FAS populations regarding primary case definition as shown in Table 15 above.

Impact of Cervical Disease Endpoint Case Definition on the Estimate of Efficacy

The efficacy analyses presented above excluded cases of HPV-related disease endpoints that were based on cervical tissue samples not being preceded by an

abnormal Pap test diagnosis. Without these exclusions,.the efficacy estimates for prevention of HPV 31, 33, 45, 52 and 58-related CIN 2/3 or worse in the PPE and HN-TS populations were 93.7% (95% CI: 81.1, 98.4) and 85.7% (95% CI: 68.3, 94.1), respectively.

6.1.11.2 Analyses of Secondary Endpoints

Comparison of 9vHPV and qHPV in Prevention of HPV 31/33/45/52/58-Related Cervical, Vulvar, or Vaginal Lesions

Table 16 presents the efficacy analysis for prevention of cervical, vulvar, and vaginal disease (including low-grade disease) related to HPV types 31, 33, 45, 52, and 58 in the PPE population. As shown in the table, the efficacy of the 9vHPV vaccine was 97.1% with an LB of 95% CI 91.8% in preventing combined cervical, vulvar, and vaginal disease of all grades related to HPV types 31, 33, 45, 52, and 58 in the PPE population.

Reviewer's comments: *This endpoint corresponds to secondary efficacy objective 4. There was no pre-specified success criterion for this endpoint*.

Table 16: Analysis of Efficacy for Prevention of HPV 31/33/45/52/58-Related Cervical, Vulvar, and Vaginal Disease (Study V503-001, Per-Protocol Efficacy Analysis Population)

Endpoints	9vHPV (N=7,099) No. of cases/n	qHPV (N=7,105) No. of cases/n	Efficacy of 9vHPV % (95% CI)
HPV 31/33/45/52/58-Related Cervical, Vulvar, and Vaginal Disease	**3/6,016**	**103/6,017**	**97.1 (91.8, 99.2)**
Cervical Disease	**2/5,948**	**88/5,943**	**97.7 (92.2, 99.6)**
CN1	1/5,948	69/5,943	98.6 (92.4, 99.9)
CIN2 or worse	1/5,948	27/5,943	96.3 (79.5, 99.8)
Vulvar and Vaginal Disease	**1/6,009**	**16/6,012**	**93.8 (61.5, 99.7)**
Condyloma	0/6,009	3/6,012	100 (-71.6, 100)
VIN 1 or VaIN 1	1/6,009	12/6,012	91.7 (51.3, 99.6)
VIN 2/3 or VaIN 2/3 or worse	0/6,009	3/6,012	100 (-71.5, 100)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p0011_CSR, Table 11-3 (p289).
The per-protocol efficacy (PPE) population consisted of individuals who received all three vaccinations within one year of enrollment, did not have major protocol deviations, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1 and PCR negative for the relevant HPV types from Day 1 through 1 month post-dose 3 (Month 7).
Subjects were counted once in each applicable endpoint category. A subject might appear in more than one category.
N=Number of randomized subjects who received at least one injection.
n=Number of subjects who had at least one follow-up visit after Month 7.
CIN=Cervical intraepithelial neoplasia; VaIN=Vaginal intraepithelial neoplasia; VIN=Vulvar intraepithelial neoplasia

Consistent with the results in the PPE population, efficacy of the 9vHPV vaccine was 91.7% (LB of 95% CI: 85.4%) in preventing combined cervical, vulvar, and vaginal disease of all grades related to HPV types 31, 33, 45, 52, and 58 in the HN-TS population (Table 17).

Table 17: Analysis of Efficacy against HPV 31/33/45/52/58-Related Cervical, Vulvar, and Vaginal Disease (Study V503-001, HN-TS Population)

Endpoints	9vHPV (N=7,099) No. of cases/n	qHPV (N=7,105) No. of cases/n	Efficacy of 9vHPV % (95% CI)
HPV 31/33/45/52/58-Related Cervical, Vulvar, and Vaginal Disease	**12/6,873**	**144/6,866**	**91.7 (85.4, 95.4)**
Cervical Disease	**9/7,735**	**125/6,718**	**92.8 (86.5, 96.5)**
CN1	5/7,735	99/6,718	95.0 (88.2, 98.1)
CIN2 or worse	5/7,735	39/6,718	87.2 (67.8, 95.2)
Vulvar and Vaginal Disease	**3/6,870**	**22/6,012**	**86.3 (56.4, 96.5)**
Condyloma	1/6,870	6/6,012	83.3 (-24.6, 99.3)
VIN 1 or VaIN 1	1/6,870	16/6,012	93.7 (61.4, 99.7)
VIN 2/3 or VaIN 2/3 or worse	1/6,870	3/6,012	66.6 (-203.1, 98.7)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p0011_CSR, Table 11-4 (p293).
HPV Naïve Type-Specific (HN-TS) population included only subjects who were seronegative and PCR negative at Day 1 to the relevant HPV types.
Subjects were counted once in each applicable endpoint category. A subject might appear in more than one category.
N=Number of randomized subjects who received at least one injection.
n=Number of subjects who had at least one follow-up visit after Month 7.
CIN=Cervical intraepithelial neoplasia; VaIN=Vaginal intraepithelial neoplasia; VIN=Vulvar intraepithelial neoplasia

Comparison of 9vHPV and qHPV in Prevention of HPV 31/33/45/52/58-Related Persistent Infection

Type specific persistent HPV infection as monitored by genotyping can identify women at increased risk of cervical neoplasia more accurately than a single or repeated presence of HPV test. Table 18 presents the efficacy analysis of 9vHPV as compared to qHPV in preventing persistent infection related to HPV types 31, 33, 45, 52, and 58 in the PPE population. As shown in the table, the pre-specified success criteria relating to persistent infection of ≥6 months duration (LB of 95% CI of efficacy >25%) and persistent infection of ≥12 months duration (LB of the 95% CI of efficacy > 0%) were met. For each of HPV types 31, 33, 45, 52, and 58, the LBs of 95% CI of efficacy against persistent infection of ≥6 months and ≥12 months duration were >90% and >85%, respectively.

Table 18: Analysis of Efficacy against HPV 31/33/45/52/58-Related Persistent Infection (Study V503-001, PPE Populations)

Endpoints	9vHPV (N=7,099) No. of Cases/n	qHPV (N=7,105) No. of Cases/n	Efficacy of 9vHPV % (95% CI)
Persistent Infection ≥6 Months			
HPV 31/33/45/52/58-Related	26/5,939	642/5,953	96.2 (94.4, 97.5)
HPV 31-Related	5/ 5,251	113/5,198	95.7 (90.0, 98.3)
HPV 33-Related	1/5,553	83/5,560	98.8 (93.8, 99.9)
HPV 45-Related	3/5,649	89/5,658	96.7 (90.6, 99.1)
HPV 52-Related	8/5,263	297/5,160	97.4 (95.0, 98.9)
HPV 58-Related	9/5,297	175/5,284	95.0 (90.3, 97.5)
Persistent Infection≥12 Months			
HPV 31/33/45/52/58-Related	15/5,939	375/5,953	96.1 (93.7, 97.9
HPV 31-Related	3/5,251	68/5,198	95.7 (87.6, 98.8)

HPV 33-Related	0/5,553	48/5,560	100 (92.9, 100)
HPV 45-Related	2/5,649	49/5,658	95.9 (85.4, 99.3)
HPV 52-Related	5/5,263	161/5,160	97.0 (93.3, 98.8)
HPV 58-Related	5/5,297	95/5,284	94.8 (87.8, 98.0)

Source: Adapted from STN 125508/0.4_Module 1.11.3, Table Q17-1.
Subjects were counted once in each applicable endpoint category. A subject might appear in more than one category.
N=Number of randomized subjects who received at least one injection.
n=Number of subjects in the population who had at least one follow-up visit after Month 7.

Similar results, albeit with slightly lower efficacy point estimates and LB 95% CI, were seen in the HN-TS population (Table 19).

Table 19: Analysis of Efficacy against HPV 31/33/45/52/58-Related Persistent Infection (Study V503-001, HN-TS Analysis Populations)

Endpoints	9vHPV (N=7,099) No. of Cases/n	qHPV (N=7,105) No. of Cases/n	Efficacy of 9vHPV % (95% CI)
Persistent Infection ≥6 Months			
HPV 31/33/45/52/58-Related	121/6,704	918/6,699	87.6 (85.1, 89.9)
HPV 31-Related	22/5,971	177/5,953	87.8 (81.1, 92.5)
HPV 33-Related	11/6,281	113/6,314	90.3 (82.6, 95.1)
HPV 45-Related	19/6,395	123/6,412	84.6 (75.6, 90.6)
HPV 52-Related	47/5,991	421/5,983	89.2 (85.5, 92.2)
HPV 58-Related	31/6,020	258/6,040	88.2 (83.1, 92.1)
Persistent Infection≥12 Months			
HPV 31/33/45/52/58-Related	83/6,704	585/6,699	86.4 (82.9, 89.3)
HPV 31-Related	16/5,971	117/5,953	86.5 (77.8, 92.5)
HPV 33-Related	9/6,281	72/6,314	87.5 (75.0, 93.9)
HPV 45-Related	13/6,395	70/6,412	81.4 (67.0, 90.2)
HPV 52-Related	32/5,991	247/5,983	87.3 (82.0, 91.3)
HPV 58-Related	22/6,020	155/6,040	85.9 (77.9, 91.4)

Source: Adapted from STN 125508/0.4_Module 1.11.3, Table Q17-1.
Subjects were counted once in each applicable endpoint category. A subject might appear in more than one category.
N=Number of randomized subjects who received at least 1 injection.
n=Number of subjects in the population at Day 1.

Reviewer's comments: *The analyses of persistent infections originally included a one month visit window, meaning that the documented duration of persistent infection could be shorter than the stated endpoints (6 or 12 months). CBER asked the Applicant to re-analyze persistent infection data by including only subjects with documented infection strictly equal to or greater than 6 or 12 months. The results shown above represent the modified analyses with strict endpoint definitions*.

Seroconversion Rates for Anti-HPV 31, 33, 45, 52, and 58 Antibodies Induced by 9vHPV

Table 20 presents the results of the per-protocol analysis of seroconversion rates at Month 7, as assessed by type-specific cLIA, for anti-HPV 31, 33, 45, 52 and 58 antibodies elicited in 9vHPV recipients. The seroconversion rates were above 99% for each of HPV types 31, 33, 45, 52, and 58 at 4 weeks post-dose 3 in the PPI population. The success criterion (LB 95% CI >90%) was met for each HPV type.

Table 20: Seroconversion Rates for anti-HPV 31, 33, 45, 52 and 58 Antibodies at Month 7 (Study V503-001, PPI Population, N=6792)

HPV Type	m/n	Seroconversion Rate[1] % (95% CI)
31	4457/4466	99.8 (99.6, 99.9)
33	4689/4702	99.7 (99.5, 99.9)
45	4773/4792	99.6 (99.4, 99.8
52	4446/4455	99.8 (99.6, 99.9)
58	4476/4486	99.8 (99.6, 99.9)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p001_CSR, Table 11-97 (690).
[1]Percent represents proportion of subjects with serum levels ≥10, 8, 8, 8, and 8mMU/mL for HPV types 31, 33, 45, 52, and 58, respectively.
N=number of randomized subjects who received at least one injection.
n=number of subjects contributing to the analysis
m=number of subjects seropositive to the relevant HPV type(s)

6.1.11.3 Subpopulation Analyses

Subpopulation analyses were conducted based on the following demographic and baseline characteristics:

- Age at the start of vaccination: ≤20 vs. ≥21 years old.
- Race: Asian, Black, White, and All others.
- Ethnicity: Hispanic vs. not Hispanic.
- Geographic region: Asia-Pacific, Europe, Latin America, North America.
- Hormonal contraception use at the start of vaccination: Using vs. Not Using hormonal contraception.
- Lifetime number of male or female sex partners at the start of vaccination: None, 1 to 2, and ≥3.

Assessments were conducted on the PPE and HN-TS analysis populations. For the HN-TS population, assessments were also conducted on the following subgroups defined based on completion of the 3-dose vaccination regimen:

- 3 doses completed vs. ≤2 doses completed
- The ≤2 doses completed was further subdivided into the subgroups: 2 doses completed and 1 dose completed.

HPV 31/33/45/52/58-Related High Grade Cervical, Vulvar, or Vaginal Lesions

Assessments in PPE Population

As seen from Table 21, estimates of efficacy against HPV 31/33/45/52/58-related high-grade cervical, vulvar, and vaginal disease were consistent across the different subgroups that were investigated.

Table 21: Analysis of Efficacy against HPV 31/33/45/52/58-Related CIN2/3. AIS, Cervical Cancer, VIN2/3, VaIN2/3, Vulvar Cancer and Vaginal Cancer by Subgroups (Study V503-001, Per Protocol Efficacy Analysis Population)

Characteristics Subgroup	**9vHPV (N=7099) No. of cases/n**	**qHPV (N=7105) No. of cases/n**	**Observed Efficacy of 9vHPV % (95% CI)**
All subjects	**1/6016**	**30/6017**	**96.7 (80.9, 99.8)**
Age			
≤20 years	0/1790	19/1889	100 (79.8, 100)
≥21 years	1/4226	11/4128	91.1 (47.4, 99.6)
Race			
Asian	0/885	1/866	100 (≤-999,100)
Black	0/199	0/187	NA
White	0/3318	21/3306	100 (82.9, 100)
All Others	1/1614	8/1658	87.3 (19.0, 99.4)
Ethnicity			
Hispanic	1/2146	11/2154	90.9 (46.6, 99.6)
Non-Hispanic	0/3870	19/3863	100 (80.6, 100)
Geographic Region			
Asia-Pacific	0/791	0/788	NA
Europe	0/2051	12/2027	100 (69.7,100)
Latin America	1/2032	11/2052	90.9 (46.2,99.6)
North America	0/1142	7/1150	100 (38.3,100)
Hormonal Contraception Use at Day 1			
Using hormonal contraception	1/3661	20/3671	95.0 (72.0, 99.8)
Not using hormonal contraception	0/2355	10/2346	100 (63.9, 100)

Source: Adapted from STN 125508/0_Module 5.3.5.1.p001_CSR, Table 11-78 (p612-14).
N=Number of randomized subjects who received at least one injection.
n=Number of subjects who had at least one follow-up visit after Month 7.

Assessments in the HN-TS Population

Similar to the assessments in the PPE population, estimates of efficacy against HPV 31/33/42/52/58-related high-grade cervical, vulvar, and vaginal disease were consistent across different subgroups except the Asia-Pacific subgroup, where there was one primary endpoint case for both 9vHPV and qHPV (Table 22). Because there was no endpoint case among all subjects who received ≤ 2 doses of 9vHPV or qHPV, efficacy of 9vHPV relative to qHPV could not be estimated for this endpoint.

Table 22: Analysis of Efficacy against HPV 31/33/45/52/58-Related CIN2/3, AIS, Cervical Cancer, VIN2/3, VaIN2/3, Vulvar Cancer and Vaginal Cancer by Subgroups (Study V503-001, HPV-Naïve Type-Specific Analysis Population)

Characteristics Subgroup	**9vHPV (N=7099) No. of cases/n**	**qHPV (N=7105) No. of cases/n**	**Observed Efficacy of 9vHPV % (95% CI)**
All subjects	**6/6873**	**42/6866**	**85.7 (68.4, 94.1)**
Age			
≤20 years	2/2078	24/2179	91.4 (68.4, 98.5)
≥21 years	4/4795	18/4687	78.1 (37.3, 93.2)
Race			
Asian	1/987	2/969	51.1 (-524.5, 989.3)

Characteristics Subgroup	**9vHPV (N=7099) No. of cases/n**	**qHPV (N=7105) No. of cases/n**	**Observed Efficacy of 9vHPV % (95% CI)**
Black	0/237	1/224	100 (≤-999, 100)
White	4/3793	29/3794	86.1 (60.7, 95.5)
All Others	1/1856	10/1879	89.9 (35.5, 99.5)
Ethnicity			
Hispanic	1/2450	15/2429	93.4 (57.9, 99.7)
Non-Hispanic	5/4423	27/4437	81.3 (52.8, 93.2)
Geographic region			
Asia-Pacific	1/873	1/874	0.3 (≤-999, 97.4)
Europe	2/2336	16/2328	87.5 (52.1, 98.0)
Latin America	1/2303	14/2301	92.9 (57.0, 99.7)
North America	2/1361	11/1363	81.4 (21.4, 97.0)
Hormonal Contraception Use at Day 1			
Using hormonal contraception	2/4127	28/4129	92.8 (74.0, 98.8)
Not using hormonal contraception	4/2746	14/2737	71.6 (13.6, 91.4)
Vaccine Dose Completion			
3 doses completed	6/6778	42/6777	85.7 (68.4, 94.1)
≤2 doses completed	0/95	0/89	NA
2 doses completed	0/83	0/77	NA
1 dose completed	0/12	0/12	NA

Source: Adapted from STN 125508/0_Module 5.3.5.1.p001_CSR, Table 11-79 (p615-17).
N = Number of randomized subjects who received at least one injection.
n = Number of subjects who had at least one follow-up visit after Day 1

Reviewer's comment: *Although the efficacy point estimates for each subgroup in both PPE and HN-TS populations are relatively consistent, the 95% CI vary greatly. This is because the numbers of primary endpoint cases in the analysis populations are small, and some subgroups have sparse case counts.*

HPV 31/33/45/52/58-Related Persistent Infection

Results of assessments in the PPE Population

Table 23 presents the observed efficacy of 9vHPV in prevention of HPV 31/33/45/52/58-related persistent infection ≥ 6 months duration in different subgroups in the PPE population. As seen from the table, efficacy estimates were consistent across subgroups. For all the evaluated subgroups, the lower bound of the 95% CI was greater than 80%. Consistent with the results in PPE, efficacy estimates were greater than 85% in all subgroups in HN-TS population. The LBs 95% CIs were greater than 75% for all subgroups in this population. In this analysis population, nine subjects in 9vHPV group and eight subjects in qHPV group received ≤2-doses of the vaccines. Of these, there were three cases of persistent infection in the qHPV group and no cases in the 9vHPV group.

Table 23: Analysis of Efficacy against HPV 31/33/45/52/58-Related Persistent Infection ≥6 Months by Subgroups (Study V503-001, Per protocol Efficacy Analysis Population)

Characteristics Subgroup	**9vHPV (N=7099) No. of cases/n**	**qHPV (N=7105) No. of cases/n**	**Observed Efficacy of 9vHPV % (95% CI)**
All subjects	**35/5939**	**810/5953**	**96.0 (94.4, 97.2)**
Age			
≤20 years	15/1770	349/1870	95.9 (93.4, 97.8)
≥21 years	20/4169	461/4083	96.0 (93.8, 97.6)
Race			
Asian	3/868	67/858	95.8 (88.0. 98.9)
Black	1/197	32/185	97.3 (84.3, 99.9)
White	12/3276	429/3273	97.4 (95.4, 98.5)
All Others	19/1598	282/1637	93.7 (90.0, 96.2)
Ethnicity			
Hispanic	20/2122	369/2129	95.0 (92.4, 97.0)
Non-Hispanic	15/3817	441/3824	96.8 (94.8, 98.2)
Geographic Region			
Asia-Pacific	4/776	66/781	94.2 (84.9, 98.1)
Europe	8/2031	257/2003	97.1 (94.5, 96.9)
Latin America	20/2009	355/2028	94.8 (92.0, 96.9)
North America	3/1123	132/1141	97.8 (93.7, 99.4)
Hormonal Contraception Use at Day 1			
Using hormonal contraception	17/3610	488/3632	96.7 (94.8, 98.1)
Not using hormonal contraception	18/2329	322/2321	94.8 (91.9, 96.8)

Source: Adapted from STN 125508/0_Module 5.3.5.1.p001_ CSR, Table 11-82 (p628-9).
N = Number of randomized subjects who received at least one injection.
n = Number of subjects who had at least one follow-up visit after Month 7.

6.1.11.4 Dropouts and/or Discontinuations

The methods regarding handling missing data are presented in Section 6.1.9.2. The dropout rates for both 9vHPV and qHPV treatment were less than 10% throughout the 60-month follow-up period. As shown in the sensitivity analyses (Section 6.1.11.1), the estimate of vaccine efficacy was not substantially different when cases were imputed among subjects who were lost to follow up.

6.1.11.5 Exploratory and Post Hoc Analyses

Efficacy of 9vHPV against HPV 31/33/45/52/58-Related Cervical and External Genital Procedures and Cervical Definitive Therapy

Table 24 shows the efficacy of 9vHPV against cervical and external genital procedures and cervical definitive therapy related to HPV types 31, 33, 45, 52, and 58 in the PPE and HN-TS populations. As shown in the table, 9vHPV significantly reduced cases of the composite endpoint of HPV 31/33/45/52/58-related biopsy (external genital and cervical biopsies combined) and cervical definitive therapy for both PPE and HN-TS populations. The point estimates of efficacy for the two populations were greater than 80% with a LB of 95% CI greater than 65%.

Table 24: Efficacy of 9vHPV against HPV 31/33/45/52/58-Related Cervical and External Genital Procedures (Study V503-001, PPE and HN-TS Population)

Analysis Population and Endpoints	**9vHPV (N=7,99) No. of Cases/n**	**qHPV (N=7,105) No. of Cases/n**	**Efficacy of 9vHPV % (95% CI)**
PPE Population			
HPV 31/33/45/52/58-Related Biopsy	7/6,016	222/6,017	96.9 (93.6, 98.6)
HPV 31/33/45/52/58-Related Definitive Therapy	4/6,012	32/6,014	87.5 (65.7, 96.0)
HN-TS Population			
HPV 31/33/45/52/58-Related Biopsy	28/6,873	317/6,866	91.3 (87.3, 94.3)
HPV 31/33/45/52/58-Related Definitive Therapy	8/6,835	48/6,718	83.3 (66.1, 93.2)

Source: Adapted from STN 125508/0_Module 5.3.5.1.p001_CSR, Tables 11-8 and 11-9(p312-315)
Subjects were counted once in each applicable endpoint category. A subject might appear in more than one category.
N=Number of randomized subjects who received at least one injection.
n=Number of subjects who had at least one follow-up visit after Day 1.

Comparison of 9vHPV and qHPV in Prevention of HPV 6/11/16/18-Related Cervical, Vulvar, or Vaginal Lesions, and Persistent Infection

The 9v HPV vaccine demonstrated equivalent protection against HPV 6-, 11-, 16-, and 18-related cervical, vulvar or vaginal lesions in PPE population. Similar results were also observed in the HN-TS population.

Overall, 6 and 7 cases of HPV 6/11/16/18-related cervical, vulvar, and vaginal disease were observed in 9vHPV and qHPV groups, respectively. In the 9vHPV group, the 6 cases were: 4 cases of HPV 6-related condyloma (SUBJID=17844, 19776, 22255, and 22418), 1 case of HPV 18-related condyloma (SUBJID=21481) and 1 case of HPV 18-related CIN 2 (SUBJID=75718). In the qHPV group, the 7 cases were: 2 cases of HPV 16-related CIN 1 (SUBJID=19087; 67886), 2 cases of HPV 16-related VIN/VaIN 1 (SUBJID=67364 and 69006), 2 cases of HPV 16-related VIN/VaIN 2/3 (SUBJID=68448 and 72000), and 1 case of HPV 6-related CIN 2/3 (SUBJID=18933).

Reviewer's comment: *For evaluation of efficacy with respect to specific HPV types (i.e., HPV types under evaluation), the PPE population could include subjects who were seropositive at Day 1 and/or PCR positive from Day 1 through Month 7 for the HPV types not under evaluation.*

As discussed in Section 6.1.11.1, co-infection is very common, which confounds the attribution of causality of the observed lesions to any particular co-infecting serotype. It cannot be determined whether cases of HPV 6/11/16/18-related cervical, vulvar, and vaginal disease were caused by HPV types other than 6/11/16/18 or were true cases of vaccine failure.

The 9vHPV vaccine also demonstrated protection against HPV 6/11/16/18-related persistent infection (≥6 months or ≥12 months) in both the PPE and HN-TS populations. For persistent infection ≥6 months, the risk reduction for 9vHPV relative to qHPV was

26.4% (95% CI: 4.3, 47.5) and 18.3% (95% CI: 2.1, 34.8) in the PPE and HN-TS populations, respectively, For persistent infection ≥12 months, the risk reduction for 9vHPV relative to qHPV was 31.3% (95% CI: 21.9, 606) in PPE population and 9.3% (95% CI: -21.0, 32.6) in HN-TS population,[Data source: V503-001 CRS, Table 11-12, p332-4].

Impact of 9vHPV on FAS Population

Impact of 9vHPV against the Rates of Persistent Infection and Cervical, Vulvar, or Vaginal Disease Related to Vaccine HPV Types

Table 25 summarizes the comparison of 9vHPV with qHPV preventing persistent infection (≥ 6 month duration) and cervical, vulvar, and vaginal disease related to vaccine HPV types in the FAS analysis population.

There was a moderate reduction in the proportion of subjects with HPV 31/33/45/52/58-related persistent infection and low grade cervical, vulvar and vaginal disease in the 9vHPV group compared with the qHPV group. However, the risk reduction estimate for the composite endpoint of HPV 31/33/45/52/58-related high-grade cervical, vulvar, and vaginal disease was not statistically significant. There were no statistically significant differences in any HPV-6/11/16/18-related efficacy endpoints between the 9vHPV and qHPV groups.

Reviewer comment: *As described above the study was not powered to demonstrate efficacy in this population.*

Table 25: Impact of 9vHPV against Rates of Persistent Infection and Cervical, Vulvar, and Vaginal Disease Related to Vaccine HPV Types (Study V503-001, FAS[1] Population)

Endpoints	9vHPV (N=7099) No. of Cases/n	qHPV (N=7105) No. of Cases/n	Efficacy of 9vHPV % (95% CI)
HPV 31/33/45/52/58-Related			
High-grade Cervical, Vulvar, and Vaginal Disease	129/7024	155/7022	16.5 (-5.8, 34.4)
Cervical, Vulvar, and Vaginal Disease (Any Grade)	208/7024	354/7022	41.5 (30.8, 51.0)
CIN 1	116/6882	228/6871	49.2 (36.6,59.5)
CIN 2 or worse	125/6882	149/6871	15.8 (-7.5, 34.1)
Vulvar and Vaginal Disease (Any Grade)	19/7021	36/7021	47.1 (8.4, 71.3)
Condyloma	9/7021	11/7021	17.9 (-118.0, 69.9)
VIN 1 or VaIN 1	10/7021	23/7021	56.4 (6.8, 81.5)
VIN 2/3 or VaIN 2/3 or worse	5/7021	6/7021	16.3 (-201.9, 75.0)
Persistent Infection ≥6 Months	795/6818	1759/6822	58.4 (54.7, 61.8)
HPV 6/11/16/18-Related			
Cervical, Vulvar, and Vaginal Disease (Any Grade)	244/7024	230/7022	-6.7 (-28.3, 11.3)
CIN 2 or worse	138/6882	117/6841	-18.5 (-52.9, 8.1)
VIN 2/3 or VaIN 2/3 or worse	11/7021	13/7021	15.1 (-95.8, 65.5)
HPV 6/11/16/18/31/33/45/52/58-Related			
Persistent Infection ≥ 6 Months	1319/6777	2154/6785	43.4 (39.4, 47.2)
Cervical, Vulvar, and Vaginal Disease	384/7024	517/7022	26.0 (15.6, 35.3)

Endpoints	9vHPV (N=7099) No. of Cases/n	qHPV (N=7105) No. of Cases/n	Efficacy of 9vHPV % (95% CI)
Cervical Disease	335/6882	443/6871	24.4 (12.9, 34.6)
CIN 1	197/6882	290/6871	32.1 (18.4, 43.7)
CIN 2 or worse	221/6882	229/6871	3.0 (-17.2, 19.8)
CIN 2	165/6882	171/6871	3.1 (-20.7, 22.2)
CIN 3	121/6882	112/6871	-8.5 (-41.6, 16.8)
AIS	10/6882	7/6871	-43.3 (-343.7, 48.9)
Cervical Cancer	0/6882	1/6871	100 (-999, 100)
Vulvar and Vaginal Disease	71/7021	92/7021	22.6 (-6.0, 43.5)
Condyloma	46/7021	51/7021	9.5 (-37.6, 40.6)

Source: Adapted from STN 125508/_Module 5.3.5.1.p001_CSR, Tables 11-45 (p453), 11-46 (p459-476), 11-47 (p479-483), 11-50 (p507-521) and 11-57 (p553-4).
[1]FAS population consisted of all individuals who received at least 1 vaccination and had at least one follow-up after Day 1.
Subjects were counted once in each applicable endpoint category. A subject might appear in more than one category.
N=Number of randomized subjects who received at least one injection.
n=Number of subjects who had at least one follow-up visit after Day 1.
AIS=Adenocarcinoma in situ; CIN=Cervical intraepithelial neoplasia; VaIN=Vaginal intraepithelial neoplasia; VIN=Vulvar intraepithelial neoplasia

Therapeutic Efficacy

Per CBER's request in Pre-BLA meeting, the Applicant conducted analyses to assess efficacy of the 9vHPV vaccine in the following populations:

- S1P0 (comprised of subjects who were seropositive and PCR-negative to the relevant HPV type at Day 1).
- S0P1 (comprised of subjects who were seronegative and PCR-positive to the relevant HPV type at Day 1).
- S1P1 (comprised of subjects who were seropositive and PCR-positive to the relevant HPV type at Day 1).

Protocol V503-001 did not include a screening visit to exclude HPV-positive subjects. This study design allowed for an investigation of the therapeutic efficacy of 9vHPV among subjects who were infected with one or more vaccine types at enrollment. Overall, there was no evidence that administration of 9vHPV impacted the course of ongoing genital HPV infections.

Reviewer's comment*: The absence of therapeutic efficacy is not surprising, as only a small proportion of PCR positive women are likely to have a viral infection that is productive of L1 viral proteins. Thus, antibody responses induced by the L1 VLP in 9vHPV are unlikely to clear the corresponding viruses or alter progression of genital epithelial cell dysplasia.*

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses were performed on all the subjects who received at least one vaccination and had safety follow-up. In this study, safety was reported separately for the dose-ranging substudy (phase 2b) and the efficacy substudy (phase 3):

- Dose-ranging substudy: The dose-ranging substudy comprised all subjects enrolled in Part A (from Day 1 through Month 7). The safety report for the dose-ranging substudy documented the respective safety profiles of the three 9vHPV vaccine dose formulations and qHPV vaccine.
- Efficacy substudy: The efficacy substudy comprised all subjects enrolled in Part A who received qHPV or the mid-dose formulation of 9vHPV as well as all subjects enrolled in Part B. The safety report for the efficacy substudy cohort represented the full extent of safety data collected in Protocol V503-001 for qHPV and the selected dose formulation of 9vHPV, from Day 1 through the visit cut-off date of April 10, 2013.

This section assesses only the safety data from Part B (phase 3, efficacy substudy) because Part B includes uniform follow-up for the vast majority of subjects exposed to the mid-dose formulation of 9vHPV. Safety data from Part A are incorporated in Section 8 of this review (Integrated Summary of Safety).

All subjects were followed for adverse experiences for 15 calendar days, including the vaccination day, after each injection using a VRC. In addition, all subjects were followed for SAEs, regardless of causality, occurring from Day 1 through Month 7 in the dose-ranging substudy, or Day 1 through 180 days post-dose 3 in the efficacy substudy.

Reviewer's comment: *Although both injection site and systemic adverse reactions were collected for 15 days after each vaccination via VRC, only temperature and injection-site pain, swelling and erythema observed in the 5 days after each vaccination were designated as solicited adverse reactions. Injection site reactions observed after 5 days were designated as unsolicited adverse events.*

6.1.12.2 Overview of Adverse Events

Table 26 provides a summary of clinical adverse experiences occurring by vaccination group from Day 1 through the visit cut-off date of April 10, 2013. As shown in Table 26, 12 subjects in the efficacy substudy discontinued study medication due to an adverse experience, including 8 in the 9vHPV group and 4 in qHPV group. Of these, 8 were vaccine-related, including 5 in 9vHPV group and 3 in qHPV group. Four hundred sixteen SAEs were reported during the entire course of this substudy, including 233 in the 9vHPV vaccine group and 183 in qHPV vaccine group (Table 26). Reported SAEs in the efficacy substudy included four vaccine-related SAEs (two in the 9vHPV group and two in the qHPV group) and 10 deaths (5 in the 9vHPV group and 5 in the qHPV group). None of the deaths were deemed vaccine-related by the investigator.

Table 26: Adverse Event Summary (Vaccination and Follow-up Periods, Day 1 through Visit Cut-Off Date) (Study V503-001, All Vaccinated Subjects, Efficacy Substudy)

	9vHPV (N=7,071) n (%)	**qHPV (N=7,078) n (%)**
Subjects with one or more adverse events	**6,661 (94.2)**	**6,444 (91.0)**
Injection-site	6,423 (90.8)	6,024 (85.1)
Systemic	4,052 (57.3)	3,957 (55.9)
Subjects with vaccine-related adverse reactions	**6,519 (92.2)**	**6,202 (87.6)**
Injection-site	6,422 (90.8)	6,024 (85.1)
Systemic	2,088 (29.5)	1,930 (27.3)
Subjects with serious adverse events (SAE)	**233 (3.3)**	**183 (2.6)**
Subjects with vaccine-related SAE	**2 (<0.1)**	**2 (<0.1)**
Subjects who died	**5 (0.1)**	**5 (0.1)**
Subjects who discontinued due to an adverse event	**8 (0.1)**	**4 (0.1)**
Subjects who discontinued due to a vaccine-related adverse event	**5 (0.1)**	**3 (<0.1)**
Subjects who discontinued due to an SAE	**3 (<0.1)**	**1 (<0.1)**
Subjects who discontinued due to a vaccine-related SAE	**1 (<0.1)**	**0 (0.0)**

Source: Adapted from STN 125508/0, Module 5.3.5.1.p001, CSR_Table 12-4, p750.
N=Subjects with any follow-up; n=subjects with any adverse event.

Summary of Injection-Site Adverse Reactions

The numbers and percentages of subjects with injection-site adverse reactions from Day 1 to 5 following any vaccination are presented in Table 27. The proportion of subjects in 9vHPV group who reported at least one injection-site adverse reaction within 5 days of any vaccination (90.2%) was higher than the corresponding proportion of subjects in the qHPV group (84.0%). Across both treatment groups, the most common injection-site adverse experiences following any vaccination visit were injection-site pain, swelling, and erythema. Erythema and swelling were reported increasingly frequently with each dose of vaccination. The frequencies of erythema (9vHPV vs. qHPV) post vaccination 1, 2 and 3 were 10.6% vs. 8.1%, 18.0% vs. 12.9% and 22.6% vs. 15.6%, respectively. The frequencies of swelling (9vHPV vs. qHPV) post vaccination 1, 2 and 3 were 12.5% vs. 9.3%, 23.3% vs. 14.6% and 28.3% vs. 18.7%, respectively.

Table 27: Injection-Site Adverse Reactions Reported 1 to 5 days Post-Vaccination at a Frequency of ≥1% (Efficacy Substudy of V503-001, Safety Population)

Adverse Reactions	**Intensity**	**9vHPV (N=7071) n (%)**	**qHPV (N=7078) n (%)**
All Injection Site AEs	Total	6,377 (90.2)	5,948 (84.0)
	Mild	3,723 (52.7)	4,036 (57.0)
	Moderate	2,339 (33.1)	1,722 (24.3)
	Severe	315 (4.5)	190 (2.7)
Bruising	Total	137 (1.9)	134 (1.9)
	Mild	123 (1.7)	116 (1.6)
	Moderate	12 (0.2)	16 (0.2)
	Severe	2 (0.0)	2 (0.0)
Erythema	Total	2,407 (34.0)	1,810 (25.6)

Adverse Reactions	Intensity	9vHPV (N=7071) n (%)	qHPV (N=7078) n (%)
	Mild	1,921 (27.2)	1,555 (22.0)
	Moderate	370 (5.2)	197 (2.8)
	Severe	114 (1.6)	57 (0.8)
Hematoma	Total	64 (0.9)	45 (0.6)
	Mild	58 (0.8)	42 (0.6)
	Moderate	6 (0.1)	3 (0.0)
Hemorrhage	Total	69 (1.0)	50 (0.7)
	Mild	55 (0.8)	48 (0.7)
	Moderate	11 (0.2)	2 (0.0)
	Severe	3 (0.0)	0(0.0)
Mass	Total	90 (1.3)	46 (0.6)
	Mild	58 (0.8)	33 (0.5)
	Moderate	29 (0.4)	10 (0.1)
	Severe	3 (0.0)	3 (0.0)
Pain	Total	6,356 (89.9)	5,910 (83.5)
	Mild	3,754 (53.1)	4,043 (57.1)
	Moderate	2,300 (32.5)	1,682 (23.8)
	Severe	302 (4.3)	185 (2.6)
Pruritus	Total	388 (5.5)	282 (4.0)
	Mild	301 (4.3)	223 (3.2)
	Moderate	80 (1.1)	56 (0.8)
	Severe	7 (0.1)	3 (0.0)
Swelling	Total	2,830 (40.0)	2,035 (28.8)
	Mild	1,958 (27.7)	1,594 (22.5)
	Moderate	597 (8.4)	332 (4.7)
	Severe	272 (3.8)	109 (1.5)

Source: Summarized from STN 125508/0, Module 5.3.5.1.p001_CSR, Tables 12-14 and 12-15 (p774-9).
N=Number of subjects vaccinated, n=number of subjects with the respective events.

Summary of Systemic Adverse Reactions

Table 28 presents the numbers and percentages of subjects with systemic clinical adverse reactions (reported by ≥1% of subjects in one or more vaccination groups) by system organ class from Day 1 to 15 following any vaccination visit. In both vaccination groups, the most common clinical adverse reactions were headache, nausea, pyrexia and nasopharyngitis, which occurred at generally similar frequencies between the vaccination groups. The frequency of systemic clinical adverse reactions numerically decreased across vaccination visits within each vaccine group. For example, the percentages of subjects with one or more systemic adverse reactions in the 9vHPV group post-vaccination 1, 2, and 3 were 17.7%, 11.8% and 10.4%, respectively.

The majority of subjects across the vaccination groups experienced systemic adverse reactions, most of which were of mild or moderate intensity. Percentages of severe systemic adverse reactions were similar in the 9vHPV group (11.7%) compared with the qHPV group (10.8%).

Table 28: Systemic Adverse Reactions by System Organ Class Reported 1 to 15 Days Post-Vaccination at a Frequency ≥ 1% (V503-001, Efficacy Substudy, Safety Population)

Adverse Events	**9vHPV (N=7,071) n (%)**	**qHPV (N=7,078) n (%)**
Subjects with one or more systemic adverse events	**3,948 (55.8)**	**3,883 (54.9)**
Gastrointestinal disorders	**1,175 (16.6)**	**1,148 (16.2)**
Abdominal pain	169 (2.4)	170 (2.4)
Abdominal pain upper	178 (2.5)	182 (2.6)
Diarrhea	236 (3.3)	246 (3.5)
Nausea	512 (7.2)	459 (6.5)
Vomiting	141 (2.0)	131 (1.9)
General disorders and administration site conditions	**932 (13.2)**	**893 (12.6)**
Fatigue	237 (3.4)	219 (3.1)
Malaise	92 (1.3)	85 (1.2)
Pyrexia	470 (6.6)	463 (6.5)
Infections and Infestations	**1,113 (15.7)**	**1,135 (16.0)**
Influenza	311 (4.4)	295 (4.2)
Nasopharyngitis	376 (5.3)	388 (5.5)
Injury, poisoning and procedural complications	**79 (1.1)**	**99 (1.4)**
Musculoskeletal and connective tissue disorders	**543 (7.7)**	**543 (7.7)**
Back pain	130 (1.8)	121 (1.7)
Myalgia	139 (2.0)	137 (1.9)
Pain in extremity	98 (1.4)	108 (1.5)
Nervous system disorders	**2,317 (30.3)**	**1,999 (28.2)**
Dizziness	346 (4.9)	307 (4.3)
Headache	1,876 (26.5)	1,756 (24.8)
Migraine	84 (1.2)	85 (1.2)
Psychiatric disorders	**82 (1.2)**	**76 (1.1)**
Reproductive system and breast disorders	**440 (6.2)**	**419 (5.9)**
Dysmenorrhea	239 (3.4)	212 (3.0)
Respiratory, thoracic and mediastinal disorders	**544 (7.7)**	**520 (7.3)**
Cough	112 (1.6)	118 (1.7)
Nasal congestion	71 (1.0)	65 (0.9)
Oropharyngeal pain	328 (4.6)	300 (4.2)
Skin and subcutaneous tissue disorders	**236 (3.3)**	**229 (3.2)**

Source: Adapted from STN 125508/0, Module 5.3.5.1.p001_CSR, Table 12-18 (p786-7).
N=Number of subjects vaccinated, n=number of subjects with the respective events.

Table 29 presents the numbers and percentages of subjects with vaccine-related systemic clinical adverse reactions, as judged by the investigators, by preferred term from Day 1 to 15 following any vaccination visit. The most common (frequency ≥2%) vaccine-related systemic clinical adverse reactions were headache, pyrexia, nausea, dizziness, and fatigue. The overall frequency of vaccine-related systemic adverse reactions was similar between the two treatment groups.

Table 29: Vaccine-Related Systemic Adverse Reactions Reported 1 to 15 Days Post-Vaccination at a Frequency of ≥1% (V503-001 Efficacy Substudy, Safety Population)

Adverse Reaction	**9vHPV (N=7071) n (%)**	**qHPV (N=7078) n (%)**

Adverse Reaction	**9vHPV (N=7071) n (%)**	**qHPV (N=7078) n (%)**
Headache	1031 (14.6)	969 (13.7)
Pyrexia	357 (5.0)	301 (4.3)
Nausea	311 (4.4)	261 (3.7)
Dizziness	211 (3.0)	197 (2.8)
Fatigue	166 (2.3)	150 (2.1)
Diarrhea	87 (1.2)	71 (1.0)
Myalgia	69 (1.0)	48 (0.7)
Oropharyngeal pain	73 (1.0)	40 (0.6)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p001_CSR, Table 14.5-38 (p1909-1918).
N=number of subjects vaccinated, n=number of subjects with respective events.

6.1.12.3 Deaths

At the time of database closure for the current analyses (April 10, 2013), 10 subjects in the efficacy substudy (5 in 9vHPV group and 5 in qHPV group) had died (no deaths occurred in the dose ranging substudy). Subject AN 22093 in 9vHPV group died of acute promyelocytic leukemia after the visit cut-off date of April 10, 2013. Table 30 summarizes the 11 deaths in this study. None of the deaths were considered by the investigator to be vaccine related.

Table 30: Summary of Deaths Occurring in Study V503-001

Treatment Group	**Subject ID**	**Age (Years)**	**Death Causality**	**Days Post-Vaccination**	**Comments**
9vHPV	69699	20	Automobile accident	226 days post dose 3	Patient died immediately at the scene of the accident.
9vHPV	70563	25	Sudden death	678 days post dose 3	Patient died during night. No history of underlying disease. No autopsy was performed.
9vHPV	71972	21	Suicide	15 days post dose 2	Patient was treated for depression with selective serotonin reuptake inhibitor. Autopsy was performed (results not available)
9vHPV	72132	17	Acute lymphoblastic leukemia	Approx. 880 days post dose 3	Patient was diagnosed with ALL 25 days post dose 3
9vHPV	72831	23	Hypovolemic shock and septic shock	530 days post dose 3	Patient was diagnosed with Ovarian tumor at 59 days post dose 3, and the tumor was removed then. The patient died approximately 15 months after the surgery due to hypovolemic and septic shock per autopsy
9vHPV	22093	29	Acute promyelocytic leukemia	1304 days post dose 3	Patient was diagnosed with leukemia at 1291 days post dose 3, died due to multiple hemorrhages, tumor lysis syndrome, and pneumonia.
qHPV	71426	25	Automobile accident	811 days post dose 3	Died due to cervical spinal cord injury per autopsy.
qHPV	75127	24	Airplane	7 days post	Patient sustained multiple

Treatment Group	Subject ID	Age (Years)	Death Causality	Days Post-Vaccination	Comments
			crash	dose 3	lesions per hospital record.
qHPV	20453	25	Cerebral hemorrhage	1114 days post dose 3	Death due to cerebral hemorrhage per autopsy. Cause of hemorrhage was not identified.
qHPV	20497	17	Trauma (gunshot)	141 days post dose 3	Patient was shot outside her home, died at ER.
qHPV	69125	23	Stomach adenocarcinoma	510 days post dose 3	Advanced stomach cancer involved in colon and ovaries with ascites.

Source: Generated by CBER reviewer from STN 125508/0_Module 5.3.5.1.p001, Section 14.6: Narratives of SEAs (p2453-2536)

***Reviewer's comments**: This reviewer concurs with the Applicant's assessment of causality that none of the deaths was related to the study vaccines.*

6.1.12.4 Nonfatal Serious Adverse Events (SAE)

The numbers and percentages of subjects in both vaccination groups with any SAE was provided in the submission (CSR for Study V503-001, Table 12-31, p826-832) by system organ class (SOC) from Day 1 through visit cut-off date. Approximately 2.9% (n=416) of subjects reported one or more SAE during the safety follow-up period in the efficacy substudy, 3.3% (n=233) in the 9vHPV group and 2.6% (n=183) in the qHPV group. The most frequent SAEs were related to pregnancy (abortion induced and abortion spontaneous) and appendicitis in both groups.

The proportion of subjects with SAEs occurring between Day 1 and the visit cut-off date was similar between the 9vHPV group and the qHPV group when examined by either preferred term or by SOC, except for abortion spontaneous and abortion induced. The numbers of spontaneous abortion and induced abortion in the 9vHPV group were 36 and 73, respectively, while the corresponding numbers for the qHPV group were 24 and 54.

***Reviewer's comments:** The slightly higher proportion of SAEs in 9vHPV group was largely driven by the higher fetal loss [31 more cases (12 more spontaneous and 19 more elective abortions) in the 9vHPV group than in the qHPV group]. However, the overall proportions of fetal loss (Day 1 throughout visit cut-off date) in the two groups were similar (23.9% vs. 24.1%, 9vHPV vs. qHPV) as shown in Table 78 (Section 9.1.1.2). This difference is likely due to the fact that not all abortions were reported as an SAE (per protocol, a fetal loss was collected as an SAE only for pregnancies with a last menstrual period between Day 1 and 180 days post-dose 3). Please refer to Section 9.1.1.1 for a more detailed discussion of the numerical imbalance between treatment groups in spontaneous abortions.*

This reviewer has reviewed the narratives of all the SAEs in this study and concurs with the Applicant's assessment of causality.

Table 31 presents non-fatal SAEs occurring within 28 days of any vaccination. There was one non-fatal SAE (appendicitis in Subject 10882) in the low-dose group and no SAE in the high-dose group reported within 28 days following any vaccination in the 9vHPV dose-ranging substudy.

Reviewer comment: *No SAEs that occurred outside the 28 day vaccination window were judged to be vaccine related by the investigator or this reviewer.*

Table 31: SAEs Reported from Day 1 through Day 28 after Each Vaccination by Subject and Treatment Group (Study V503-001)

Treatment Group Subject ID	**SAE**	**Dose**	**Day of Onset**	**Related**	**Outcome**
9vHPV Group					
10882	Appendicitis	1	2	N	Resolved
10645	Malignant Melanoma	1	6	N	Resolved
73662	Syncope	1	11	N	Resolved
10603	Endometriosis	1	1	N	Resolved
18372	Bipolar disorder	2	2	N	Resolved
71222	Urinary tract infection	3	16	N	Resolved
75503	Pyelonephritis acute	2	7	N	Resolved
20344	Cholangitis	2	7	N	Resolved
67672	Malignant melanoma	3	1	N	Resolved
19765	Tonsillitis streptococcal	1	14	N	Resolved
69495	Pyrexia	3	2	Y	Resolved
19912	Chronic tonsillitis	3	10	N	Resolved
18222	Hemorrhagic fever	2	2	N	Resolved
18091	Vertigo positional	1	12	N	Resolved
69530	Cervical dysplasia	2	23	N	Resolved
70385	Pyelonephritis	3	24	N	Resolved
69797	Cervical dysplasia	2	1	N	Resolved
18389	Bipolar disorder	2	24	N	Resolved
73025	Cholecystitis infective	1	18	N	Resolved
74701	Major depression	2	16	N	Resolved
72684	Ligment rupture	3	9	N	Resolved
74921	Anemia Anaphylactic reaction	3 3	1 6	N N	Resolved Resolved
22026	Ovarian cyst	2	5	N	Resolved
72886	Pharyngitis	1	19	N	Resolved
72970	Hypersensitivity	3	4	N	Resolved
73689	Sensory disturbance	3	17	N	Resolved
19805	Crohn's disease	3	3	N	Continuing
75481	Allergy to vaccine	1	1	Y	Resolved
22332	Appendicitis	2	16	N	Resolved
68617	Bladder injury Femur and humerus fracture Hypovolemic shock	2 2 2	2 2 2	N N N	Resolved Sequelae Resolved
68617	Multiple injuries Pelvic fracture Humerus fracture	1 1 1	2 2 21	N N N	Resolved Resolved Resolved
67890	Hyperglycemia	3	15	N	Resolved
75726	Urinary tract infection	1	8	N	Resolved
72178	Deep vein thrombosis	1	17	N	Resolved
qHPV Group					
71483	Anemia	3	27	N	Resolved
20358	Gastroenteritis	3	8	N	Resolved
72752	Urinary tract infection	3	23	N	Resolved
10174	Malignant palate neoplasm	2	19	N	Resolved

Treatment Group Subject ID	**SAE**	**Dose**	**Day of Onset**	**Related**	**Outcome**
19620	Cystitis hemorrhagic	2	6	N	Resolved
18065	Conjunctivitis	1	28	N	Continuing
69410	Appendicitis	1	9	N	Resolved
69716	Gastritis	2	1	N	Resolved
21301	Pyelonephritis acute	1	7	N	Resolved
67318	Cleft lip and palate	2	10	N	Resolved
70242	Cervical dysplasia	2	25	N	Resolved
68675	Foreign body in eye	2	26	N	Resolved
17856	Dysmenorrhoea	2	11	N	Resolved
21343	Dyspnoea	3	19	N	Resolved
74925	Hypoaesthesia	3	18	Y	Resolved
69320	Cervical dysplasia	2	1	N	Resolved
72039	Abdominal pain lower	1	4	N	Resolved
70312	Appendicitis	3	2	N	Resolved
22112	Urinary tract infection	1	12	N	Resolved
21785	Pyelonephritis	3	18	N	Resolved
21291	Cholelithiasis	1	7	N	Resolved
71271	Bipolar disorder	2	12	N	Resolved
68223	Headache	2	2	Y	Resolved
71111	Nasal polyps	3	15	N	Resolved

Source: Generated by CBER clinical reviewer from STN 125508/0_Module 5.3.5.1.p001_Table14.5-42 (p1939-2015)

Four SAEs were considered by the investigators to be vaccine-related (two in the 9vHPV group and two in the qHPV group) are summarized below:

- Pyrexia: A 26 year-old White female (AN 69495) presented with fever, body pain, headache and malaise two days after the third dose of 9vHPV. She was referred to an infectious disease physician. She had a fever of 38.6^0C. Physical exam was normal, and no laboratory tests were ordered. The infectious disease physician prescribed Paracetmol and Nimesulide to her. The symptoms had completely disappeared within one day. She was not hospitalized and was diagnosed as fever of unknown etiology. She was followed up by the study site three days later, and she stated that she was well without symptoms. The event was considered severe in intensity and was related to 9vHPV by the reporting investigator.
- Allergy to vaccine: A 20 year-old Asian female (AN 75481) from Denmark with a medical history of asthma but no medical history of allergic reaction had a severe allergic reaction three hours after the administration of the first dose of 9vHPV. Symptoms included swelling of the mouth and throat, rhinorrhea, rash over all her body, and difficulty breathing. She self-treated with two inhalations of beta-adrenergic agonist terbutaline sulfate for breathing problems and one oral dose of 10 mg cetirizine hydrochloride for urticaria. The reaction duration was 23 hours. She recovered and did not receive any further doses of the vaccine. The reporting investigator felt that allergic reaction was serious (life-threatening) and was related to 9vHPV because there was a close temporal association and there was no clear alternate food or drug identified as the cause.
- Headache: A 23 year old Multi-racial female (AN 68223) from Columbia developed a headache two days after she received her second dose of qHPV. The headache was persistent with dizziness and nausea. She experienced intense occipital headache nearly two months later that was intolerable despite

medication. She then went to the emergency room due to the increased intensity, and was hospitalized overnight and treated with naproxen. The subject reported the headache as well as associated phonophobia, nausea and chills without fever. Brain CT was normal. No additional laboratory tests were performed. She recovered from headache the following day, naproxen was discontinued, and she was discharged on the same date. The headache lasted for approximately eight weeks. She received her third dose of qHPV one and a half months later. The reporting investigator felt that headache was related to qHPV.

- Hypoesthesia: A 21 year old white female (AN 74925) from Canada with a history of migraine headaches experienced bilateral numbness of her extremities and perioral area 18 days after her third dose of qHPV (on April 14, 2010). The symptoms were episodic in nature, with fluctuations in frequency and duration. She was referred by her family doctor to a neurologist on December 29, 2010. She described symptoms of episodic burning and paresthesias involving the perioral area, fingers and toes. These symptoms lasted less than 1 minute. She also described joint pain in multiple areas including wrist, fingers, ankles and knees; they felt swollen and were tender to palpation. These symptoms also fluctuated and were episodic in nature. The patient also described multiple areas of muscle soreness and stiffness, and occasional blurred vision of the right eye. Other than those symptoms the patient was healthy. Laboratory workup including blood chemistry, live functions, serology for autoimmune disorders, and MRI for brain and spine were performed. The results from these tests were unremarkable. The neurologist and the patient reported symptoms improving in severity and frequency on a follow up visit on March 11, 2011. No definitive evidence of underlying neurological cause for symptoms was reported by the neurologist. On January 1, 2012, she recovered from all her symptoms without treatment. She was currently well and denied any new symptoms or focal neurological deficits. The reporting investigator felt that bilateral numbness to extremities was related to qHPV.

Reviewer's comments: *There was no pattern or any cluster of the same SAE in terms of SOC or preferred term in either group for SAEs reported within 28 days following any vaccination. This reviewer concurs with the investigators' causality assessments. Based on the information provided, the case of pyrexia (AN 69495) does not appear to be an SAE as specified in 21 CFR 312.32.*

SAEs of hypersensitivity or allergy were rare. Three such events were reported, all in 9vHPV group. One event (AN 75481, narrative of this case is described above) was deemed related to 9vHPV by the investigator, and the other two events were deemed unrelated to 9vHPV by the investigator, but were deemed related to the concomitant medications, Dolol (AN 72970) and parenteral iron (AN 74921).

Deep vein thrombosis (DVT) was reported in the post-marketing experience of Gardasil. Subject AN 72178, a 26 year-old white female, experienced pain and swelling of the right leg 17 days after her first dose of 9vHPV and was then hospitalized because of worsening symptoms. She was diagnosed with DVT and treated with Innohep and Marevan. Her symptoms improved and she was discharged two days later. She had no known risk factor other than hormonal contraception, and no prior episodes of DVT. The contraceptive was interrupted. The reporting investigator considered that DVT was not related to 9vHPV but was related to hormonal contraceptives. She received her second and third doses of 9vHPV as scheduled without problems.

Reviewer's comments: *This reviewer concurs with the reporting investigator that DVT was unlikely related to 9vHPV because of the proposed alternate etiology.*

6.1.12.5 Adverse Events of Special Interest (AESI)

New Medical Conditions Considered Potentially Indicative of Autoimmune Disorders

Table 32 displays the numbers and percentages of subjects by vaccination group who reported new medical conditions potentially indicative of an autoimmune disorder (reported by at least one subject in one or more vaccination groups), regardless of relatedness. A total of 104 subjects [57 in 9vHPV group (0.8%) and 47 in qHPV group (0.7%)] reported such conditions that were considered autoimmune conditions by the investigators. Two subjects in the 9vHPV group reported 3 conditions considered to be autoimmune, as well as related to study vaccine, by the investigators including: AN 72316 (Raynaud's phenomenon) and AN 17613 (goiter and hyperthyroidism).

Table 32: Subject with Adverse Events Potentially Indicative of An Autoimmune Disorder Considered As Autoimmune Conditions by Reporting Investigators by System Organ Class (Study V503-001, Day 1 through Visit Cut-off Date, Efficacy Substudy)

Adverse Events	**9vHPV (N=7106) n (%)**	**qHPV (N=7109) n (%)**
Blood and lymphatic system disorders	**1 (<0.1)**	**1 (<0.1)**
Antiphospholipid syndrome	1 (<0.1)	0 (0.0)
Idiopathic thrombocytopenic purpura	0 (0.0)	1 (<0.1)
Endocrine disorders	**19 (0.3)**	**22 (0.3)**
Autoimmune thyroiditis	4 (0.1)	5 (0.1)
Basedow's disease	1 (<0.1)	0 (0.0)
Goiter	2 (<0.1)	1 (<0.1)
Hyperthyroidism	3 (<0.1)	7 (0.1)
Hypothyroidism	10 (0.1)	9 (0.1)
Thyroid dysfunction in pregnancy	0 (0.0)	1 (<0.1)
Eye disorders	**1 (<0.1)**	**0 (0.0)**
Uveitis	1(<0.1)	0 (0.0)
Gastrointestinal disorders	**12 (0.2)**	**9 (0.1)**
Coeliac disease	5 (0.1)	4 (0.1)
Colitis ulcerative	1 (0.1)	3 (<0.1)
Crohn's disease	3 (<0.1)	2 (<0.1)
Immune system disorders	**1 (<0.1)**	**0 (0.0)**
Sarcoidosis	1 (<0.1)	0 (0.0
Metabolism and nutrition disorders	**3 (<0.1)**	**0 (0.0)**
Type 1 diabetes mellitus	3 (<0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	**9 (0.1)**	**5 (0.1)**
Ankylosing spondylitis	1 (<0.1)	0 (0.0)
Arthralgia	2 (<0.1)	0 (0.0)
Arthritis	1 (<0.1)	0 (0.0)
Connective tissue disorder	0 (0.0)	1 (<0.1)
Juvenile idiopathic arthritis	0 (0.0)	1 (<0.1)
Polyarthritis	1 (<0.1)	0 (0.0)
Rheumatoid arthritis	2 (<0.1)	1 (<0.1)
Sjogren's syndrome	1 (<0.1)	1 (<0.1)
Systemic lupus erythematosus	2 (<0.1)	1 (<0.1)

Adverse Events	**9vHPV (N=7106) n (%)**	**qHPV (N=7109) n (%)**
Nervous system disorders	**5 (0.1)**	**2 (<0.1)**
Multiple sclerosis	5 (0.1)	2 (<0.1)
Renal and urinary disorders	**0 (0.0)**	**1 (<0.1)**
IgA nephropathy	0 (0.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	**5 (0.1)**	**9 (0.1)**
Alopecia areata	0 (0.0)	1 (<0.1)
Cutaneous vasculitis	0 (0.0)	1 (<0.1)
Pigmentation disorder	0 (0.0)	1 (<0.1)
Psoriasis	4 (0.1)	5 (0.1)
Vitiligo	1 (<0.1)	1 (<0.1)
Vascular disorders	**2 (<0.1)**	**0 (0.0)**
Raynaud's phenomenon	2 (<0.1)	0 (0.0)

Source: Adapted from STN 125508/0_Module 5.3.51.p001, Table 12-50 (P896-7).

Reviewer's comment: *One case of multiple sclerosis (MS) in the qHPV group (AN 70545) was not reported in the Table 12-50 of the clinical study report of Study V503-001 but was reported in Table 12-49, p893-5. In addition, Subject AN 21474 in the qHPV group developed spondylitic myelopathy in March 2010 and was also diagnosed with MS after the visit cut-off date (April 10, 2013) and before database lock date (July 26, 2013). The table above has been modified to include these two cases.*

Table 33 summarizes the cases of MS reported in Study V503-001.

Table 33: Cases of Multiple Sclerosis (MS) Diagnosed in Study V503-001

Subject ID	Demographics/ Country	Medical History	Vaccination Dates	Onset Date	Diagnosis Date	Confounders	Outcome	Sponsor Assessment
qHPV								
AN 21474	23 Yrs, Multi-racial, Columbia	Inguinal herniorrhaphy, hallux valgus and tonsilectomy	4/1/09 5/29/09	8/16/09 78 days post dose 2	3/24/10 (Spondylitic myelopathy) 12/1/11 (MS)	Took Tamiflu from 8/15-8/20/09	unknown	Not related
AN 70545	22 Yrs, White, Denmark	None reported	6/17/09 8/24/09	A few hours after the second dose	11/17/09	None reported	Asymptomatic as of 12/16/09, but on therapy with Avonex	Not related
9vHPV								
AN 17698	21 Yrs, White, Canada	Eczema, gastroesophageal reflux, headache, migraine and psoriasis	10/1/08 11/25/08 3/23/09	4/30/09 37 days post dose 3	3/16/10	Enteritis stating on 4/24/09 and treatment with Cipro on 4/28/09	continuing	Not related
AN 73675	25 Yrs, White, Denmark	Gastric acid reflux	9/9/09 11/9/09 3/17/10	1/6/10 59 days post dose 2	1/6/10	None reported	Asymptomatic, Avonex treatment from 3/1/10 to 12/27/11, and Fingolimod hydrochloride was initiated on 12/17/11.	Not related
AN 20852	26 Yrs, Multi-racial, Mexico	Depression and pharyngotonsilitis	3/9/09 4/17/09 8/10/09	10/2010 >14 months post dose 3	4/1/11	None reported	Treatment on Avonex	Not related
AN 21266	21 Yrs, White, USA	None	3/24/09 5/22/09 8/24/09	9/1/10 374 days post dose 3	9/1/10	None	Treatment on Avonex	Not related
AN 70728	25 Yrs, Asian, Japan	None	6/22/09 8/22/09 11/30/09	1/20/11 417 days post dose 3	1/20/11	None	Treatment on pridol and methycobal	Not related

Reviewer's comments: *Three cases of MS [one in the qHPV group (AN70545), two in the 9vHPV group (AN17698 and AN 73675)] had onset of symptoms temporally associated with vaccination (within two months of vaccination).*

Four subjects, three in 9vHPV group (AN20852, AN 21266 and AN 70728) and one in qHPV (AN 21474), experienced onset of MS related symptoms at more than one year after last vaccination.

Subject AN 21474 had onset of symptoms on August 18, 2009 (78 days post-dose 2 of qHPV), was diagnosed as spondylitic myelopathy on March 24, 2010, and was then diagnosed with MS on December 1, 2011. The case narrative and data submitted for this patient in Clinical Study Report describe that the patient recovered from the spondylitic myelopathy on May 25, 2010. However, it is possible that these two diagnoses represent evolving assessment of the same process. The Applicant was unable to provide additional information, stating that it was "unable to obtain the neurological consultation report despite multiple attempts. This patient was uncooperative with the investigator. Additional information is not expected."

Narratives of 9vHPV Related Autoimmune Disorders other than MS

Subject AN 72316, a 23-year-old White female, reported numbness, tingling and coolness in both hands and feet on October 2, 2010 (213 days after dose 3 of 9vHPV) and was diagnosed as Raynaud's syndrome based on the clinical symptoms. The reporting investigator considered the Raynaud's syndrome to be possibly related to 9vHPV because the subject experienced similar symptoms intermittently during the winter 2009 (after the second dose of 9vHPV, November 19, 2009). However, the symptoms were absent in spring and summer 2010 (The third dose of 9vHPV was administered on March 4, 2010) and became bothersome immediately prior to diagnosis in October 2010. Although the relatedness of the event to 9vHPV could be not excluded, the symptoms did not appear to be closely associated with the administration of the study vaccine.

Subject AN 17613, a 20-year-old female from Thailand, received her first, second and third doses of 9vHPV on October 2, 2008, November 26, 2008, and April 20, 2009, respectively. On February 16, 2011 (668 days post-dose 3), the subject reported palpitation, weight loss, mild tremor, and a large thyroid gland. After laboratory testing (free T4 >7.77 ng/dl, free T3 >32.55 pg/ml, and TSH <0.005 mlU/L), she was diagnosed with thyrotoxicosis and diffuse goiter. The reporting investigator felt this could be related to the vaccine because in 2006 the subject's average pulse rate was 80 beats per minute (BPM) and blood pressure (BP) was 115/70 mmHg, but after entering the study they began to rise (Day 1: pulse rate=71 BPM, BP=116/70 mmHg; Month 2: pulse rate=123 BPM, BP=112/75 mmHg; Month 6: pulse rate=143 BPM, BP=135/78 mmHg and before starting treatment of thyrotoxicosis: pulse rate=137 BPM, BP=143/75 mmHg). This reviewer concurs with the investigator that the thyrotoxicosis is possibly related to the study vaccine.

Reviewer's comments: *The potential autoimmune disorders observed in the two groups in general are balanced by preferred term except MS, type 1 diabetes mellitus, and Raynaud's disease. The incidence rate of MS observed in the 9vHPV group is on the upper end of the range (<5 to 30 per 100,000 person-years) of incidences of MS reported in the general population of similar ages [(34)]. The rates observed in V503-001*

for the 9vHPV and qHPV treatment groups, respectively, were 20.7/100,000 and 8.3/100,000 person-years. The five cases observed in the 9vHPV group appeared to be randomly distributed across the study regions.

Overall the numbers of reported cases are small and the clinical significance of the imbalances between the treatment groups are unknown. The rates of autoimmune disorders following 9vHPV as compared with qHPV are discussed in further detail in Section 8 (Integrated Summary of Safety).

6.1.12.6 Clinical Test Results

No routine laboratory safety tests were conducted in this study.

6.1.12.7 Dropouts and/or Discontinuations

Table 34 presents the adverse events leading to study discontinuation by treatment group, their relatedness, intensity and outcome. In total, 14 subjects did not complete the 3-dose regimen due to an adverse event, 10 from the 9vHPV group (two of them from the low-dose 9vHPV cohort: AN 10849 and AN 10424), and four subjects from the qHPV group. In general, adverse events that led to discontinuation were related to early local and systemic reactogenicity and hypersensitivity.

Table 34: Summary of Subjects with Clinical Adverse Events That Led to Discontinuation (Study V503-001, Day 1 through Visit Cut-Off Date, All Vaccinated Subjects)

Treatment Group Subject ID	SAE	Dose	Day of Onset	Intensity	Related	Outcome
9vHPV Group						
AN 10849	Rash	1	8	Mild	Y	Resolved
AN 10424	Dysmenorrhoea	2	9	Severe	N	Resolved
AN 18464	Asthenia, Dizziness, Fatigue, Hyperhidrosis, Injection site pain, Nausea and Pyrexia	2	1	Severe[1]	Y	Resolved
AN 68226	Injection site pain	1	1	Moderate	Y	Resolved
AN 10888	Hypoesthesia, Paresthesia	1	1	Moderate	N	Resolved
AN 71291	Headache	1	2	Severe	Y	Resolved
AN 21275	Abortion Spontaneous	1	93	SAE[2]	N	NA
AN 20790	Injection site swelling	2	1	Mild	Y	Resolved
AN 75481	Allergy	1	1	SAE[2]	Y	Resolved
AN 71972	Complete suicide	1	15	SAE[2]	N	Dead
qHPV Group						
AN 18065	Tension headache	1	40	SAE[2]	N	Not resolved
AN 20609	Rash papular	2	6	Severe	Y	Resolved
AN 22087	Swollen tongue	2	2	Moderate	Y	Resolved
AN 75312	Urticarial	2	5	Moderate	Y	Resolved

Source: Generated by CBER reviewer from STN 125508/0.2_Module 1.11.3_Reponses to CBER's Information Request#1 (p7-11).
[1]All were severe except injection site pain and nausea that were moderate in intensity.
[2]SAE was not rated in intensity.
[3]Per protocol, abortion was counted as an SAE.

Reviewer's comments: *Subject AN 71972, a 21 year old female from Sweden, had treatment for depression with selective serotonin reuptake inhibitor medication. The suicide was likely related to her underlying medical condition. Please also refer to Section 6.1.12.3.*

Subject AN 75481 developed a severe allergic reaction three hours after the administration of her first dose of 9vHPV. Please refer to Section 6.1.12.4 for details.

This reviewer concurs with the Applicant's assessments of causality of the adverse events that led to discontinuation except hypoesthesia and paresthesia that occurred in Subject AN 10888. The subject experienced hypoesthesia and paresthesia on the same day of administration of her first dose of 9vHPV and events lasted for 3 days. There was no alternative explanation for the events. Because of the close temporal association with the treatment, this reviewer concludes that the events are possibly related to 9vHPV. Of note, one subject (AN 74925) in the qHPV group experienced hypoesthesia and paresthesia 18 days after her third dose, which was assessed by the Applicant as related to qHPV (Please refer to Section 6.1.12.4 for details)

6.1.13 Study Summary and Conclusions

6.1.13.1 Summary of Efficacy

New HPV Types (HPV 31, 33, 45, 52, 58)

The 9vHPV vaccine significantly reduced the primary efficacy cases of the composite endpoints of HPV type 31-, 33-, 45-, 52-, and 58-related high-grade cervical, vulvar, and vaginal disease, HPV type 31-, 33-, 45-, 52-, and 58-related cytological abnormalities, and HPV type 31-, 33-, 45-, 52-, and 58-related invasive cervical and external genital procedures. Efficacy of 9vHPV in the PPE population for all these endpoints was greater than 90% with the LB of 95% CI greater than 60%. Efficacy was also demonstrated in the PPE population with respect to high-grade cervical, vulvar, and vaginal disease related to the individual HPV types 31, 33, or 52, but the study was underpowered to demonstrate vaccine efficacy against this endpoint for the other two HPV types (45 and 58) individually. However, 9vHPV efficacy in preventing HPV 58-related high-grade cervical, vulvar, and vaginal lesions was established in the HN-TS population. Moreover, efficacy of 9vHPV was consistently demonstrated against cervical, vulvar, and vaginal disease (any grade), as well as persistent infection, caused by each of the new HPV types. As persistent HPV infection is a requirement for the development of anogenital malignancies related to HPV, and persistent infection with HPV types 16, 18, 31 or 33 is associated with progression to high-grade cervical lesions[35, 36], it is reasonable to conclude that 9vHPV vaccine will prevent high-grade cervical disease caused by each of the new HPV types.

Most of the cases of HPV type 31-, 33-, 45-, 52-, and 58-related high grade disease were cervical disease cases. Limited endpoint cases precluded demonstration of efficacy in preventing HPV 31-, HPV 33-, HPV 45-, HPV 52-, and HPV 58-related high-grade vulvar, vaginal, and anal lesions. Given that pathobiology of HPV-related high-grade vulvar, vaginal, and anal disease is similar to that of high-grade cervical disease, and that 9vHPV prevents HPV 31-, HPV 33-, HPV 45-, HPV52-, and HPV 58-related persistent infection and high-grade cervical disease, it can be inferred that 9vHPV also

prevents HPV 31-, HPV 33-, HPV 45-, HPV52-, and HPV 58-related high-grade vulvar, vaginal, and anal disease.

Original HPV Types (6, 11, 16, 18)

The qHPV vaccine was shown to prevent HPV 6, 11, 16 and 18-related cervical, vulvar, vaginal and anal disease. V503-001 results demonstrated that the 9vHPV induced non-inferior anti-HPV 6, 11, 16, and 18 antibody GMTs compared with qHPV in females 16 through 26 years of age. The GMT ratios of 9vHPV/qHPV were 1.02, 0.8, 0.99, and 1.19 for HPV types 6, 11, 16, and 18, respectively, with the LB 95% CI for GMT ratio greater than 0.67 for each HPV type.

Supportive analyses assessed 9vHPV efficacy in preventing disease and persistent infection caused by the original types compared to the historical placebo group of the Gardasil Vaccine Program as well as the concurrent qHPV comparator. These analyses showed 90% efficacy of 9vHPV compared with historical placebo in preventing disease caused by original types in the PPE population. In addition, the efficacy of 9vHPV in preventing persistent infection related to HPV types 6, 11, 16 and 18 was similar to that of concurrent qHPV comparator.

6.1.13.2 Safety: 9vHPV Vaccine Versus qHPV Vaccine

The 9vHPV vaccine had an acceptable safety profile in females 16 through 26 years of age. The safety profile was generally similar to that of the qHPV vaccine with the notable exception of higher rates of injection-site reactions following 9vHPV. Please also refer to Section 6.1.12.5 for discussion of the small numerical imbalance with a higher rate of MS (5 cases in the 9vHPV group and 2 cases in the qHPV group) and to Section 9.1 for discussion of the numerical imbalance with a higher rate of spontaneous abortions in women who became pregnant within 30 days of any vaccination [19.1% in the 9vHPV group (17 of 89 pregnancies with known outcome) and 8.0% in the qHPV group (7 of 88 pregnancies with known outcome)].

6.1.13.3 Conclusion

This reviewer concludes that Study V503-001 provides evidence to support the effectiveness of 9vHPV in females 16 through 26 years of age in preventing persistent infection and anogenital disease caused by the 9 HPV types included in the vaccine. The safety profile of 9vHPV was favorable in the study population and was generally similar to the licensed qHPV vaccine. Further assessment of the observed small numerical imbalances in rates of multiple sclerosis and spontaneous abortions would require much larger studies best conducted in a post-marketing setting (see Section 11, Risk-Benefit Considerations).

6.2 Trial #2: V503-002 (Designated as Study 2 in the Draft Package Insert)

Title: A Phase 3 Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of 9vHPV in Preadolescents and Adolescents (9 through 15 year olds) with a Comparison to Young Women (16 through 26 year olds)

6.2.1 Objectives

6.2.1.1 Primary Safety Objective

- To evaluate the tolerability of 9vHPV in preadolescent and adolescent boys and girls 9 through 15 years of age and young women 16 through 26 years of age.

6.2.1.2 Primary Immunogenicity Objectives

Adolescent-Adult Immunobridging Substudy

- To demonstrate that administration of 9vHPV induces non-inferior GMTs for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibodies in girls and boys 9 through 15 years of age compared with young women 16 through 26 years of age.

Manufacturing Lot Consistency Substudy

- To demonstrate that the final manufacturing process (FMP) results in 9vHPV that induced consistent anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses.

6.2.1.3 Secondary Objectives

- To demonstrate that 9vHPV induces non-inferior immune responses with respect to seroconversion rates for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in girls and boys 9 through 15 years of age compared with young women 16 through 26 years of age.
- To demonstrate that the FMP results in 9vHPV that induces consistent seroconversion percentages to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

6.2.2 Design Overview

This was a multicenter immunogenicity and safety/tolerability phase 3 trial with a target enrollment of approximately 2800 subjects (1800 preadolescent and adolescent girls, 600 preadolescent and adolescent boys and 400 young women). Two immunogenicity substudies were conducted: an adult-adolescent immunobridging substudy that included approximately 600 girls, 600 boys and 400 young women; and a lot consistency substudy that included all 1800 girls equally randomized to 3 FMP lots. The lot consistency substudy was double-blinded with respect to FMP lot number. All subjects were followed for safety for 12 months.

6.2.3 Population

6.2.3.1 Boys and Girls 9 through 15 Years of Age

- Male or female subjects between the ages of 9 years and 0 days and 15 years and 364 days on the day of enrollment, in good physical health.
- Must not yet have had coitarche and did not plan on becoming sexually active during the Day 1 through Month 7 period.

6.2.3.2 Women 16 through 26 Years of Age

- Female subjects between the ages of 16 years and 0 days and 26 years and 364 days on the day of enrollment, in good physical health.
- Had never had Pap testing or only had normal Pap test results.

- Had a lifetime history of 0 to 4 male and/or female sexual partners at the time of enrollment.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Please refer to Section 6.1.4 for study treatment.

The product formulations used for this study were Lots WL00033284, WL00033286 and WL00033287 (Data source: Table 2, page 5 of Module 3.2.P.5.4, STN 125508/0)

6.2.5 Directions for Use

Please refer to Section 6.1.5 for directions for use.

6.2.6 Sites and Centers

The study was conducted in 70 centers; 21 centers in the U.S. and 49 centers Ex-U.S. The median number of subjects enrolled at each center was 40 (ranging 10 – 228).

***Reviewer's comments**: The trial was conducted in 72 centers internationally as reported in the original submission. Two study centers (Study Sites ---------(b)(4)----------) were excluded from assessment in this review because of GCP non-compliance issue. As a result, the total study centers included in this review were reduced to 70. Please refer to Section 3.2 for detailed discussion of the issue.*

6.2.7 Surveillance/Monitoring

6.2.7.1 Immunogenicity

Serum samples were collected from all subjects at Day 1 and Month 7. Serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody titers were measured using a competitive Luminex Immunoassay (HPV-9 cLIA). The following endpoints were collected from each study subject to assess immunogenicity:

- cLIA titers for each of the vaccine HPV types.
- Serostatus (i.e., above or below assay cutoff) for each of the vaccine HPV types.

All subjects who were part of the defined PPI population were included in the immunogenicity summary.

6.2.7.2 Safety

The following measures were collected from each study subject to assess safety:

- Temperatures (within 5 days following any vaccination) via VRC.
- All adverse events (within 14 days following any vaccination) via VRC.
- All SAEs that occurred from Days 1 through 180 following the last vaccination
- All SAEs that resulted in death or were determined to be related to the study vaccine that occurred at any time during the study. All subjects who received at least one injection of study vaccine and had safety follow-up data were included in the safety summary.

6.2.8 Endpoints and Criteria for Study Success

Safety

- Adverse reactions from Day 1 through 15 after each vaccination via VRC.
- SAEs from Day 1 through 6 months after the last vaccination.

- New medical conditions throughout the study.

Immunogenicity

- Anti-HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 antibody responses (GMTs and seroconversion rates) at Month 7.

Criteria for Study Success

- Demonstration of non-inferior immunogenicity for individual HPV types GMTs of the 9vHPV vaccine in children 9 through 15 years of age compared with those in females 16 through 26 years of age.
- Demonstration of lot consistency of the three lots of the 9vHPV vaccine.

Please refer to Section 6.2.9.1 for details.

6.2.9 Statistical Considerations and Statistical Analysis Plan

6.2.9.1 Statistical Criteria for Success

Non-inferiority Comparison of Immunogenicity between Pre-adolescents/Adolescents and Young Women

The primary analyses of antibody GMTs for each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 were addressed by one-sided tests of non-inferiority conducted at the α=0.025 level for each HPV type. Testing was conducted using an analysis of variance (ANOVA) model with a response of log individual titers and a fixed effect for comparison group. The statistical criterion for non-inferiority required that the LB of the two-sided 95% CI for the GMT ratio (9- to 15-year-old boys vs. 16- to 26-year-old young women, or 9- to 15-year-old girls vs. 16- to 26-year-old young women) be greater than 0.67 for each HPV type.

Similarly, the secondary analyses of seroconversion rates for each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 was conducted at the α=0.025 level using the method of Miettinen and Nurminen. The statistical criterion for non-inferiority required that the LB of the two-sided 95% CI for the difference in seroconversion rate (9- to 15-year-old boys minus 16- to 26-year-old young women, or 9- to 15-year-old girls minus 16- to 26-year-old young women) be greater than -5 percentage points for each HPV type.

Lot Consistency Analyses

The primary analyses of antibody GMTs for lot consistency were addressed by 3 pairwise (Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3) comparisons for each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Each pairwise comparison tested the equivalence of the 2 lots using 2 one-sided tests at the 0.025 level. Testing was conducted using an analysis of covariance (ANCOVA) model with a response of the natural log of individual titers and fixed effects for vaccine lot and age strata. Successful demonstration of lot consistency required that the 95% CI for the GMT ratio for each pairwise comparison between lots be contained entirely within the interval (0.5, 2.0).

The secondary analyses of seroconversion rates for lot consistency were addressed similarly as immunobridging study as described above. Successful demonstration of lot

consistency required that the 95% CI for the difference in seroconversion rates for each pairwise comparison between lots be entirely contained within the interval (-5%, 5%).

Safety

Adverse experiences were summarized descriptively as frequencies and percentages by vaccination group and type of adverse experience, by vaccination visit and across all vaccination visits. Elevated temperatures (≥100.0°F or ≥37.8°C, oral) within 5 days following each vaccination were summarized in a similar manner. In addition, risk differences and associated 95% CIs were computed comparing the groups across all vaccination visits with respect to injection-site adverse reactions on the VRC, specific systemic adverse events, severe injection-site adverse reactions, SAEs and elevated temperatures. P-values were computed only for those adverse experiences that were solicited on the VRC (pain/tenderness/soreness, swelling, and redness) and elevated temperatures. The probability of observing at least one SAE in this study depended on the number of subjects enrolled and the rate of SAEs in the general population. If no SAEs were observed among all 2800 study subjects, this study would provide 97.5% probability that the true rate for SAEs was <0.14%.

6.2.9.2 Sample Size Calculation and Power for Immunobridging Substudy

Immunobridging hypotheses were tested by comparing the approximately 600 preadolescent and adolescent girls (or boys) vs. the approximately 400 young women (16 through 26 years of age) who received the same lot of vaccine. The sample size for the preadolescent and adolescent group (~600 per group) was primarily driven by the lot consistency objective and also by consideration of the overall safety database in 9- to 15-year-old subjects. The power and sample size were calculated based on the following assumptions: 1) the exclusion rates for the PPI population were approximately 20% for the 9- to 15-year-old girls and boys group and 40% for the 16- to 26-year-old young women group, 2) a standard deviation (SD) of the natural-log-transformed titers of 1.2, and 3) non-inferiority margin for GMT ratio was 1.5 fold. The estimates of exclusion rates and SD were based on data from previous qHPV vaccine studies. Under these assumptions, the study would provide >90% power to show non-inferiority of 9vHPV to qHPV at an overall one-sided, 2.5% alpha-level.

6.2.9.3 Sample Size and Power for Manufacturing Lot Consistency Substudy

This study randomized 1800 girls (9 through 15 years of age) into each of the 3 manufacturing lots (600 girls per lot). The sample size was driven by lot consistency objective and overall safety database consideration in 9- to 15-year-old girls. The power and sample size calculation for lot-consistency were based on the following assumptions: 1) each lot had an approximately 20% exclusion rate for the PPI population, 2) between-lot variance was not above 1.2% of total variance (between-lot variance + within-lot variance), and 3) equivalence margin for GMT ratio was 2.0 fold. The power and sample size were calculated to take consideration of both within-lot and between-lot variability. Under these assumptions, the study would provide >90% power to show consistency of the 3 lots for all 9 HPV types at an overall one-sided, 2.5% alpha-level

6.2.9.4 Handling of Dropouts or Missing Data

The ANCOVA model used in the primary immunogenicity analyses allowed inclusion of data from patients who had missing/non-evaluable antibody titers either at pre-

vaccination or at post-vaccination, but not at both time points. The statistical inference from this ANCOVA model was valid under the assumption that the missing data mechanism was ignorable (or more specifically, missing at random). Based on prior study results, the missing data rate for the titer response was relatively small and was not related to unobserved response or vaccination group.

For immunogenicity assessments, antibody titers below the lower limit of test were imputed to half of the detection limit, and titers above the upper limit of test imputed to the upper limit. There was no other imputation for missing data.

6.2.9.6 Multiple Comparisons/Multiplicity

The immunobridging and manufacturing lot consistency substudies were considered separately. The success of one substudy was not contingent on the success of the other. Therefore, either or both of the substudies could be successful for the study in general to be a success. No multiplicity adjustment was taken relative to the two substudies.

For immunobridging primary hypotheses, success was required on all 9 vaccine HPV types. Therefore, no multiplicity adjustment was made to account for the multiple HPV types. However, for testing the co-primary hypotheses of non-inferiority of GMTs in girls vs. young women and in boys vs. young women, a closed stepwise testing procedure was used to control the overall Type I error rate at 0.025 (1-sided).

For lot consistency primary hypotheses, success required that consistency be established for all 9 vaccine HPV types. Therefore, no multiplicity adjustment was necessary for the manufacturing lot consistency substudy.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Per Protocol Immunogenicity (PPI) Population: Please refer to Section 6.1.10.1.

All Type-Specific Naïve Subjects with Serology (ANSS) Population
A supportive immunogenicity analysis was carried out on the all type-specific naïve subjects with serology population. To be included in this population, subjects must:

1. Have received all 3 vaccinations.
2. Have provided post dose 3 serology data.
3. Be seronegative for the relevant HPV type at Day 1 and (for the 16-26 year old female group only) PCR negative for the relevant HPV type on all swabs and biopsies from Day 1 through Month 7.

Safety Population: All subjects who received at least one study vaccination and have follow-up data.

6.2.10.1.1 Demographics

Table 35 summarizes the demographic data for the participants enrolled in the study. In general, the population for females 16 through 26 years of age was similar to that of Study V503-001 except that V503-002 had a higher proportion of Asians (26.5% in V503-002 vs. 14.3% in V503-001), and lower proportions of multi-racial population

(11.4% in V503-002 vs. 26.8% in V503-001) and Hispanic or Latino population (27.5% in V503-002 vs. 35.4% in V503-001). The demographics among the three lot groups (Lot 1, Lot 2 and Lot 3) were balanced regarding age, race, ethnicity and geographic region.

Table 35: Subject Characteristics at Baseline (Study V503-002, All Randomized Subjects)

Characteristics	**9- to 15-Year-Old Females (Lot 1) n (%)**	**9- to 15-Year-Old Females (Lot 2) n (%)**	**9- to 15-Year-Old Females (Lot 3) n (%)**	**9- to 15-Year-Old Males n (%)**	**16- to 26-Year-Old Females n (%)**	**Total n (%)**
Subjects in population	632	626	632	644	465	2999
Age (Years)						
9 to 12	427 (67.6)	420 (67.1)	425 (67.2)	434 (67.4)	0 (0.0)	1706 (56.9)
13 to 15	205 (32.4)	206 (32.9)	207 (32.8)	210 (32.6)	0 (0.0)	850 (27.7)
16 to 26	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	465 (100.0)	470 (100.0)
Mean	11.7	11.6	11.6	11.7	21.3	13.1
SD	1.8	1.8	1.9	1.8	2.7	4.0
Median	12	11	11	12	21	12
Race						
American Indian Or Alaska Native	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Asian	134 (21.2)	124 (19.8)	127 (20.1)	161 (25.0)	123 (26.5)	669 (22.3)
Black	50 (7.9)	59 (9.4)	52 (8.2)	37 (5.7)	48 (10.3)	246 (8.2)
Multi-Racial	81 (12.8)	91 (14.5)	86 (13.6)	149 (23.1)	53 (11.4)	460 (15.3)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	1 (0.2)	4 (0.1)
White	366 (57.9)	351 (56.1)	367 (58.1)	292 (45.3)	240 (51.6)	1616 (53.9)
Ethnicity						
Hispanic or Latino	176 (27.8)	191 (30.5)	193 (30.5)	195 (30.3)	128 (27.5)	883 (29.4)
Not Hispanic Or Latino	456 (72.2)	435 (69.5)	439 (69.5)	449 (69.7)	337 (72.5)	2116 (70.6)
Region						
Africa	32 (5.1)	34 (5.4)	29 (4.6)	30 (4.7)	40 (8.6)	165 (5.5)
Asia-Pacific	132 (20.9)	120 (19.2)	126 (19.9)	160 (24.8)	120 (25.8)	658 (21.9)
Europe	206 (3268)	182 (29.1)	185 (29.3)	143 (22.2)	183 (39.4)	899 (30.0)
Latin America	125 (19.8)	147 (23.5)	136 (21.5)	160 (24.8)	60 (12.9)	628 (20.9)
North America	137 (21.7)	143 (22.8)	156 (24.7)	151 (23.4)	62 (13.3)	649 (21.6)

Source: Adapted from STN 125508/0.43, Module 1.11.3_Table 1 (p15-17).

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Per enrollment eligibility criteria, girls and boys 9 through 15 years of age had no sexual history and the girls had no baseline cervicovaginal examination. The sexual history, gynecological and pregnancy history and contraceptive use at enrollment of the young women 16 through 26 years of age was similar to the subjects enrolled in V503-001.

6.2.10.2 Subject Disposition

A total of 3036 subjects were screened in this study, 2999 were randomized, and 2991 received at least one vaccination. A summary of subject disposition is presented in Table 36.

Among the 2999 randomized subjects, a total of 101 subjects (3.4%) discontinued during the entire study period (Day 1 through Month 12). Most subjects who discontinued prior to Month 12 either were lost to follow-up or withdrew. Only one subject discontinued due to a clinical adverse experience (Please refer to Section 6.2.12.7).

Eight randomized subjects were discontinued prior to their first vaccination: ANs 28015, 28057, 31900, 30684, 31649, and 31650 withdrew consent; and ANs 32898 and 32964 were discontinued due to protocol violation.

Table 36: Subject Disposition (Study V503-002, All Randomized Subjects)

Population and Disposition	9- to 15-Year-Old Females (Lot 1) n (%)	9- to 15-Year-Old Females (Lot 2) n (%)	9- to 15-Year-Old Females (Lot 3) n (%)	9- to 15-Year-Old Males n (%)	16- to 26-Year-Old Females n (%)	Total n (%)
Subjects in population	632	626	632	644	465	2999
Vaccinated at						
Vaccination 1	630 (99.7)	625 (99.8)	632 (100)	641 (99.5)	463 (99.6)	2991(99.7)
Vaccination 2	621 (98.3)	616 (98.4)	626 (99.1)	635 (98.6)	457 (98.3)	2955 (98.5)
Vaccination 3	619 (97.9)	610 (97.4)	625 (98.9)	630 (97.8)	450 (96.8)	2934 (97.8)
Subject Disposition						
Completed	**607 (96.0)**	**604 (96.5)**	**619 (97.9)**	**624 (96.9)**	**440 (94.6)**	**2894 (96.5)**
Discontinued	**25 (4.0**)	**22 (3.5)**	**13 (2.1)**	**20 (3.1)**	**21 (4.5)**	**101 (3.4)**
Adverse Events	0 (0.0)	0 (0, 0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)
Lost to Follow up	12 (1.9)	8 (1.2)	10 (1.6)	6 (0.9)	10 (2.2)	46 (1.5)
Physician Decision	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.1)
Pregnancy	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)
Protocol Violation	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.1)
Withdrawal by Subjects	12 (1.9)	13 (2.1)	2 (0.3)	13 (2.0)	8 (1.7)	48 (1.6)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	4 (0.1)

Source: Adapted from STN 125508/0.43, Module 1.11.3_Table 2 (p18-19).

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Adolescent-Adult Immunobridging Substudy

Table 37 displays the non-inferiority analysis of Month 7 type-specific anti-HPV antibody GMTs comparing 9- to 15-year-old boys and girls to 16- to 26-year-old young women in the PPI population. For each vaccine HPV type, the LB 95% CI for the GMT ratio exceeded 0.67. Therefore, the success criterion was met, supporting the conclusion that GMTs in 9- to 15-year-olds were non-inferior to those in 16- to 26-year-old young women. In fact, antibody GMTs were higher in 9-15 year-olds than in 16-26 year old young women, with GMT ratios ranging from 1.83 to 3.35 and LB 95% CI exceeding 1.7 for all HPV types. The results from the analysis in the ANSS population were similar to the results from the PPI analysis population.

Table 37: Non-Inferiority Analyses of Month 7 Anti-HPV Antibody Geometric Mean Titers (GMT) Comparing Boys and Girls 9 through 15 Years of Age with Young Women 16 through 26 Years of Age (Study V503-002, Per-Protocol Immunogenicity Population)

Antibody Assay	Group A (N=630) n/GMT	Group B (N=641) n/GMT	Group C (N=463) n/GMT	A/C GMT Ratio [95% CI]	B/C GMT Ratio [95% CI]
Anti-HPV 6	503/1703.1	537/2083.4	328/900.8	1.89 [1.68, 2.12]	2.31 [2.06, 2.60]
Anti-HPV 11	503/1291.5	537/1486.3	332/706.6	1.83	2.10

Antibody Assay	Group A (N=630) n/GMT	Group B (N=641) n/GMT	Group C (N=463) n/GMT	A/C GMT Ratio [95% CI]	B/C GMT Ratio [95% CI]
				[1.63, 2.05]	[1.88, 2.36]
Anti-HPV 16	513/6933.9	546/8683.0	329/3522.6	1.97 [1.75, 2.21]	2.46 [2.20, 2.76]
Anti-HPV 18	516/2148.3	544/2855.4	345/882.7	2.43 [2.13, 2.80]	3.23 [2.83, 3.70]
Anti-HPV 31	506/1894.7	543/2255.3	340/753.9	2.51 [2.12, 2.79]	2.99 [2.63, 3.40]
Anti-HPV 33	518/985.8	544/1207.4	354/466.8	2.11 [1.88, 2.37]	2.59 [2.31, 2.90]
Anti-HPV 45	518/707.7	547/912.1	368/272.2	2.60 [2.25, 3.00]	3.35 [2.90, 3.87]
Anti-HPV 52	517/926.2	545/1055.5	337/419.6	2.21 [1.96, 2.49]	2.52 [2.22, 2.84]
Anti-HPV 58	516/1289.0	544/1593.3	332/590.5	2.18 [1.94, 2.46]	2.70 [2.40, 3.03]

Source: Adapted from STN 125508/0.43, Module 1.11.3, Tables 3 and 4 (p 20-1)
All subjects in these analyses received the same lot of 9vHPV (Lot 1). Group A: 9-15 year old females; Group B: 9-15 year old males; Group C: 16-26 year old females.
N=Number of subjects who were randomized to the respective vaccination group and received at least one injection.
n=Number of subjects contributing to the analysis.

Manufacturing Lot Consistency Substudy

Table 38 displays the analysis of type-specific Month 7 anti-HPV antibody GMT comparing subjects in the PPI population randomized to the 3 manufacturing lots of 9vHPV vaccine. For each HPV type, the 95% CI of the GMT ratio for all three pairwise comparisons was contained between the interval (0.5, 2.0), which was the pre-specified success criterion for lot consistency. Overall, for all HPV vaccine types, the Month 7 anti-HPV GMT responses from the 3 manufacturing lots of 9vHPV vaccine were consistent.

Table 38: Lot Consistency Analyses of 9vHPV Anti-HPV Antibody Geometric Mean Titers (GMT) at Month 7 (Study V503-002, PPI Population)

Antibody Assay	Lot 1 GMT/Lot 2 GMT Ratio [95% CI]	Lot 1 GMT/Lot 3 GMT Ratio [95% CI]	Lot 2 GMT/Lot 3 GMT Ratio [95% CI]
Anti-HPV 6	1594.3/1655.5 0.96 [0.87, 1.07]	1594.3/1546.5 1.03 [0.92, 1.15]	1655.5/1546.5 1.07 [0.96, 1.20]
Anti-HPV 11	1219.6/1233.6 0.99 [0.89, 1.10]	1219.6/1136.5 1.07 [0.96, 1.20]	1233.6/1136.5 1.09 [0.97, 1.22]
Anti-HPV 16	6429.5/6801.5 0.95 [0.85, 1.05]	6429.5/6411.3 1.00 [0.90, 1.12]	6801.5/6411.3 1.06 [0.95, 1.19]
Anti-HPV 18	1975.5/1990.9 0.99 [0.88, 1.12]	1975.5/1768.2 1.12 [0.98, 1.27]	1990.9/1768.2 1.13 [0.99, 1.28]
Anti-HPV 31	1745.8/1759.1 0.99 [0.88, 1.1a]	1745.8/1693.4 1.03 [0.91, 1.16]	1759.1/1693.4 1.04 [0.92, 1.18]
Anti-HPV 33	917.7/886.8 1.03 [0.93, 1.15]	917.7/867.2 1.06 [0.95, 1.18]	886.8/867.2 1.02 [0.91, 1.14]
Anti-HPV 45	638.4/786.6 0.81 [0.71, 0.93]	638.4/615.5 1.04 [0.91, 1.19]	786.8/615.5 1.28 [1.11, 1.47]
Anti-HPV 52	857.8/954.8 0.90 [0.84, 1.07]	857.8/904.2 0.95 [0.84, 1.07]	954.8/904.2 1.06 [0.94, 1.19]
Anti-HPV 58	1198.9/1271.8 0.94 [0.85, 1.05]	119897/1112.5 1.08 [0.96, 1.21]	1271.8/1112.5 1.14 [1.02, 1.28]

Source: Adapted from STN 125508/0.43, Module 1.11.3, Table 5 (p 22-24)

6.2.11.2 Analyses of Secondary Endpoints

Adolescent-Adult Immunobridging Substudy

Table 39 displays the non-inferiority analysis comparing 9- to 15-year-old boys and girls to 16- to 26-year-old young women with regard to the proportion in the PPI population who became seropositive for each vaccine HPV type by Month 7. The LB 95% CI exceeded -5.0 percentage points, the pre-specified success criterion, for all HPV types.

Table 39: Non-Inferiority Comparison of Month 7 HPV Type-Specific Seroconversion Rates among 9- to 15-Year-Old Boys and Girls and 16- to 26-Year-Old Young Women (Study V503-002, PPI Population)

Antibody Assay	Group A SCR (%)	Group B SCR (%)	Group C SCR (%)	A-C % [95% CI]	B-C % [95% CI]
Anti-HPV 6	99.8%	99.8%	99.7%	0.1 [-0.8, 1.5]	0.1 [-0.8, 1.5]
Anti-HPV 11	100.0%	100.0%	100.0%	0.0 [-0.8, 1.2]	0.0 [-0.7, 1.2]
Anti-HPV 16	100.0%	100.0%	100.0%	0.0 [-0.7, 1.2]	0.3 [-0.7, 1.2]
Anti-HPV 18	99.8%	100.0%	99.7%	0.1 [-0.8, 1.4]	0.3 [-0.4, 1.6]
Anti-HPV 31	100.0%	100.0%	99.7%	0.3 [-0.5, 1.7]	0.3 [-0.4, 1.7]
Anti-HPV 33	100.0%	100.0%	99.7%	0.3 [-0.5, 1.6]	0.3 [-0.4, 1.6]
Anti-HPV 45	99.8%	100.0%	99.5%	0.4 [-0.6, 1.8]	0.5 [-0.2, 2.0]
Anti-HPV 52	100.0%	100.0%	99.7%	0.3 [-0.4, 1.7]	0.3 [-0.4, 1.7]
Anti-HPV 58	100.0%	100.0%	100.0%	0.0 [-0.7, 1.2]	0.0 [-0.7, 1.2]

Source: Adapted from STN 125508/0.43, Module 1.11.3, Tables 6 and 7 (p 25-28).
All subjects in these analyses received the same lot of 9vHPV (Lot 1). Group A: 9-15 year old females; Group B: 9-15 year old males; Group C: 16-26 year old females.
N=Number of subjects who were randomized to the respective vaccination group and received at least one injection. The numbers of subjects who contributed to these analyses are the same as those in Table 37.
SCR=seroconversion rate

Lot Consistency Analyses

Table 40 displays the lot-to-lot comparison of Month 7 HPV type-specific seroconversion rates in the PPI population. Equivalence was established in all 3 pairwise comparisons for each vaccine HPV type.

Table 40: Lot Consistency Analysis by Month 7 HPV Type-Specific Seroconversion Rates (Study V503-002, PPI Population)

Antibody Assay	Lot 1 SCR (%)	Lot 2 SCR (%)	Lot 3 SCR (%)	Lot 1 - Lot 2 % (95%CI)	Lot 1 - Lot 3 % (95%CI)	Lot 2 - Lot 3 % (95%CI)
Anti-HPV 6	99.8	99.8	99.3	-0.0 (-1.0, 0.9)	0.5 (-0.4, 1.7)	0.5 (-0.4, 1.7)
Anti-HPV 11	100	100	99.6	0.0 (-0.8, 0.7)	0.4 (-0.4, 1.4)	0.4 (-0.4, 1.4)
Anti-HPV 16	100	100	99.6	0.0 (-0.7, 0.7)	0.4 (-0.4, 1.3)	0.4 (-0.4, 1.3)
Anti-HPV 18	99.8	100	99.7	-0.2 (-1.1, 0.5)	0.2 (-0.7, 1.1)	0.4 (-0.4, 1.3)
Anti-HPV 31	100	100	99.8	0.0 (-0.8, 0.7)	0.2 (-0.6, 1.0)	0.2 (-0.5, 1.0)
Anti-HPV 33	100	100	99.6	0.0 (-0.7, 0.7)	0.4 (-0.4, 1.3)	0.4 (-0.4, 1.3)
Anti-HPV 45	99.8	100	99.7	-0.2 (-1.1, 0.5)	0.2 (-0.7, 1.1)	0.4 (-0.4, 1.3)
Anti-HPV 52	100	100	99.7	0.0 (-0.7, 0.7)	0.4 (-0.4, 1.3)	0.4 (-0.4, 1.3)
Anti-HPV 58	100	100	99.7	0.0 (-0.7, 0.7)	0.4 (-0.4, 1.3)	0.4 (-0.4, 1.33)

Source: Adapted from STN 125508/0.43, Module 1.11.3, Table 8 (p 29-32)

The numbers of subjects who were randomized to the respective groups and received at least one injection, and the numbers of subjects who contributed to these analyses are the same as those in Table 38.
SCR=seroconversion rate

6.2.11.3 Subpopulation Analyses

In general, antibody responses to each HPV type among ethnic groups and races were similar. Boys had numerically higher anti-HPV antibody responses than girls, and females in younger age category generally had higher anti-HPV antibody responses than older subjects. Subgroup analyses of pooled 9vHPV immunogenicity data from all studies are discussed in Section 7.1.7.2.

6.2.11.4 Dropouts and/or Discontinuations

The overall dropout rate was 3.4% (range 2.0% to 4.7% among the different groups). The small percentage of dropouts likely did not significantly affect the immunogenicity analyses. In addition, the statistical inference from the ANCOVA model is valid under the assumption that the missing data mechanism is ignorable (or missing at random).

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety analyses were performed on all subjects who received at least one dose of the vaccine and had at least one follow up visit.

All subjects were followed for adverse reactions for 15 days after each injection via VRC and for SAEs from Day 1 through 6 Months post-dose 3 regardless of causality.

6.2.12.2 Overview of Adverse Events

Injection-Site Adverse Reactions

Table 41 displays the numbers and percentages of subjects with injection-site adverse reactions (and severe injection site reactions) from Days 1 to 5 following any vaccination visit (reported by ≥1% of subjects in one or more vaccination groups).

In general, the overall rates of injection site reactions were similar among the three groups. Boys 9 through 15 years of age tended to have numerically lower rates of injection site reactions compared with the other two groups, especially for injection site pain, erythema and swelling. The percentages of subjects with injection site reactions following each vaccination were consistent. The percentage of subjects with injection site erythema and swelling increased in each group following the second and the third vaccination. Most of the adverse reactions resolved within one week of onset.

Table 41: Injection-Site Adverse Reactions (Days 1 to 5 Following Any Vaccination) Reported by ≥1% of Subjects in Any Group (Study V503-002)

Adverse Reactions	Intensity Grading	9-15-Year-Old Females (N=1878) n (%)	9-15-Year-Old Males (N=639) n (%)	16-26-Year-Old Females (N=461) n (%)
All Reactions	Any Severe	1533 (81.6) 80 (4.3)	460 (72.0) 5 (0.8)	395 (85.7) 12 (2.6)
Anesthesia	Any Severe	2 (0.1) 0 (0.0)	2 (0.3) 0 (0.0)	5 (1.1) 0 (0.0)
Erythema	Any Severe	567 (29.8) 42 (2.2)	160 (24.9) 12 (1.9)	132 (28.6) 5 (1.1)
Hematoma	Any Severe	31 (1.6) 0 (0.0)	8 (1.2) 0 (0.0)	16 (3.4) 0 (0.0)
Hemorrhage	Any Severe	19 (1.1) 0 (0.0)	4 (0.6) 0 (0.0)	3 (0.6) 0 (0.0)
Induration	Any Severe	19 (1.1) 1 (0.1)	7 (1.1) 1 (0.2)	2 (0.4) 0 (0.0)
Pain	Any Severe	1525 (81.2) 78 (4.2)	457 (71.5) 3 (0.5)	391 (84.8) 16 (3.4)
Pruritus	Any Severe	62 (3.2) 1 (0.1)	6 (0.9) 1 (0.2)	16 (3.4) 0 (0.0)
Swelling	Any Severe	666 (35.5) 86 (4.6)	172 (26.9) 33 (5.2)	151 (32.8) 17 (3.7)

Source: Generated by the clinical review from Table 9 (p33-35) and Table 10 (p36), SNT 125508/0.43, Module 1.11.3

Systemic Adverse Reactions

Table 42 presents the numbers and percentages by MedDRA SOC of subjects with systemic clinical adverse reactions from Days 1 to 15 following any vaccination visit (reported by ≥1% of subjects in one or more vaccination groups). In all vaccination groups, the most common clinical adverse experiences were headache and pyrexia, which occurred at similar frequencies among all demographic groups. The frequency of systemic clinical adverse reactions was similar across vaccination visits among all demographic groups. However, women 16 through 26 years of age had a numerically higher proportion of severe AEs (7.9%), as compared to 9 through 15 year-old girls (5.1%) and boys (4.5%).

Most subjects (>90%) had a maximum temperature below 37.8^{o}C from Days 1 to 5. There was no difference in percentage of subjects with temperature ≥ 37.8^{o}C between 9- to 15-year-old males or females and the 16- to 26-year-old females.

Table 42: Systemic Adverse Events (Days 1 to 15 Following Any Vaccination) by System Organ Class (Reported by ≥ 1% of Subjects in One or More Groups, Study V503-002)

Adverse Events	9- to 15-Year-Old Females n (%)	9- to 15-Year-Old Males n (%)	16- to 26-Year-Old Females n (%)
No. subjects with follow-up No. of subjects with one or more AE	1878 863 (46.0)	639 277 (43.3)	461 266 (57.7)
Ear and labyrinth disorders	**18 (1.0)**	**4 (0.6)**	**6 (1.3)**

Adverse Events	9- to 15-Year-Old Females n (%)	9- to 15-Year-Old Males n (%)	16- to 26-Year-Old Females n (%)
Eye disorders	**13 (0.7)**	**2 (0.3)**	**6 (1.3)**
Gastrointestinal disorders	**220 (11.7)**	**65 (10.2)**	**69 (15.0)**
Abdominal pain	38 (2.0)	11 (1.7)	9 (2.0)
Abdominal pain upper	61 (3.2)	14 (2.2)	10 (2.2)
Diarrhoea	34 (1.8)	15 (2.3)	17 (3.7)
Nausea	37 (2.0)	12 (1.8)	10 (2.2)
Toothache	6 (0.3)	6 (0.9)	7 (1.5)
Vomiting	41 (2.2)	9 (1.4)	8 (1.7)
General disorders and administration site conditions	**260 (13.8)**	**106 (16.6)**	**74 (16.1)**
Fatigue	31 (1.7)	8 (1.3)	13 (2.8)
Feeling hot	5 (0.3)	1 (0.2)	7 (1.5)
Malaise	8 (0.4)	5 (0.8)	9 (2.0)
Pyrexia	195 (10.2)	85 (13.3)	43 (9.3)
Infections and infestations	**270 (14.4)**	**105 (16.4)**	**79 (17.1)**
Gastroenteritis	28 (1.5)	16 (2.5)	2 (0.4)
Influenza	22 (1.1)	9 (1.4)	10 (2.2)
Nasopharyngitis	83 (4.4)	19 (3.0)	23 (5.0)
Upper respiratory tract infection	55 (2.9)	27 (4.2)	16 (3.5)
Urinary tract infection	2 (0.1)	0 (0.0)	5 (1.1)
Injury, poisoning and procedural complications	**39 (2.1)**	**24 (3.8)**	**8 (1.7)**
Musculoskeletal and connective tissue disorders	**78 (4.2)**	**17 (2.7)**	**29 (6.3)**
Back pain	14 (0.7)	3 (0.5)	10 (2.2)
Myalgia	16 (0.9)	1 (0.2)	5 (1.1)
Neck pain	11 (0.6)	3 (0.5)	5 (1.1)
Pain in extremity	20 (1.1)	4 (0.6)	3 (0.7)
Nervous system disorders	**396 (21.1)**	**108 (16.9)**	**119 (25.8)**
Dizziness	52 (2.8)	9 (1.4)	15 (3.3)
Headache	352 (18.7)	98 (15.3)	105 (22.8)
Psychiatric disorders	**4 (0.2)**	**3 (0.5)**	**5 (1.1)**
Reproductive system and breast disorders	**31 (1.7)** 23 (1.2)	**0 (0.0)**	**25 (5.4)**
Dysmenorrhoea		0 (0.0)	17 (3.3)
Respiratory, thoracic and mediastinal disorders	**155 (8.3)**	**34 (5.3)**	**31 (6.7)**
Cough	51 (2.7)	17 (2.7)	7 (1.5)
Oropharyngeal pain	71 (3.8)	12 (1.9)	16 (3.5)
Rhinorrhea	10 (0.5)	4 (0.6)	5 (1.1)
Skin and subcutaneous tissue disorders	**47 (2.5)**	**11 (1.7)**	**21 (4.6)**

Source: Adapted from STN 125508/0.43, Module 1.11.3,Table 11 (p37-38).

Vaccine-Related Systemic Adverse Reactions

Table 43 presents the numbers and percentages by SOC of subjects with systemic clinical adverse reactions from Day 1 to 15 following any vaccination visit (reported by ≥1.0% of subjects in one or more vaccination groups) considered by the investigator to be vaccine-related.

- The most common (≥2.0%) vaccine-related systemic clinical adverse reactions across treatment groups were headache and pyrexia.

- The overall frequency of vaccine-related systemic adverse reactions was higher among 16- to 26-year-old females.
- The overall profile of vaccine-related systemic clinical adverse reactions was generally similar across all demographic cohorts.

Table 43: Vaccine-Related Systemic Adverse Reactions (Days 1 to 15 Following Any Vaccination Visit) by System Organ Class (Reported by ≥ 1% of Subjects in One or More Vaccination Groups, Study V503-002)

Adverse Events	9- to 15-Year-Old Females n (%)	9- to 15-Year-Old Males n (%)	16- to 26-Year-Old Females n (%)
No. subjects with follow-up	1878	639	461
No. of subjects with one or more vaccine-related AE	400 (21.3)	144 (22.5)	121 (26.2)
Gastrointestinal disorders	**68 (3.56**	**25 (3.9)**	**15 (3.3)**
Nausea	24 (1.3)	8 (1.3)	6 (1.3)
General disorders and administration site conditions	**164 (8.7)**	**64 (10.0)**	**57 (12.4)**
Fatigue	19 (1.0)	3 (0.5)	12 (2.6)
Feeling hot	4 (0.2)	1 (0.2)	6 (1.3)
Malaise	6 (0.3)	4 (0.6)	8 (1.7)
Pyrexia	127 (6.8)	57 (8.9)	32 (6.9)
Infections and infestations	**32 (1.7)**	**9 (1.4)**	**8 (1.7)**
Musculoskeletal and connective tissue disorders	**23 (1.2)**	**3 (0.5)**	**7 (1.5)**
Nervous system disorders	**211 (11.2)**	**68 (10.6)**	**54 (11.7)**
Dizziness	32 (1.7)	4 (0.6)	8 (1.7))
Headache	183 (9.7)	60 (9.4)	46 (10.0)
Respiratory, thoracic and mediastinal disorders	**16 (0.8)**	**7 (1.1)**	**1 (0.2)**
Skin and subcutaneous tissue disorders	**10 (0.5)**	**5 (0.8)**	**8 (1.7)**

Source: Adapted from STN 125508/0.43, Module 1.11.3, Table 12 (p39).

6.2.12.3 Deaths

No subject died during the entire course of the study.

6.2.12.4 Nonfatal Serious Adverse Events

Thirty-four subjects (15 from the 9- to 15-year-old female cohort, 11 from the 9- to 15-year-old male cohort, and 8 from the 16- to 26-year-old female cohort) experienced a nonfatal SAE (excluding events of fetal loss) during the entire study period. The rates of these events varied among the 3 demographic cohorts. The most common SAEs were appendicitis and asthma among the 9- to 15-year-old male and female cohorts. All SAEs resolved.

Table 44 presents the SAEs that occurred within 28 days following any vaccination. Two subjects (1 from the 9- to 15-year-old male cohort, and 1 from the 16- to 26-year-old female cohort) experienced SAEs that were considered by the investigator to be vaccine related. Subject 31765 discontinued the study due to asthmatic crisis and did not complete the 3-dose regimen.

Table 44: SAEs Reported by Subjects Immunized with 9vHPV from Day 1 to Day 28 after Any Vaccination (Study V503-002)

Subject Number	SAE	Dose	Day of Onset	Related[a]	Outcome
28763[b]	Acute tonsillitis, Gastritis	3	23	No	Resolved
28668[b]	Pneumonia	2	9	No	Resolved
28195[b]	Asthma	3	3	No	Resolved
28655[b]	Appendicitis	2	16	No	Resolved
28471[b]	Concussion, Tongue injury	1	4	No	Resolved
31765[c]	Asthmatic crisis	1	2	Yes	Resolved
31824[c]	Appendicitis	2	11	No	Resolved
32402[c]	Suicidal ideation	3	8	No	Resolved
31751[c]	Ankle fracture	1	24	No	Resolved
31743[c]	Pharyngotonsillitis	3	2	No	Resolved
31678[c]	Tibia fracture	2	4	No	Resolved
33221[d]	Foot fracture	2	12	No	Resolved
33179[d]	Headache	3	1	Yes	Resolved
32875[d]	Biliary colic	3	25	No	Resolved

Source: Generated by the clinical review from information in STN 125508/0, Module 5.3.5.1.p002, CSR, Table 12-21 (282-296)
[a]As judged by the investigators; [b]9-15 year-old females; [c]9-15 year-old males; [d]16-26 year-old females.

Subject AN 33179, a 21-year-old white female from Belgium, experienced a severe headache, fever, and photophobia on the same day that she received her third dose of 9vHPV. On July 2, 2010, the subject was bitten by a spider and treated with clindamycin (July 5 to 9, 2010). She received her third dose of 9vHPV on July 7, 2010. On the same day (July 7, 2010), she complained of a severe headache, fever and photophobia for which she took paracetamol at home with no improvement. She also reported that she had experienced some neck pain for a few days. On July 8, 2010, she was hospitalized for further observation of neck stiffness, fever (39°C), and headache. She had a normal neurologic examination and terminal neck stiffness. X-rays of the thorax and cervical spine, brain CT, lumbar puncture, urine culture and hemoculture were all negative. On July 9, 2010, both the fever and the infected spider bite were resolved and only a mild headache remained. The subject was discharged on July 10, 2010 with a diagnosis of viral infection or adverse event due to study vaccination. No action was taken with study therapy, and the subject continued in the study. The investigator felt that the headache was related to study therapy.

Reviewer's comment: *Based on the limited information, it is difficult to determine the cause of fever, headache and photophobia. Because of the close temporal association, the events were possibly caused by the vaccination.*

Subject AN 31765, a 10 year-old white male with a history of seasonal allergic rhinitis and bronchial asthma, experienced cough, breathing difficulty and weakness on December 17, 2009 (one day after his first dose of 9vHPV). On December 18, 2009, he was hospitalized due to the asthma crisis with wheezing and moderate breathing difficulty. The asthma crisis was treated with albuterol, prednisone, cephradine, beclomethasone, ipratriopium, and cetrizine. Cough, breathing difficulty and weakness stopped on December 19, 2009. On December 22, 2009, he was discharged from

hospital. The investigator determined that the asthma crisis was possibly related to the vaccine solely based on temporal association.

Reviewer's comment: *The patient had a history of asthma and the most current episode of asthma was one year ago (in December 2008). However, no triggering factor for the asthma crisis was identified. Because of the close temporal association of the asthma crisis and the administration of the vaccine, this reviewer agrees that the asthma crisis is possibly related to the vaccine.*

Reviewer's comment: *After review of case narratives for all of the SAEs including those that occurred not in the 28-day window of vaccination in this study, this reviewer concurs with the Applicant that all of the SAEs other than those discussed in detail above were not related to the study vaccine.*

6.2.12.5 Adverse Events of Special Interest (AESI)

Twenty-two subjects experienced new medical conditions that were potentially indicative of a systemic autoimmune disorder. Among them, 17 subjects reported mild or moderate arthralgia, which resolved shortly after onset in a majority of cases. None of these episodes of arthralgia was considered to be autoimmune disorder or vaccine related by the investigators.

- Among 9- to 15-year-old females: 13 subjects reported arthralgia, 1 subject reported a goiter, 1 subject reported ulcerative colitis, and 1 subject reported vitiligo.
- Among 9- to 15-year-old males: 1 subject reported arthralgia, and 1 subject reported post-traumatic pain.
- Among 16- to 26-year-old females: 3 subjects reported arthralgia, and 1 subject reported androgenic alopecia.

Reviewer's comment: *The Applicant provided individual narratives of subjects AN 30613 (goiter), AN 29201 (vitiligo), AN 33111 (androgenic alopecia) and AN 28183 (ulcerative colitis) in Sections 14.5.1 and 14.5.4 of the clinical study report. Subject AN 30613 had a history of hypothyroidism. Subject AN 29201 noted a single white patch of skin on her face two days post dose 1. Androgenic alopecia and ulcerative colitis occurred approximately six months after the last vaccination in Subjects AN33111 and AN 28183, respectively. The reviewer agrees with the reporting investigators that none of these cases are likely to be related to the vaccine due to either pre-existing medical condition, or lack of a biological plausibility.*

6.2.12.6 Clinical Test Results

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

6.2.12.7 Dropouts and/or Discontinuations

Among the 2999 randomized subjects, a total of 101 subjects (3.4%) discontinued during the entire study period (Day 1 through Month 12). In the opinion of this clinical reviewer, the low dropout rate would not significantly impact safety evaluation. Please refer to Section 6.2.10.2 for reasons for discontinuation.

One subject (AN 31765) discontinued study due to an episode of asthma crisis (discussed above).

6.2.13 Study Summary and Conclusions

6.2.13.1 Summary of Immunogenicity Results

Adult-Adolescent Immunobridging Substudy

Immunogenicity was assessed at 4 weeks after dose 3. The results showed that:

- All three demographic groups responded to vaccination with marked increases in antibody titers to anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibodies in >99% of subjects in the PPI population. Post-dose 3 antibody GMTs were numerically higher in boys and girls 9 through 15 years of age than in girls and women 16- to 26-year-olds.
- Non-inferiority was demonstrated with regard to GMTs and seroconversion rates for Month 7 anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibodies in the 9-15 year-old girls as well as 9-15 year-old boys compared with 16-26 year-old women.

Manufacturing lot consistency substudy

- The three vaccine lots induced consistent antibody responses, in terms of GMTs and seroconversion rates, against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

6.2.13.2 Summary of Safety Data

- The proportion of subjects who reported at least one injection-site adverse reaction within 5 days of any vaccination was generally similar between the 9- to 15-year-old females (1533/1878 [81.6%]) and the 16- to 26-year-old females (395/461 [85.7%]). The percentage of subjects with injection-site adverse experiences was numerically lower among 9- to 15-year-old males (460/639 [72.0%]). The percentages of subjects with injection site reactions following each vaccination were consistent. However, the percentage of subjects with injection site erythema and swelling increased in each group following the second and the third vaccination.
- The proportion of subjects who reported at least one systemic adverse experience within 15 days of any vaccination was generally lower among 9- to 15-year-old females (863/1878 [46.0%]) and 9- to 15-year-old males (277/639 [43.3%]) as compared with 16- to 26-year-old females (266/461 [57.7%]).
- One subject discontinued the study due to an adverse experience, and two subjects experienced an SAE (asthmatic crisis and headache, n=1 each) that was judged to be vaccine-related.
- Four subjects reported adverse events considered to be a systemic autoimmune disorder: goiter, vitiligo, androgenic alopecia, and ulcerative colitis. However, none was deemed vaccine-related.
- During the study period, 42 SAEs were reported during the entire course of the study, including 2 vaccine-related SAEs.
- No subject died during the entire course of the study.
- The overall safety of 9vHPV in this study population was generally similar to the overall safety profile of qHPV and of 9vHPV in the context of study V503-001.

6.2.13.3 Conclusions

Immunogenicity

- Immune responses to HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 following a 3-dose regimen of 9vHPV were non-inferior in 9-15 year-old boys and girls compared with those observed in 16-26 year-old women. These results support the bridging of efficacy findings in 16-26 year-old women to 9-15-year-old boys and girls.
- Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 antibody GMTs at four weeks post-dose 3 were equivalent in 9 through 15 year-old girls randomized to three separate lots of the Final Manufacturing Process, supporting lot-to-lot manufacturing consistency.

Safety

- The 9vHPV vaccine had an acceptable safety profile in 9 through 15 year-old girls and boys and 16 through 26 year-old women.

6.3 Trial #3: V503-009 (Designated as Study 3 in the Draft Package Insert)

Title: A Randomized, Double-Blinded, Controlled with Gardasil (qHPV), Phase 3 Clinical Trial to Study the Immunogenicity and Tolerability of 9vHPV in 9- to 15-Year-old Girls

6.3.1 Objectives

6.3.1.1 Primary Objective

- To demonstrate that administration of 9vHPV induces non-inferior GMTs for serum anti-HPV 16 and anti-HPV 18 compared to qHPV in preadolescent and adolescent girls 9 through 15 years of age.

6.3.1.2 Secondary Objectives

- To evaluate the tolerability of 9vHPV in the girls 9 through 15 years of age.
- To summarize humoral immune responses (including anti-HPV 6, 11, 16, 18, GMTs and seroconversion rates at four weeks post-dose 3) in girls 9 through 15 years of age who received 9vHPV or qHPV.

6.3.2 Design Overview

The study was a qHPV controlled, randomized, double-blinded, multicenter, phase 3 clinical trial to study the immunogenicity and tolerability of 9vHPV in preadolescent and adolescent girls 9 through 15 years of age. Enrolment was stratified 1:1 for 9 to 12 year-old and 13 to 15 year-old girls to ensure comparable representation of both age strata. The planned study duration for each subject was 7 months.

6.3.3 Population

The study population included 9 through 15 year-old healthy girls, who had:

- Not yet experienced coitarche and did not plan on becoming sexually active during the study period.
- No known allergy to any vaccine component or history of severe allergic reaction that required medical intervention.
- No history of immunosuppressive condition or treatment or autoimmune condition
- Not previously received a marketed HPV vaccine or participated in an HPV vaccine clinical trial.

- No history of a positive HPV test.

6.3.4 Study Treatments or Agents Mandated by the Protocol

6.3.4.1 Treatment

Please refer to Section 6.1.4 for details of study treatment.

6.3.4.2 Batch number used in this Study

The 9vHPV Vaccine: WL00034579 (expiry date: 27 May 2012).
The qHPV Vaccine: WL00029942 (expiry date: 11 June 2011) and WL00040674 (expiry date: 23 October 2013).

6.3.5 Directions for Use

Refer to Section 6.1.5.

6.3.6 Sites and Centers

Twenty-four centers participated to the study: 3 in Belgium, 4 in Denmark, 4 in Finland, 3 in Italy, 5 in Spain and 5 in Sweden. The number of subjects enrolled in each center ranged from 4 to 69, with the majority of the centers enrolled around 20 subjects.

6.3.7 Surveillance/Monitoring

All subjects were randomized to a standard 3-dose regimen (Day 1, Month 2, Month 6) of either 9vHPV or qHPV. Serum samples were collected at Day 1 before vaccination and Month 7 for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody assays. The primary time point for comparison of immune responses was Month 7, i.e. approximately 4 weeks following the third vaccination.

Safety information was collected Day 1 through approximately 4 weeks following the third vaccination or for a total of approximately 7 months for each subject as scheduled in the protocol.

6.3.8 Endpoints

6.3.8.1 Immunogenicity

- Primary immunogenicity endpoints: cLIA GMTs for anti-HPV 16 and 18 antibodies at 4 weeks post-dose 3.
- Secondary immunogenicity endpoints: cLIA GMTs for anti-HPV 6 and 11 antibodies at 4 weeks post-dose 3 and cLIA seroconversion rates for each of anti-HPV 6, 11, 16 and 18 antibodies by 4 weeks post-dose 3.

6.3.8.2 Safety

Safety assessment focused on the injection site adverse reactions and elevated temperatures during Day 1 to Day 5 post-vaccination and systemic adverse events during Day 1 to Day 15 post-vaccination, reported on the VRC. In addition, SAEs were collected regardless of causality throughout the study.

6.3.9 Statistical Considerations and Statistical Analysis Plan

The sample size and power calculations were based on the primary immunogenicity endpoints. It was expected that there would be an approximately 20% exclusion rate from the Per Protocol Set (PPS) used for the primary analyses. Thus, with a total sample size of 600 enrolled subjects, the primary analysis would include 480 girls (240 in each group)., The true GMT ratio was assumed to be 1, and the standard deviation was estimated at 1.2 for both the anti-HPV 16 and 18 post-vaccination antibody titers (natural log scale). The statistical criterion for non-inferiority required that the LB of the two-sided 95% CI for the GMT ratio (9vHPV vs. qHPV) be greater than 0.67 for each of the HPV types 16 and 18. Based on 240 evaluable subjects per group and the above assumptions, the study would have over 90% power to demonstrate the non-inferiority of 9vHPV compared to qHPV for anti-HPV 16 and 18 antibody responses.

Descriptive summaries of adverse event rates were provided for each group, and comparisons were made between subjects receiving the 9vHPV vaccine and those receiving the qHPV vaccine.

No multiplicity adjustment was conducted and no interim analysis was planned.

For immunogenicity assessments, results below the lower limit of quantification were imputed to half of the detection limit, and results above the upper limit of quantification were imputed to the upper limit. There was no other imputation for missing data.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

The planned and enrolled numbers of subjects were 600 in total and 300 per arm.

Per Protocol Immunogenicity (PPI) Population
The PPI population served as the primary set of subjects for the analysis of immune responses to each of the 9 HPV types. To be included in this set of subjects, subjects must:

1. Have received all three vaccinations with the correct dose of the correct clinical material, and each vaccination visit must have occurred within acceptable day ranges as specified in the protocol.
2. Have provided Month 7 serology result within 21 to 49 days post dose 3.
3. Have been seronegative to the relevant HPV type at Day 1.
4. Have had no other protocol violations that could have interfered with the evaluation of subject's immune response to the study vaccine.

Safety Set
Safety analyses included all subjects who received at least 1 study vaccination and had safety follow-up data.

6.3.10.1.1 Demographics

Demographic data and other baseline characteristics were similar for subjects receiving the 9vHPV vaccine and subjects receiving the qHPV vaccine. Table 45 summarizes the demographic characteristics at baseline for the subjects randomized in the study. All subjects were recruited from Europe.

Table 45: Summary of Demographic Characteristics at Baseline (Study V503-009)

Characteristics	9vHPV (n=300)	qHPV (n=300)	Total (n=600)
Age (Years)			
9 to 12	150	150	300
13 to 15	150	150	300
Mean ± SD	12.5 ± 1.9	12.6 ± 1.9	12.6 ± 1.9
Race			
Black	1 (0.3%)	1 (0.3%)	2 (0.3%)
White	296 (98.7%)	294 (98.0%)	590 (98.3%)
Asian	0 (0.0%)	1 (0.3%)	1 (0.2%)
Multi-Racial	3 (1.0%)	4 (1.3%)	7 (1.2%)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p009, CSR, Table 10-5 (p69)

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Overall, 34.1% of the subjects received concomitant medications between Day 1 and Day 15 following any vaccination (32.4% in the group receiving 9vHPV vaccine and 35.7% in the group receiving qHPV vaccine). The most frequently reported concomitant medications were analgesics (16.2%), anti-inflammatory and anti-rheumatic products (15.2%), antibacterial for systemic use (4.0%), cough and cold preparations (2.8%) and antihistamines for systemic use (2.7%).

6.3.10.1.3 Subject Disposition

A total of 603 subjects were screened, and of those 600 subjects were enrolled in the study. The disposition of subjects is presented in Table 46.

Table 46: Disposition of Study Subjects (Study V503-009)

	9vHPV N (%)	qHPV N (%)	Total N (%)
Randomized	300	300	600
Received at least one dose	300 (100%)	300 (100%)	600 (100%)
Received only one dose	2 (0.7%)	0 (0.0%)	2 (0.3%)
Received only two doses	2 (0.7%)	4 (1.3%)	6 (1.0%)
Received all three doses	296 (98.7%)	296 (98.7%)	592 (98.7%)
Completed the study	294 (98.0%)	295 (98.3%)	589 (98.2%)
Subject withdrew	6 (2.0%)	5 (1.7%)	11 (1.8%)
Adverse events	1 (0.3%)	1 (0.3%)	2 (0.3%)
Withdrawal of consent	2 (0.7%)	3 (1.0%)	5 (0.8%)
Protocol violation	1 (0.3%)	0 (0.0%)	1 (0.2%)
Lost to follow-up	2 (0.7%)	1 (0.3%)	3 (0.5%)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p009, CSR, Table 14.1 (p110)

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoints

The primary analysis was the non-inferiority comparison of post-dose 3 anti-HPV 16 and 18 antibody GMTs for 9vHPV versus qHPV in the PPS population. As seen from Table 47, non-inferiority of antibody response to 9vHPV compared to qHPV was demonstrated

for HPV types 16 and 18 since the LB of the two-sided 95% CI of anti-HPV GMT ratio (9vHPV/qHPV) was greater than 0.67 for both HPV types.

Similar non-inferiority was also demonstrated for HPV types 6 and 11 (Table 47). In addition, all subjects in the PPS population in both groups seroconverted against HPV types 6, 11, 16 and 18 (Table 47).

Table 47: Comparison of Immune Responses Between 9vHPV and qHPV for HPV 6, 11, 16 and 18 in PPI Population of 9 through 15 Year-old Girls (Study V503-009, PPI population)

Antibody Assay	9vHPV[1] %SC (95% CI)	qHPV[1] %SC (95% CI)	9vHPV[1] GMT mMU/ml (95% CI)	qHPV[1] GMT mMU/ml (95% CI)	9vHPV/qHPV GMT Ratio (95% CI)
Anti-HPV6	100 (98.7, 100)	100 (98.6, 100)	1679 (1519, 1857)	1566 (1412, 1736)	1.07 (0.93, 1.23)
Anti-HPV11	100 (98.7, 100)	100 (98.6, 100)	1316 (1184, 1462)	1417 (1274, 1577)	0.93 (0.80, 1.08)
Anti-HPV16	100 (98.7, 100)	100 (98.6, 100)	6740 (6135, 7404)	6887 (6221, 7626)	0.97 (0.85, 1.11)
Anti-HPV18	100 (98.7, 100)	100 (98.6, 100)	1957 (1737, 2204)	1795 (1567, 2057)	1.08 (0.91, 1.29)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p009, CSR, Tables 11.1, 11.2 and 11.3 (p75-76)
[1]The numbers of individuals contributing to the analysis for HPV 6, 11, 16 and 18 were 273, 273, 276 and 276, respectively in 9vHPV group, and 261, 261, 270 and 269, respectively in qHPV group. The numbers of individuals randomized to each group were 300.
PPI=Per protocol immunogenicity
SC=Seroconversion

6.3.11.2 Analyses of Secondary Endpoints

Please refer to Section 6.3.11.1 for comparisons between 9vHPV and qHPV of anti-HPV 6 and 11 antibody GMTs and of seroconversion rates for HPV types 6, 11, 16 and 18.

6.3.11.3 Subpopulation Analyses

No subpopulation analysis was conducted for this study, as subpopulation analyses were conducted for the integrated immunogenicity data as described in Section 7.1.7.2.

6.3.11.4 Dropouts and/or Discontinuations

Overall, 11 subjects (1.8%) withdrew from the study: 6 subjects (2.0%) in 9vHPV group and 5 (1.7%) in qHPV group.

Reviewer's comment*: The low dropout rate in this study would not have significant impact on the immunogenicity results.*

6.3.12 Safety Analyses

6.3.12.1 Methods

Please refer to Section 6.2.12.1.

6.3.12.2 Overview of Adverse Events

In total, 599 subjects were enrolled and included in the safety database, 299 subjects in 9vHPV group and 300 subjects in qHPV group. Overall 287 subjects (96.0%) in the 9vHPV group and 281 subjects (93.7%) in the qHPV group reported at least one adverse event during the entire study. Vaccine related adverse events were reported for 93.3% of 9vHPV recipients and 90.3% of qHPV recipients from Day 1 to Month 7.

Injection-Site Adverse Reactions

Table 48 summarizes the numbers and percentages of subjects reporting at least one injection-site adverse reaction from Day 1 to Day 5 following any dose of vaccine. The most frequent injection-site reaction was injection-site pain, reported with similar percentages for both vaccines. Injection-site swelling was more frequently reported with 9vHPV (47.8%) compared with qHPV (36.0%), with a risk difference of 11.8% [95% CI: (3.9, 19.6)]. Other injection-site reactions were similar between the two groups in terms of frequencies and severity. No injection site bruising or mass was reported in either group.

Injection-site reactions were overall reported with the same frequency after each dose. Consistent with the results observed in Studies V503-001 and V503-002, injection site swelling and erythema tended to be more frequent after Dose 2 and Dose 3.

Table 48: Injection-Site Adverse Reactions Reported 1 to 5 days Post-Vaccination at a Frequency of ≥1% (Study V503-009 Safety Population)

Adverse Reactions	**Intensity**	**9vHPV (N=299) n (%)**	**qHPV (N=300) n (%)**
All Injection Site Reactions	Total	267(89.3)	265 (88.3)
	Mild	139 (46.5)	157 (52.3)
	Moderate	111 (37.1)	96 (32.0)
	Severe	17 (5.7)	12 (4.0%)
Erythema	Total	102 (34.1)	88 (29.3)
	Mild	86 (28.8)	67 (22.3)
	Moderate	11 (3.7)	15 (5.0)
	Severe	5 (1.6)	6 (2.0)
Hematoma	Total	11 (3.7)*	14 (4.7)
	Mild	10 (3.3)	12 (4.0)
	Moderate	0 (0.0)	0 (0.0)
Hemorrhage	Total	3 (1.0)	6 (2.0)
	Mild	3 (1.0)	5 (1.7)
	Moderate	0 (0.0)	1 (0.3)
Induration	Total	6 (2.0)	3 (1.0)
	Mild	2 (0.7)	2 (0.7)
	Moderate	4 (1.3)	1 (0.3)
Pain	Total	267 (89.3)	265 (88.3)
	Mild	142 (47.5)	158 (52.7)
	Moderate	108 (36.1)	97 (32.3)
	Severe	17 (5.7)	10 (3.3)
Pruritus	Total	12 (4.0)	8 (2.7)
	Mild	8 (2.7)	6 (2.0)
	Moderate	4 (1.3)	1 (0.3)
	Severe	0 (0.0)	1 (0.3)

Adverse Reactions	**Intensity**	**9vHPV (N=299) n (%)**	**qHPV (N=300) n (%)**
Reaction	Total Mild Moderate	1 (0.3) 0 (0.0) 1 (0.3)	3 (1.0) 3 (1.0) 0 (0.0)
Swelling	Total Mild Moderate Severe	143 (47.8) 100 (33.4) 25 (8.4) 18 (6.0)	108 (36.0) 68 (22.7) 21 (7.0) 19 (6.3)
Warmth	Total Mild Moderate Severe	2 (0.7) 2 (0.7) 0 (0.0) 0 (0.0)	5 (1.7) 3 (1.0) 1 (0.3) 1 (0.3)

Source: Generated by CBER reviewer from STN 125508/0, Module 5.3.5.1.p009_CSR, Tables 14.48 (p175-6) and 14.49 (p177).
N=Number of subjects vaccinated, n=number of subjects with the respective events.
*Missing intensity data for one subject.

Systemic Adverse Events

Systemic adverse events, regardless of assessed causality, were reported for 47.5% of the 9vHPV recipients and 52.0% of qHPV recipients. Table 49 summarizes the proportions of subjects (≥ 1% in either treatment group) with systemic adverse events from Day 1 to Day 15 following any dose of vaccine that were considered to be vaccine-related by the reporting investigators. The most frequently reported systemic adverse reactions were headache, pyrexia, nausea and orpharyngeal pain. There were no statistically significant differences between 9vHPV and qHPV in vaccine-related systemic adverse reactions except for fatigue, which was more frequent in the qHPV group.

Table 49: Summary of Vaccine-Related Systemic Adverse Reactions Reported at A Frequency of ≥ 1% in at Least One Group from Day 1 to Day 15 Following Any Dose (Study V503-009 Safety Population)

Adverse Reactions	9vHPV (N=299) n (%)	qHPV (N=300) n (%)
Total vaccine-related systemic adverse reactions	62 (20.7)	73 (24.3)
Abdominal pain upper	5 (1.7)	4 (1.3)
Fatigue	0 (0.0)	8 (2.7)
Headache	34 (11.4)	34 (11.3)
Nausea	9 (3.0)	11 (3.7)
Oropharyngeal pain	8 (2.7)	2 (0.7)
Pyrexia	15 (5.0)	8 (2.7)
Upper respiratory tract infection	1 (0.3)	3 (1.0)

Source: Adapted STN 125508/0, Module 5.3.5.1.p009_CSR, Tables 12.9 (p92-3).
N=Number of subjects vaccinated, n=number of subjects with the respective events.

6.3.12.3 Deaths

No death was reported in this study.

6.3.12.4 Nonfatal Serious Adverse Events

Three subjects (two in the qHPV group and one in the 9vHPV group) experienced SAEs during the study (from Day 1 to Month 7), none assessed by the Investigator as vaccine-related. The three cases are summarized below.

Subject AN 51204

Subject AN 51204, a 13-year-old white girl from Spain, developed pulmonary vasculitis and anemia diagnosed approximately 2 months after receiving the second dose of 9vHPV on 23 June 2011. She had received a first dose of 9vHPV on 19 April 2011. The subject was healthy, with no relevant medical family history. She had menarche in December 2010, with cycles every 15-20 days, lasting approximately 5 days, with profuse bleeding. She had been hospitalized in March 2011 for abdominal pain due to ovarian cyst.

On 1 September 2011, the subject presented to medical attention with tiredness for approximately four months, dyspnea for two months, tachycardia on slight exertion, and appetite decrease with weight loss of 5 kg since the symptoms started. She had an episode of fever (max. 39.5°C). Lab tests showed anemia. Chest X-ray showed baseline multifocal disease with poorly defined “nodular” images in both the inferior lobes, indicating edema or hemorrhage, with probable interstitial thickening. The subject was hospitalized on 8 September 2011. Lab investigations on admission showed hemoglobin 8.4 g/dl, leukocytes 4,130/mm^3 (59% neutrophils, 30% lymphocytes, 5.3% monocytes), platelets 355,000/mm^3, ESR 40 mm (the first hour), iron 31 mcg/dL, transferrin saturation index 13%, and LDH 421 IU/l. Complement testing (C2, C3, C4, CH50) was within normal range. Antinuclear Antibodies (ANA) were positive at 1/1280 as well as anti-DNA antibodies; Anti-neutrophils cytoplasmic antibodies (ANCA), anti-proteinase 3, antimyeloperoxidase, antireticulin, and anti-glomerular basement membrane antibodies testing were all negative. Anti-transglutaminase and antiendomysial antibodies were negative. Viral serology were negative (HBV, HCV, HIV, herpes simplex virus, CMV, Adenovirus and Parvovirus B19). Chest CT scan showed extensive diffuse bilateral opacities predominantly in the inferior lobes, and small parenchymatous consolidations in both lung bases, also in the middle lobe. Lung function tests showed lung disorder of restrictive nature consistent with the suspected diagnosis of vasculitis or hemosiderosis. Fibrobronchoscopy showed that bronchial trees contained erythematous mucosa and traces of blood, both old and recent, combined with small areas of inflammation of the interalveolar septum (focal capillaritis).

The subject received oral ferrous sulphate, cyclophosphamide (planned for 6 courses) and oral prednisone. During hospitalization, her condition gradually improved. She was discharged on 5 October 2011. Final diagnosis was isolated pulmonary capillaritis with positive ANA and multifactorial anemia. Anemia was mainly related to profuse menstrual bleeding cycles before the current disease but was exacerbated by diffuse alveolar hemorrhage secondary to main diagnosis. It was considered to be resolved on 5 December 2011 as the last hemoglobin (1 December 2011) was 13.8 g/dL. The latest information received on March 2012 was that the subject was asymptomatic since 21 December 2011, considered as the date of resolution of the pulmonary vasculitis. Thoracic CT-scan showed resolution of previous lesions. ANA: 1/1280 with anti-DNA antibody: 25 (Normal: 0-10) on 12 September 2011; and ANA: 1/320 with anti-DNA

antibody: 13 on 03 February 2012. The subject had received 5 courses of cyclophosphamide. Prednisone was stopped on 23 February 2012.

The subject was withdrawn from the study due to adverse event, because the drug used to treat pulmonary capillaritis was immunosuppressive.

According to the investigator, the diagnosis of diffuse alveolar hemorrhage secondary to focal pulmonary capillaritis, together with the high level of antinuclear antibodies, suggested an underlying connective tissue disease. Anemia was mainly related to profuse menstrual bleeding cycles before the current disease but was exacerbated by diffuse alveolar hemorrhage. The investigator assessed the relationship of both SAEs as not vaccine-related.

Reviewer's comments*: This reviewer agrees with the reporting investigator that anemia was most likely due to profuse menstrual bleeding.*

An information request (IR) was sent to the Applicant on September 16, 2014 requesting a rationale for assessing the pulmonary vasculitis as vaccine unrelated. On October 10, 2014, the Applicant submitted a response to STN 125508 and confirmed its assessment that the event was unlikely related to the vaccine because the subject was ANA positive before vaccination. Although the subject was ANA positive (ANA titer: 1/320) at baseline, the ANA titer at the onset of pulmonary vasculitis increased to 1/1280, and was reduced to the baseline level (i.e., 1/320) when symptoms resolved after treatment with cyclophosphamide and prednisone*. Based on the provided information, the condition appears to have been preexisting. However, given that the subject became symptomatic and her ANA titers increased post vaccination it is impossible to exclude vaccine-induced exacerbation.*

Subject AN 51128

Subject AN 51128, a 14-year-old white girl from Sweden, experienced partial complex epilepsy 36 days after she had received her first dose of qHPV on 2 April 2011. The subject had no familial history of neurological disease or epilepsy. On 08 May 2011, she had a left-sided occipital headache after a run. She went to bed and was woken up by her father about one hour later. He found that she had 'aberrant rapport', but thought that this was due to the fact that she was half asleep. She slept for another hour and when she woke up she still had a headache, vomited once and was dysphasic. When she arrived at the Emergency Unit Care her condition worsened. She could not orientate herself in time or place. The right pupil was dilated but reacted normally to light. She also had episodes similar to apnea. She was admitted to the hospital. A CT scan of the skull, MRI, chest X-ray and lumbar puncture were normal. EEG showed several short seizures starting in the left temporal lobe but also regional slowing. She was treated with Oxacarbezin. The subject's condition improved and she was discharged on 16 May 2011. She received her Dose 2 and Dose 3 of qHPV and did not experience any adverse event. The latest information received on March 2012 was that the subject was doing fine. She was still treated with Oxacarbezin and had no more seizures.
The Investigator assessed the event was not related to study vaccine or study procedure.

Reviewer's comments*: This reviewer agrees with the reporting investigator that the event was unlikely related to the qHPV vaccine based on a negative work-up that did not*

point to an inflammatory or immune mediated event that might implicate the vaccine and based on the de novo presentation and unknown etiology of most epilepsy diagnoses.

Subject AN 50011

Subject AN 50011, a 12 year-old white girl from Finland, experienced a Henoch-Schönlein purpura of moderate intensity 46 days following administration of the second dose of qHPV on 2 May 2011. The subject was healthy and was not taking any concomitant treatment. On 15 June 2011 the subject had otitis media treated with Amoxicillin trihydrate and ciproxinhydrocortison eardrops. On 17 June 2011 purpura and swelling of lower limbs and hands were noticed. Amoxicillin and eardrops were stopped. Then the subject complained of stomach pain and had diarrhea and arthralgia in elbow, wrists and calves. She was hospitalized on 24 June 2011. Physical exam was normal except tender calves. Lab tests showed leukocytosis at 14,000 with mainly neutrophils at 66%, hemoglobin at 145, CRP at 64 and normal thrombocytes value. Urine sample showed 10 leukocytes and 5 erythrocytes per visual fields. The subject was treated with cefuroxim with paracetamol for pain. On 26 June 2011 the urine culture did not show any pathogens, and antibiotics were stopped. Urine albumin/creatinine ratio was (slightly) increased at 5.42 mg/mmol. The subject was discharged in good general condition on 26 June 2011. Henoch-Schönlein purpura was diagnosed. On 7 July 2011 the subject still had petechiae without other symptoms. Lab test showed 1 erythrocyte per visual fields. Urine albumin/creatinine ratio was increased at 13.6 mg/mmol. She had two other site visits on 18 August 2011 and 01 September 2011. On 10 November 2011 the subject was considered as recovered, as her physical examination was normal as well as all lab values. The subject was withdrawn from the study due to the serious adverse event. The investigator assessed the adverse event as not related to study vaccine or procedure.

Reviewer's comments*: Considering that about 50% of cases of Henoch-Schönlein purpura are preceded by an upper respiratory infection, the otitis media preceding the disorder is a much more likely etiology than qHPV. This reviewer concurs with the investigator's assessment of causality.*

6.3.12.5 Adverse Events of Special Interest (AESI)

Overall 8 subjects presented with a new condition potentially indicative of an autoimmune disorder: 3 subjects receiving 9vHPV vaccine and 5 subjects receiving qHPV vaccine.

Subjects receiving 9vHPV vaccine:

- One subject (AN 51204) experienced an SAE considered of isolated pulmonary capillaritis with positive ANA, which was diagnosed approximately two months after the second dose of 9vHPV vaccine. The isolated pulmonary capillaritis was considered not to be related to 9vHPV by the reporting investigator. As discussed in Section 6.3.12.4 above, the pulmonary vasculitis was likely a pre-existing condition. However, exacerbation by the vaccination could not be ruled out.
- Knee pain was reported for one subject (AN 51154) 33 days after Dose 1 and joint pain in arms for one subject (AN 50113) 3 days after Dose 1. None of these conditions were assessed as vaccine-related and the investigator did not consider that they were autoimmune conditions. This reviewer concurs that knee

pain and joint pain reported in these two subjects are unlikely autoimmune conditions. Please refer to the Reviewer's comments below.

Subjects receiving qHPV vaccine:

- One subject (AN 50011) experienced an SAE of Henoch-Schönlein purpura that started 46 days after Dose 2. The narrative of this subject is presented in Section 6.3.12.4 above.
- Alopecia areata was reported in an 11-year old girl (AN 50205) 3 days after Dose 3 of qHPV vaccine. The event was of mild intensity, considered to be an autoimmune condition and not related to qHPV by the Investigator. The subject had not yet recovered at the end of the study. This reviewer concurs with the investigator that alopecia areata is an autoimmune condition. However, this reviewer considers the event as possibly related to the qHPV vaccine because of the temporal association. In addition, alopecia areata was also reported in the package insert of Gardasil, two cases of alopecia areata in Gardasil group (N=3093) and none in placebo control group (N=2303).
- Knee pain was reported for subjects AN 51114 and AN 50270 at 14 days after Dose 1 and 98 days after Dose 2, respectively, and was considered by the investigator not to be vaccine-related.
- One subject (AN 51039) experienced arthralgia two days after Dose 3 of qHPV. The event, of mild intensity, lasted 2 days and resolved, was considered by the investigator to be vaccine related but not to be an autoimmune condition.

***Reviewer's comments**: Some cases of knee pain or arthralgia reported in this study were temporally associated with the vaccines. As described in the package insert of Gardasil, the proportions of subjects with arthralgia among subjects who received Gardasil and subjects who received placebo were similar [1.1% in Gardasil (N=10,706), and 1.0% in placebo (N=9,412)]. Based on these results, this reviewer concurs that arthralgia observed in this study is unlikely caused by the vaccines.*

No allergic reactions were deemed related to the vaccine by the investigator. This reviewer concurs with the assessment.

Six subjects experienced one episode of syncope or presyncope during the study, including two episodes after 9vHPV vaccine and four episodes after qHPV vaccine. Of them, three cases were considered by the investigator to be vaccine related (one in 9vHPV and two in qHPV group). All these events were of mild or moderate intensity, and none led to discontinuation.

No pregnancies were reported during the course of the study. No syncope with fall resulting in injury was reported in this study.

6.3.12.6 Clinical Test Results

No clinical laboratory parameters were analyzed for this study.

6.3.12.7 Dropouts and/or Discontinuations

Eleven subjects (1.8%) withdrew from the study, six in 9vHPV and five in qHPV groups. Two subjects, one subject in each group, withdrew from the study due to AE. Please refer to Section 6.3.12.4 for details.

6.3.13 Study Summary and Conclusions

The study was conducted to provide a comparative assessment of the immunogenicity and safety of 9vHPV versus qHPV in girls of 9 through 15 years of age.

A total of 600 girls were enrolled to receive 3 doses of either 9vHPV or qHPV, at Day 1, Months 2 and 6. Post-vaccination anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody titers were evaluated one month after the third dose of study vaccine by cLIA in the per protocol immunogenicity analysis population.

The primary objective, non-inferiority of anti-HPV 16 and 18 antibodies following 9vHPV compared with qHPV, was demonstrated since the lower bound of the two-sided 95% CI of the GMT ratio was greater than 0.67 for both HPV types. In addition, GMTs for anti-HPV 6 and 11 antibodies were non-inferior for 9vHPV compared with qHPV.
The overall safety profile of 9vHPV was similar to that of qHPV with the exception of injection-site swelling (reported by 47.8% of 9vHPV recipients vs. 36.0% of qHPV recipients, $p<0.05$). Importantly, most events of injection-site swelling were mild or moderate in intensity, and the number of subjects reporting severe injection-site swelling was similar in the two groups. Three subjects reported serious adverse events, two of which (1 in each treatment group) were auto-immune in nature and possibly vaccine related.

In conclusion, the immunogenicity data from this study further support the effectiveness of 9vHPV in girls 9 through 15 years of age with respect to prevention of disease due to HPV types 6, 11, 16, and 18, while the safety profile of 9vHPV vaccine in this population is similar qHPV and to the safety profile of 9vHPV observed in the other studies reviewed in this submission.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The 9vHPV vaccine is indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by 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:

- CIN 2/3 and AIS
- CIN 1
- VIN 2/3
- VaIN 2/3
- VIN 1 and VaIN 1
- AIN 1, 2 and 3

The 9vHPV vaccine is indicated in boys 9 through 15 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- AIN Grades 1, 2 and 3

Reviewer's comment: *The Applicant did not conduct a study assessing the efficacy of 9vHPV in preventing anal lesions. Effectiveness of GARDASIL 9 against anal lesions was inferred from the efficacy of GARDASIL against anal lesions caused by HPV types 6, 11, 16 and 18 in men and antibody responses elicited by GARDASIL 9 against the HPV types covered by the vaccine, which was agreed upon by CBER in pre-submission discussions. Please refer to Section 2.5.1.4 for Reviewer's Comments regarding this issue.*

7.1.2 Demographics and Baseline Characteristics

Table 50 presents the basic characteristics of subjects enrolled in the clinical development program for 9vHPV by age group and gender.

For all three populations, the most common race was White, and subjects were mostly of non-Hispanic/Latino ethnicity. Furthermore, the most common regions were Europe, Latin America and North America. Compared with the adult population, the younger female population on average included a higher percentage of White subjects and less subjects of Hispanic or Latino ethnicity. The younger female subjects also were less likely to be from Latin America. Compared with the adult population, the younger male population on average included less subjects of Hispanic or Latino ethnicity, and the regional mix was slightly different with somewhat more subjects from Asia-Pacific and North America and fewer subjects from Europe and Latin America.

Table 50: Subject Characteristics in the Immunogenicity Population of 9vHPV Program (Studies V503-001, -002, -005, -007, and -009)

	16-26 y/o Women[1] N (%)	**9-15 y/o Girls[2] N (%)**	**9-15 y/o Boys[3] N (%)**
Subjects in population	7264	2764	1218
Gender			
Male			1218 (100.0)
Female	7264 (100.0)	2764 (100.0)	
Age (Years)			
Mean ± SD	22 ± 2	12 ± 2	12 ± 2
Median	22	12	12
Range	16 to 26	9-15	9-15
Race			
White	4004 (55.1)	1749 (63.3)	665 (54.6)
Black	281 (3.9)	182 (6.6)	60 (4.9)
Asian	1108 (15.3)	425 (15.4)	199 (16.3)
Other	1871 (25.8)	408 (14.8)	294 (24.1)
Ethnicity			
Hispanic or Latino	2,526 (34.8)	750 (27.1)	381 (31.3)
Not Hispanic or Latino	4,737 (65.2)	2014 (72.9)	837 (68.7)
NULL	1 (<0.1)		

	16-26 y/o Women[1] N (%)	**9-15 y/o Girls[2] N (%)**	**9-15 y/o Boys[3] N (%)**
Region			
Africa	40 (0.6)	95 (3.4)	30 (2.5)
Asia-Pacific	993 (13.7)	413 (14.9)	194 (15.9)
Europe	2531 (34.8)	1102 (39.9)	373 (30.6)
Latin America	2319 (31.9)	545 (19.7)	286 (23.5)
North America	1381 (19.0)	609 (22.0)	335 (27.5)

Source: Adapted from STN 125508/0.43_Module 1.11.3, Table 14-16 (p49-51).
Note: For Protocol 005 and 007, subjects in the concomitant groups were excluded.
[1]Data from Protocol 001 and 002
[2]Data from Protocol 002, 005, 007 and 009
[3]Data from Protocol 002, 005, and 007

7.1.3 Subject Disposition

Table 51 presents subject disposition for subjects enrolled in the clinical development program for 9vHPV by age group and gender. Overall, over 96% of vaccinated subjects completed the vaccination phase of the studies (i.e., received all 3 vaccinations) in each of these three populations. Overall, 353 subjects discontinued from vaccination or from study participation during the vaccination period, and 8 subjects discontinued from the studies due to adverse events (please refer to the discussions in the individual studies). The most common reasons for discontinuation were withdrawal of consent or subjects being lost to follow-up.

Table 51: Disposition of Subjects in Immunogenicity Population (Protocol 001, 002, 005, 007 and 009)[1]

Population and Disposition	16-26 y/o Women[2] N (%)	9-15 y/o Girls[3] N (%)	9-15 yo Boys[4] N (%)
Subjects in Population	7264	2764	1218
Vaccinated at			
Dose 1	7255 (99.9)	2760 (99.9)	1214 (99.7)
Dose 2	7172 (98.7)	2721 (98.4)	1191 (97.8)
Dose 3	7087 (97.6)	2704 (97.8)	1182 (97.0)
Completed	7,012 (96.5)	2675 (96.8)	1174 (96.4)
Discontinued (Total)	244 (3.4)	68 (2.5)	41 (3.4)
Due to Adverse Event	5 (0.1)	1 (0.0)	2 (0.2)
Lost to Follow up	124 (1.7)	28 (1.0)	14 (1.1)
Physician Decision	4 (0.1)	1 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	1 (0.0)	-
Protocol Violation	6 (0.1)	2 (0.1)	1 (0.1)
Withdrawal by Subject	105 (1.4)	35 (1.3)	24 (2.0)
Unknown[5]	8 (0.1)	21 (0.8)	1 (0.1)

Source: Adapted from STN 125508/0.43, Module 1.11.3, Tables 17-19 (p52-54).
Note: For Protocol 005 and 007, subjects in the concomitant groups were excluded.
[1]For Protocol 002 the disposition records were collected Day 1 through Month 12, for all other protocols, the records were collected Day 1 through Month 7.
[2]Data from Protocol 001 and 002
[3]Data from Protocol 002, 005, 007 and 009
[4]Data from Protocol 002, 005, and 007
[5]Unknown: A disposition record did not exist at the time of reporting

7.1.4 Analysis of Primary Endpoint(s)

7.1.4.1 Efficacy Endpoint Analyses

Protocol 001 (V503-001) was the only study that examined histopathologic endpoint efficacy data, which is reviewed in Section 6.1. Therefore, there is no integrated analysis of efficacy.

7.1.4.2 Integrated Analyses of 9vHPV Immunogenicity in 16 through 26 Year-old Women and 9 through 15 Year-old Males and Females

The primary immunogenicity endpoints were antibody GMTs at Month 7 (4 weeks post-dose 3) corresponding to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The secondary immunogenicity endpoints were the Month 7 seroconversion rates for each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. A subject with a cLIA titer at or above the serostatus cutoff for a given HPV type was defined as seropositive for that HPV type (or seroconverted if baseline titers were below the cutoff). The seropositivity cutoffs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 were 30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/mL, respectively.

The PPI populations from Studies V503-001, -002,-005, -007, and -009 (except subjects in the concomitant vaccination groups in Studies 005 and 007) were pooled together as an integrated PPI population for comparison of immunogenicity between subgroups.

Table 52 summarizes the anti-HPV responses in the integrated PPI population across protocols at Month 7 in terms of antibody GMTs and seroconversion rates by HPV types, ages and genders.

The seroconversion rates for each HPV type at Month 7 were generally similar. At least 99.6% of subjects in the integrated PPI population were seropositive for the respective vaccine HPV type at 4 weeks post-dose 3 in all three demographic cohorts.

Both females and males 9 through 15 years of age had higher GMTs for each vaccine HPV type compared with females 16 through 26 years of age. Males 9 through 15 years of age tended to have higher GMTs than females in the same age group.

Reviewer's comments*: The difference in immunogenicity of 9vHPV between children (boys and girls 9 through 15 years of age) and young women 16 through 26 years of age is unlikely caused by the difference in demographics between the young male population and the adult women population. As shown in Section 7.1.7.2 (subgroup analyses), the anti-HPV antibody responses among race, ethnic group and geographic region are similar, and antibody responses in the younger population, regardless of gender, are higher than in the older population.*

For all three cohorts, antibody GMTs at Month 7 were generally consistent within the same cohorts among the different protocols, with variations no greater than 15%.

Table 52: Summary of Month 7 Anti-HPV Antibody Responses in the PPI[1] Population Across Studies (V503-001, -002, -005, -007, and -009)

Population	N[2]	n[3]	GMT (95%CI) mMu/ml	% Seroconversion (95% CI)

Population	N[2]	n[3]	GMT (95%CI) mMu/ml	% Seroconversion (95% CI)
Anti-HPV 6				
9-15 Year-old Girls	2760	2306	1745.0 (1684.4, 1807.8)	99.7 (99.4, 99.9)
9-15 year-old Boys	1214	1033	2087.4 (1982.0, 2192.6)	99.9 (99.5, 100)
16-26 Year-old Women	7255	4321	893.7 (873.5, 914.3)	99.8 (99.6, 99.9)
Anti-HPV 11				
9-15 Year-old Girls	2760	2307	12905 (1244.6, 1338.0)	99.9 (99.7, 100)
9-15 year-old Boys	1214	1033	1468.4 (1395.9, 1544.7)	100 (99.7, 100)
16-26 Year-old Women	7255	4327	669.3 (653.6, 685.4)	100 (99.9, 100)
Anti-HPV 16				
9-15 Year-old Girls	2760	2362	7154.7 (6912.8, 7405.0)	99.9 (99.7, 100)
9-15 year-old Boys	1214	1053	8468.3 (8071.1, 8885.0)	100 (99.6, 100)
16-26 Year-old Women	7255	4361	3159.0 (3088.6, 3231.1)	100 (99.9, 100)
Anti-HPV 18				
9-15 Year-old Girls	2760	2376	2087.6 (2003.6, 2175.0)	99.9 (99.6, 100)
9-15 year-old Boys	1214	1051	2631.7 (2483.2, 2789.2)	100 (99.6, 100)
16-26 Year-old Women	7255	4884	809.9 (789.2, 831.1)	99.8 (99.7, 99.9)
Anti-HPV 31				
9-15 Year-old Girls	2760	2354	1888.7 (1815.9, 1964.3)	100 (99.6, 100)
9-15 year-old Boys	1214	1048	2189.8 (2070.9, 2315.5)	100 (99.7, 100)
16-26 Year-old Women	7255	4806	664.8 (647.4, 682.6)	99.8 (99.6, 99.9)
Anti-HPV 33				
9-15 Year-old Girls	2760	2373	965.0 (931.6, 999.6)	99.9 (99.7, 100)
9-15 year-old Boys	1214	1053	1182.6 (1124.0, 1244.4)	100 (99.7, 100)
16-26 Year-old Women	7255	5056	419.2 (409.6, 429.1)	99.7 (99.5, 99.8)
Anti-HPV 45				
9-15 Year-old Girls	2760	23851056	729.6 (698.2, 762.5)	99.8 (99.6, 100)
9-15 year-old Boys	1214	5160	842.7 (790.4, 898.5)	100 (99.7, 100)
16-26 Year-old Women	72		254.1 (247.0, 261.5)	99.6 (99.4, 99.7)
Anti-HPV 52				
9-15 Year-old Girls	2760	2381	981.8 (946.0, 1018.9)	99.9 (99.7, 100)
9-15 year-old Boys	1214	1054	1072.0 (1015.9, 1131.3)	100 (99.7, 100)
16-26 Year-old Women	7255	4792	382.4 (373.0, 392.0)	99.8 (99.6, 99.9)
Anti-HPV 58				
9-15 Year-old Girls	2760	2353	1309.2 (1262.5, 1357.6)	99.9 (99.7, 100)
9-15 year-old Boys	1214	1050	1558.3 (1481.7, 1638.9)	100 (99.6, 100)
16-26 Year-old Women	7255	4818	489.2 (477.5, 501.2)	99.8 (99.6, 99.9)

Source: Generated by the clinical reviewer from STN 125508/0.43, Module 1.11.3_Tables 20-22 (p55-62)

[1]PPI population consisted of all individuals who received all 3 doses of 9vHPV, did not have major protocol deviations, and were naïve (PCR negative and seronegative) to the relevant HPV types prior to dose 1 and PCR negative from Day 1 through 1 month after dose 3.

[2]N=Number of subjects who were randomized to the respective group and received at least one injection.

[3]n=Number of subjects who contributed to the analysis (i.e., PPI).

***Reviewer's comment**: The number of subjects contributing to each category of the integrated analyses varies depending on the baseline status of HPV positivity for each HPV type.*

7.1.5 Analysis of Secondary Endpoint(s)

Please refer to Section 7.1.4 for the results of seroconversion rates (the secondary endpoints).

7.1.6 Other Endpoints

7.1.6.1 Study of 9vHPV Immunogenicity in Prior Gardasil Recipients (Study V503-006, Designated as Study 4 in the Draft Packaging Insert)

A phase 3 randomized, international, placebo-controlled, double-blind clinical trial was conducted to assess the tolerability and immunogenicity of 9vHPV in females 12-26 years of age who had previously received qHPV.

The number of subjects enrolled in this study was 924: 618 subjects randomized to 9vHPV and 306 subjects randomized to placebo. The two vaccination groups were well balanced with respect to the demographic characteristics. The mean age of randomized subjects was 19 years. All subjects were between 12 and 26 years of age as specified in the protocol, including 182 subjects 12 to 15 years of age, and 742 subjects 16 through 26 years of age. The geographic locations indicated that 44.2% were from Europe, 32.0% were from North America, 18.5% were from Latin America, and 5.3% of the subjects were from the Asia-Pacific region. The largest race/ethnicity category was White (77.3%) followed by Multi-racial (16.1%), Asian (5.8%), Black or African American (0.6%), and American Indian or Alaska Native (0.1%).

Table 53 presents a summary by vaccination group of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody GMTs at Day 1, Month 2, and Month 7, with associated 95% CI's. The results show that antibody GMTs for HPV types 6, 11, 16, and 18 increased substantially following the first vaccination with 9vHPV but did not change much with further vaccinations. Antibody GMTs for HPV types 31, 33, 45, 52, and 58 increased substantially following each of the first and third vaccinations in the 9vHPV vaccine group, while antibody GMTs for subjects in the placebo group remained around or below the assay limits of detection. The highest antibody GMTs for HPV types 6, 11 and 16 were observed at Month 2 in all vaccine groups. For the rest of the six HPV types, the highest antibody GMTs were observed at Month 7.

The seroconversion rates for HPV types 31, 33, 45, 52 and 58 were all ≥98.3% with the LB of the 95% CI ≥96.7% at one month after the third vaccination (data not shown). The results met the pre-specified statistical criterion for success that the LB of the 95% CI for seroconversion rate be greater than 90% for the five new HPV types.

Antibody GMTs were numerically higher in 12- to 15-year-old subjects than in 16- to 26-year-old subjects at both Month 2 and Month 7 (data not shown), which is consistent with other studies in this submission and with previous immunogenicity data for qHPV.

Table 53: Summary of Anti-HPV Antibody GMTs by Vaccination Group (Study V503-006, Modified PPI Population)

Antibody Assay	Time Point	9vHPV N	9vHPV GMT (95% CI)	Placebo N	Placebo GMT (95% CI)
Anti-HPV 6	Day 1	499	348.2 (320.2, 378.8)	248	372.4 (330.6, 419.6)
	Month 2	505	2426.7 (2254.2, 2612.3)	245	363.4 (326.9, 404.0)
	Month 7	511	2207.4 (2052.7, 2373.9)	251	323.8 (291.9, 359.2)
Anti-HPV 11	Day 1	513	253.0 (232.3, 275.6)	261	263.6 (233.8, 297.1)
	Month 2	511	2,077.8 (1,925.9, 2,241.6)	256	253.3 (227.6, 282.0)
	Month 7	515	1,824.0 (1,695.5, 1,962.2)	261	225.4 (203.4, 249.7)
Anti-HPV 16	Day 1	513	1,066.1 (973.8, 1,167.1)	261	1,103.7 (972.2, 1,253.1)
	Month 2	511	13,877.6 (12,846.3, 14,991.7)	256	1,076.1 (964.9, 1,200.1)
	Month 7	515	11,192.8 (10,393.6, 12,053.6)	261	966.9 (871.3, 1,072.9)
Anti-HPV 18	Day 1	513	154.2 (135.4, 175.5)	261	136.1 (113.4, 163.2)
	Month 2	511	2,187.9 (1,975.2, 2,423.5)	256	130.1 (112.6, 150.3)
	Month 7	515	2,285.8 (2,067.4, 2,527.3)	261	112.8 (98.0, 129.9)
Anti-HPV 31	Day 1	513	4.1(<4, 4.5)	261	4.3 (<4, 5.0)
	Month 2	511	201.1 (180.5, 224.0)	256	4.3 (<4, 5.0)
	Month 7	515	260.0 (237.6, 284.5)	261	4.7 (4.1, 5.3)
Anti-HPV 33	Day 1	513	< 4 (<4, <4)	261	< 4 (<4, <4)
	Month 2	511	70.0 (63.2, 77.4)	256	< 4 (<4, <4)
	Month 7	515	175.2 (162.5, 188.9)	261	< 4 (<4, <4)
Anti-HPV 45	Day 1	513	< 3 (<3, <3)	261	< 3 (<3, <3)
	Month 2	511	15.1 (13.5, 16.8)	256	< 3 (<3, <3)
	Month 7	515	97.4 (89.8, 105.7)	261	< 3 (<3, <3)
Anti-HPV 52	Day 1	513	< 3 (<3, <3)	261	< 3 (<3, <3)
	Month 2	511	56.0 (51.2, 61.2)	256	< 3 (<3, <3)
	Month 7	515	264.1 (244.6, 285.1)	261	< 3 (<3, <3)
Anti-HPV 58	Day 1	513	< 4 (<4, <4)	261	< 4 (<4, <4)
	Month 2	511	83.2 (76.4, 90.5)	256	< 4 (<4, <4)
	Month 7	515	269.7 (250.8, 290.0)	261	< 4 (<4, <4)

Source: Adapted from STN 125508/0, Module 5.3.5.1.p006_ CSR, Table 10-11 (p118-120)
The modified PPI population includes all subjects who did not have general protocol violations, received all 3 vaccinations within acceptable day ranges, and had a Month 7 serum sample collected within an acceptable day range.
The numbers of subjects who were randomized to 9vHPV and the placebo groups and received at least one injection were 615 and 306, respectively. N = Number of subjects contributing to the analysis.

7.1.6.2 Antibody Responses to the 9vHPV vaccine among Prior qHPV Recipients (Study V503-006) Compared with Subjects Naïve to HPV Vaccination (Studies V503-001, -002, -005, -007 and -009)

Table 54 shows summaries of Month 7 anti-HPV antibody responses among 12 to 26 year-old females who had previously completed 3 doses of qHPV and received 9vHPV in Protocol V503-006, compared with the same age group of HPV vaccine-naïve females who received 9vHPV in Protocols V503-001, -002, -005 (non-concomitant arm), -007 (non-concomitant arm), and -009. Summaries are provided within two age strata (12- to 15-year-old and 16- to 26-year-old subjects).

- The 9vHPV vaccine was immunogenic, both in prior qHPV recipients and in subjects naïve to HPV vaccination, as shown by high seroconversion rates (>99%) for all vaccine HPV types.
- Anti-HPV 6, 11, 16, and 18 antibody GMTs following completion of the 9vHPV vaccination series were greater in prior qHPV recipients than in subjects naïve to HPV vaccination.

- Anti-HPV 31, 33, 45, 52, and 58 antibody GMTs following completion of the 9vHPV vaccination series were lower in prior qHPV recipients than in subjects naïve to HPV vaccination

Table 54: Month 7 Anti-HPV Antibody Responses to 9vHPV in 12 to 26 Year Old Females Comparing Prior qHPV Recipients to HPV Vaccine Naïve Subjects (Studies V503-001, -002, -005, -006, and -007, PPI Population)

Assay (cLIA)	Age Group	n[1]	Prior qHPV Recipients (N=615)[1] GMT (95% CI)	n[2]	Subjects Naïve to HPV Vaccine (N=8,761)[2] GMT (95% CI)
Anti-HPV6	12 to 15 16 to 26	98 413	3209 (2708, 3802) 2020 (1875, 2176)	1278 4321	1488 (1419, 1559) 894 (873, 915)
Anti-HPV11	12 to 15 16 to 26	100 415	2747 (2319, 3255) 1653 (1531, 1784)	1279 4327	1104 (1053, 1157) 669 (654, 685)
Anti-HPV16	12 to 15 16 to 26	100 415	16122 (13740, 18918) 10251 (9526, 11031)	1305 4361	6046 (5784, 6320) 3159 (3088, 3231)
Anti-HPV18	12 to 15 16 to 26	100 415	3647 (2990, 4447) 2043 (1870, 2232)	1314 4884	1700 (1610, 1796) 810 (789, 831)
Anti-HPV31	12 to 15 16 to 26	100 415	423 (352, 510) 231 (211, 253)	1302 4806	1538 (1461, 1619) 665 (647, 683)
Anti-HPV33	12 to 15 16 to 26	100 415	256 (217, 302) 160(147, 174)	1319 5056	822 (785, 860) 419 (410, 429)
Anti-HPV45	12 to 15 16 to 26	100 415	148 (119, 183) 88 (80, 97)	1321 5160	591 (557, 627) 254 (247, 262)
Anti-HPV52	12 to 15 16 to 26	100 415	395 (331, 472) 240 (220, 261)	1318 4792	823 (784, 864) 382 (373, 392)
Anti-HPV58	12 to 15 16 to 26	100 415	425 (359, 503) 242 (223, 262)	1300 4818	1111 (1060, 1164) 489 (478, 501)

Source: Adapted from STN 125508/0_Module 2.7.3_Table 2.7.3-hpvdiseases: 132 & 134 (p398 and p400)
N=Subjects contributing to the analysis.
[1]Data from Study V503-006.
[2]Data from Studies V503-001, -002, -005, and -007.

Reviewer's comment*: Stronger responses to HPV types 6, 11, 16, and 18 in prior qHPV vaccine recipients are consistent with an anamnestic response.*

The clinical significance of lower responses to HPV 31, 33, 45, 52, and 58 in prior qHPV recipients is not clear. The Applicant stated that within the range of anti-HPV responses observed, vaccine efficacy was not correlated with Month 7 anti-HPV 31, 33, 45, 52, or 58 antibody titers. Specifically, 9vHPV prevented HPV 31, 33, 45, 52, and 58-related persistent infection and disease in HPV vaccine naïve subjects with relatively low anti-HPV 31, 33, 45, 52, or 58 levels at Month 7 [Section 2.7.3.2.1.9 of the ISE, p186]. The Applicant speculated that the lower anti-HPV 31, 33, 45, 52, and 58 antibody responses in prior qHPV vaccine recipients were not expected to negatively impact the efficacy of the 9vHPV vaccine in that population. However, clinical efficacy data to confirm this assertion in prior qHPV recipients are not presently available.

7.1.7 Subpopulations

7.1.7.1 Subgroup Analyses of Clinical Efficacy

Subpopulation analyses were conducted based on the demographic and baseline characteristics in PPE and HN-TS populations. The efficacy point estimates for each subgroup in both PPE and HN-TS populations are relatively consistent (range from 87% to 100%); the 95% CI vary greatly.

Please refer to Section 6.1.11.3 (subgroup analyses of efficacy) for details.

7.1.7.2 Subgroup Analyses of Immunogenicity

Impact of Race, Ethnicity and Geographic Region on Immunogenicity of 9vHPV in 16 through 26 Year-old Females

Table 55 and Table 56 present the Month 7 antibody GMTs against the original HPV types and new HPV types, respectively, in 16 through 26 year-old females, by race, ethnicity, region, and age.

Compared with the other ethnic groups, Asians had slightly lower anti-HPV 6 and 11 antibody responses and slightly higher anti-HPV 58 antibody responses; Blacks had slightly higher anti-HPV 16, 18, 31, 45, and 52 antibody responses, and Caucasians had slightly lower anti-HPV 18, 31, and 45 antibody responses. Hispanics or Latinos generally (except for HPV 58) had slightly higher anti-HPV antibody responses compared with other ethnicities.

Females in the 16-17 year of age category generally had higher anti-HPV antibody responses than older subjects.

Table 55: Month 7 Anti-HPV 6, 11, 16 and 18 Antibody GMTs by Baseline Subject Characteristics Among 16 through 26 Year-old Females Who Received 9vHPV in Protocols 001 and 002 (PPI Population)

Subgroup	HPV 6		HPV 11		HPV 16		HPV 18	
	N	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
Race								
Asian	763	837 (793, 884)	764	595 (562, 629)	792	3,071 (2,913, 3,238)	831	851 (799, 906)
Black	123	935 (817, 1,071)	122	670 (582, 772)	152	3,984 (3,532, 4,494)	170	995 (867, 1,142)
Caucasian	2,415	895 (869, 923)	2,421	691 (670, 713)	2,361	3,078 (2,985, 3,173)	2,669	756 (730, 782)
Other	1,020	929 (887, 974)	1,020	678 (645, 712)	1,056	3,308 (3,160, 3,462)	1,214	886 (842, 933)
Ethnicity								
Hispanic or Latino	1,415	937 (900, 975)	1,415	687 (659, 716)	1,452	3,335 (3,207, 3,468)	1,668	873 (836, 913)
Not Hispanic or Latino	2,906	873 (850, 898)	2,912	661 (642, 680)	2,909	3,075 (2,991, 3,161)	3,216	779 (755, 804)
Region								
Africa	16	1,030 (709, 1,496)	15	764 (511, 1,143)	20	5,218 (3,747, 7,267)	21	1,377 (930, 2,038)
Asia-Pacific	691	818 (773, 866)	692	589 (555, 625)	722	2,943 (2,785, 3,110)	758	827 (775, 883)
Europe	1,454	851 (818, 885)	1,458	660 (634, 688)	1,412	2,929 (2,816, 3,047)	1,604	714 (683, 747)
Latin America	1,292	947 (908, 987)	1,458	686 (657, 716)	1,336	3,355 (3,222, 3,494)	1,537	888 (848, 929)
North America	868	953 (906, 1,003)	870	730 (692, 769)	871	3,413 (3,246, 3,589)	964	838 (791, 888)
Age (Years)								
16 to 17	135	1,106 (973, 1,259)	136	838 (733, 958)	148	4,056 (3,590, 4,583)	150	1,052 (908, 1,219)
18 to 26	4,186	888 (867, 908)	4,191	664 (649, 681)	4,213	3,131 (3,061, 3,204)	4,734	803 (782, 825)

Source: Adapted from STN125508/0_Module 2.7.3_Table 2.7.3-hpvdiseases: 81 (p280-281)

Table 56: Month 7 Anti-HPV 31, 33, 45, 52 and 58 Antibody GMTs by Baseline Subject Characteristics Among 16 through 26 Year-old Females Who Received 9vHPV in Protocols 001 and 002 (PPI Population)

Subgroup	HPV 31		HPV 33		HPV 45		HPV 52		HPV 58	
	N	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	N	GMT (95% CI)	n	GMT (95% CI)
Race										
Asian	858	711 (668, 757)	865	420 (397, 445)	885	281 (263, 301)	788	354 (333, 376)	814	520 (491, 552)
Black	169	786 (683, 906)	189	415 (368, 468)	190	345 (298, 400)	166	444 (388, 508)	161	493 (432, 563)
Caucasian	2631	621 (598, 642)	2733	417 (404, 431)	2824	227 (219, 236)	2690	388 (376, 401)	2720	484 (468, 499)
Other	1141	725 (687, 765)	1278	424 (405, 444)	1261	290 (274, 307)	1148	381 (362, 401)	1123	481 (457, 506)
Ethnicity										
Hispanic or Latino	1579	718 (685, 752)	1752	428 (412, 446)	1747	285 (271, 299)	1597	390 (373, 407)	1554	482 (462, 503)
Not Hispanic or Latino	3227	640 (620, 661)	3304	415 (403, 427)	3413	240 (232, 248)	3195	379 (367, 391)	3264	493 (478, 507)
Region										
Africa	23	986 (674, 1444)	18	443 (300, 653)	24	518 (343, 782)	20	553 (377, 812)	15	707 (458, 1091)
Asia-Pacific	785	674 (631, 719)	782	407 (384, 432)	810	268 (249, 287)	717	341 (319, 363)	743	497 (468, 529)
Europe	1584	579 (553, 606)	1635	397 (381, 413)	1714	208 (198, 218)	1620	365 (350, 381)	1647	468 (449, 488)
L. America	1454	726 (692, 761)	1616	429 (412, 447)	1604	291 (277, 306)	1465	391 (374, 409)	1425	483 (462, 505)
N. America	960	717 (676, 761)	1005	451 (428, 475)	1008	272 (255, 290)	970	432 (409, 457)	988	527 (500, 556)
Age (Years)										
16 to 17	153	967 (833, 1121)	158	506 (444, 577)	156	343 (292, 404)	152	487 (424, 560)	150	629 (548, 721)
18 to 26	4,653	657 (639, 675)	4,898	417 (407, 427)	5004	252 (245, 259)	4640	379 (370, 389)	4668	485 (474, 497)

Source: Adapted from STN125508/0_Module 2.7.3_Table 2.7.3-hpvdiseases: 82 (p282-283)

Compared with other regions, subjects from the Asia-Pacific region had slightly lower anti-HPV 6 and anti-HPV 11 antibody responses, while subjects from Europe had slightly lower anti-HPV 18 and anti-HPV 31 antibody responses (and to lesser degree anti-HPV 58 antibody responses). Subjects from Latin America and North America had generally higher anti-HPV antibody responses compared to other regions (except for Africa). Subjects from Africa were few, and those available had generally the highest anti-HPV antibody responses compared with other regions.

Impact of Race, Ethnicity and Geographic Region on Immunogenicity of 9vHPV in 9 through 15 Year-old Females

The subgroup analyses for 9 through 15 year-old females are shown in Table 57 (for HPV 6, 11, 16 and 18) and Table 58 (for HPV31, 33, 45, 52 and 58)

Females 9 to 12 years of age generally had higher anti-HPV antibody responses than 13 to 15 year-old females.

Compared with the other ethnic groups, Asians had slightly lower anti-HPV 11 and anti-HPV 52 antibody responses. Blacks had the highest antibody responses especially for anti-HPV 18, and anti-HPV 52 antibodies, and Caucasians had slightly lower anti-HPV 45 antibody responses. Hispanics or Latinos generally (except for HPV type 58) had slightly higher anti-HPV antibody responses compared with other ethnicities.

Compared with subjects from Latin America, North America and Africa, subjects from Asia-Pacific and Europe tended to have lower antibody responses across HPV types. For HPV types 18 and 45, subjects from Europe had somewhat lower antibody responses than other regions. The highest antibody titers tended to be among subjects from North America.

Table 57: Month 7 Anti-HPV 6, 11, 16 and 18 Antibody GMTs by Baseline Subject Characteristics in 9 through 15 Year-old Females Who Received 9vHPV in Protocols 002, 005, 007 and 009 (PPI Population)

Subgroup	HPV 6		HPV 11		HPV 16		HPV 18	
	N	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
Race								
Asian	384	1544 (1417, 1683)	383	1078 (987, 1177)	392	639 (5922, 7001)	392145	2056 (1860, 2273)
Black	136	2128 (1841, 2458)	136	1596 (1376, 1851)	142	9698 (8438, 11147)	1467	3042 (2579, 3589)
Caucasian	1427	1698 (1624, 17765)	1428	1284 (,227, 1344)	1463	6827 (6537, 7130)	372	1926 (1829, 2029)
Other	360	2055 (1880, 2246)	360	1472 (1344, 1612)	365	8588 (7874, 9368)		2516 (2269, 2789)
Ethnicity								
Hispanic or Latino	606	1811 (1690, 1940)	606	1318 (1229, 1415)	623	7497 (7011, 8017)	630	2121 (1958, 2298)
Not Hispanic or Latino	1700	1722 (1652, 1795)	1701	1281 (1228, 1336)	1739	7036 (6760, 7323)	1746	2076 (1979, 2177)
Region								
Africa	73	1785 (1468, 2170)	73	1385 (1134, 1693)	78	8670 (7197, 10445)	79	2870 (2298, 3583)
Asia-Pacific	373	1527 (1400, 1665)	373	1069 (978, 1168)	382	6367 (5854, 6925)	382	2036 (1841, 2251)
Europe	932	1541 (1459, 1628)	933	1173 (1109, 1241)	955	6159 (5840, 6495)	957	1706 (1601, 1819)
Latin America	460	1944 (1798, 2101)	460	1407 (1299, 1524)	469	8157 (7561, 8801)	474	2389 (2182, 2616)
North America	468	2227 (2062, 2406)	468	1647 (1522, 1783)	478	9029 (8375, 9735)	484	2639 (2413, 2887)
Age (Years)								
9 to 12	1470	2027 (1942, 2116)	1471	1492 (1428, 1561)	1511	8424 (8081, 8781)	1521	2530 (2407, 2658)
13 to 15	836	1341 (1266, 1420)	836	998 (941, 1058)	851	5354 (5065, 5659)	855	1484 (1389, 1585)

Source: Adapted from STN125508/0.43, Module 1.11.3 _Table 25 (p67-68)

Table 58: Month 7 Anti-HPV 31, 33, 45, 52 and 58 Antibody GMTs by Baseline Subject Characteristics in 9 through 15 Year-old Females Who Received 9vHPV in Protocols 002, 005, 007 and 009 (PPI Population)

Subgroup	HPV 31		HPV 33		HPV 45		HPV 52		HPV 58	
	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
Race										
Asian	385	1809 (1643, 1992)	392	877 (804, 956)	395	790 (710, 880)	392	852 (778, 933)	389	1241 (1135, 1357)
Black	144	2604 (2224, 3049)	147	1178 (1022, 357)	148	1099 (923, 1309)	147	1292 (1114, 1500)	147	1519 (1313, 1757)
Caucasian	1459	1759 (1674, 1848)	1466	935 (894, 978)	1469	645 (610, 681)	1469	966 (921, 1012)	1448	12818 (1223, 1342)
Other	366	23152 (2097, 2556)	368	1118 (1023, 1223)	373	928 (831, 1036)	373	1092 (995, 1199)	369	1423 (1298, 1559)
Ethnicity										
Hispanic or Latino	632	1976 (1831, 2133)	627	1003 (937, 1075)	632	765 (703, 834)	631	979 (911, 1053)	623	1252 (1167, 1344)
Not Hispanic or Latino	1731	1858 (1775, 1945)	1746	952 (913, 992)	1753	717 (681, 755)	1750	983 (941, 1026)	1730	1330 (1275, 1388)
Region										
Africa	79	2546 (2060, 3145)	79	1037 (856, 1255)	80	1044 (824, 1322)	80	1255 (1027, 1533)	79	1342 (1102, 1634)
Asia-Pacific	375	1783 (1619, 1965)	382	865 (793, 943)	385	781 (7001, 870)	382	840 (767, 920)	379	1224 (1119, 1338)
Europe	947	1580 (1486, 1679)	955	839 (794, 886)	956	574 (536, 615)	957	879 (830, 932)	938	1175 (1109, 1243)
L. America	468	2150 (1971, 2345)	472	1075 (994, 1162)	475	864 (784, 952)	474	1450 (967, 1140)	470	1352 (1247, 1466)
N. America	485	2352 (2160, 2562)	485	1234 (1143, 1333)	489	885 (805, 974)	488	1239 (1143, 1344)	487	1642 (1517, 1778)
Age (Years)										
9 to 12	1505	2252 (2147, 2362)	1514	1112 (1065, 1161)	1524	880 (834, 928)	1524	1153 (1102, 1206)	1506	1517 (1452, 1586)
13 to 15	849	1383 (1298, 1473)	859	752 (710, 796)	861	524 (488, 563)	857	738 (695, 784)	847	1007 (949, 1068)

Source: Adapted from STN125508/0.43, Module 1.11.3 _Table 26 (p69-70)

Impact of Race, Ethnicity and Geographic Region on Immunogenicity of 9vHPV in 9 through 15 Year-old Males

Table 59 and Table 60 display summaries of the Month 7 antibody GMTs against the original HPV types and the new HPV types, respectively, in 9 through 15 year-old males by race, ethnicity, region, and age.

Compared with the other ethnic groups, Asians had the lowest antibody responses across HPV types, except for HPV type 45. Blacks had slightly higher anti-HPV 16, anti-HPV 45 and anti-HPV 52 antibody responses, and Caucasians generally had antibody responses in-between other ethnic groups. Hispanics or Latinos generally had slightly higher anti-HPV antibody responses compared to other subjects.

Compared with subjects from Latin America, North America and Africa, subjects from Asia-Pacific and Europe had lower antibody responses across HPV types. For HPV types 18 and 45, subjects from Europe had somewhat lower antibody titers than subjects from other regions.

Males 9-12 years of age category generally had higher anti-HPV antibody responses than older subjects.

Table 59: Month 7 Anti-HPV 6, 11, 16 and 18 Antibody GMTs by Baseline Subject Characteristics in 9 through 15 Year-old Males Who Received 9vHPV in Protocols 002, 005 and 007 (PPI Population)

Subgroup	HPV 6		HPV 11		HPV 16		HPV 18	
	N	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
Race								
Asian	185	1755 (1558, 1975)	185	1184 (1052, 1333)	190	7606 (6800, 8510)	188	2478 (2161, 2841)
Black	39	2025 (1566, 2619)	39	1438 (1111, 1862)	44	10145 (8042, 12799)	44	2958 (2230, 3924)
Caucasian	560	2065 (1930, 22109)	560	1517 (1417, 1624)	567	8027 (7524, 8564)	566	2485 (2297,2688)
Other	249	2432 (2197, 2692)	249	1607 (1451, 1780)	252	10035 (9107, 11058)	253	3067 (2726, 3450)
Ethnicity								
Hispanic or Latino	320	2458 (2247, 2688)	320	1623 (1483, 1776)	324	9668 (8873, 40534)	325	3036 (2737, 3368)
Not Hispanic or Latino	713	1936 (1823, 2056)	713	1404 (1321, 1492)	729	7984 (7539, 8456)	726	2469 (2303, 2647)
Region								
Africa	20	1614 (1132, 2301)	20	1225 (855, 1748)	22	8853 (6388, 12270)	22	2632 (1773, 3907)
Asia-Pacific	182	1730 (1537, 1947)	182	1171 (1040, 1319)	186	7573 (6766, 8476)	184	2469 (2154, 2831)
Europe	315	1797 (1643, 1965)	315	1333 (1219, 1459)	319	7178 (6589, 7820)	318	2097 (1889, 2326)
Latin America	248	2472 (2235, 2734)	248	1659 (1499, 1837)	251	10090 (9161,11114)	252	3260 (2901, 3663)
North America	268	2452 (2226, 2702)	268	1736 (1575, 1914)	275	9394 (8566,10303)	275	2936 (2626, 3283)
Age (Years)								
9 to 12	667	2249 (2113, 2394)	667	1585 (1489, 1687)	676	9316 (8781, 9885)	677	2959 (2755, 3177)
13 to 15	366	1815 (1668, 1974)	366	1278 (1174, 1390)	377	7136 (6592, 7725)	374	2129 (1934, 2343)

Source: Adapted from STN125508/0.43, Module 1.11.3_Table 27 (p71-72)

Table 60: Month 7 Anti-HPV 31, 33, 45, 52 and 58 Antibody GMTs by Baseline Subject Characteristics in 9 through 15 Year-old Males Who Received 9vHPV in Protocols 002, 005, and 007 (PPI Population)

Subgroup	HPV 31		HPV 33		HPV 45		HPV 52		HPV 58	
	n	GMT (95% CI)	N	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
Race										
Asian	189	1790 (1571, 2039)	189	933 (829, 1051)	190	794 (681, 923)	189	823 (729, 938)	189	1380 (1225, 1553)
Black	44	2573 (1966, 3367)	43	1201 (936, 1540)	44	1174 (860, 1602)	43	1232 (947, 1603)	44	1449 (1133, 1852)
Caucasian	563	2132 (1978, 2299)	567	1182 (1103, 1265)	566	766 (703, 836)	566	1151 (1070, 1237)	562	1567 (1463, 1379)
Other	252	2629 (2350, 2942)	254	1409 (1272, 1561)	256	1027 (902, 1168)	256	1085 (974, 1209)	255	1705 (1540, 1888)
Ethnicity										
Hispanic or Latino	324	2560 (2318, 2828)	326	1417 (1295, 1551)	328	1007 (898, 1128)	328	1085 (985, 1194)	328	1724 (1576, 1886)
Not Hispanic or Latino	724	2042 (1910, 2183)	727	1090 (1026, 1159)	728	778 (721, 840)	726	1085 (999, 1138)	722	1488 (1401, 1581)
Region										
Africa	22	2086 (1431, 3042)	21	998 (702, 1417)	22	937 (605, 1450)	22	1015 (703, 1467)	22	1162 (823, 1641)
Asia-Pacific	185	1772 (1555, 2019)	185	926 (823, 1042)	186	792 (681, 921)	185	830 (731, 943)	185	1371 (1217, 1545)
Europe	316	1864 (1688, 2059)	319	1007 (920, 1101)	319	662 (590,743)	318	1086 (986, 1197)	314	1446 (1320, 1584)
L. America	251	2690 (2406, 3008)	253	1436 (1298, 1588)	255	1088 (957, 1237)	255	1082 (972, 1206)	255	1772 (1601, 1962)
N. America	274	2529 (2272, 2814)	275	1425 (1293, 1570)	274	910 (804, 1030)	274	1249 (1126, 1386)	274	1681 (1525, 1854)
Age (Years)										
9 to 12	675	2421 (2260, 2594)	677	1310 (1230, 1394)	679	941 (870, 1019)	678	1199 (1123, 1282)	676	1735 (1631, 1845)
13 to 15	373	1826 (1664, 2003)	376	984 (904, 1070)	377	690 (621, 768)	376	875 (801, 957)	374	1283 (1181, 1394)

Source: Adapted from STN125508/0.43, Module 1.11.3_Table 28 (p73-74)

Summary of Subgroup Analyses

Younger subjects, regardless of gender, race, ethnicity or region, generally had numerically higher antibody GMTs than older subjects. Boys had numerically higher antibody GMTs than girls among the corresponding age groups. There were some variations in antibody GMTs against different HPV types across different races, ethnicities or regions. However, the clinical significance of these variations in antibody GMTs is unclear, as antibody GMTs for all 9 HPV types were robust across the race, ethnicity, or region category.

7.1.8 Persistence of Efficacy

7.1.8.1 Persistence of Efficacy

As described in Section 6.1, both 9vHPV and qHPV groups were generally comparable with respect to the proportions of subjects completing each of the scheduled follow-up visits. The only primary endpoint case in PPE population was observed at Month 12, and all the six primary endpoint cases in the HN-TS population were observed at or before Month 18, in the 9vHPV vaccine group. In contrast, primary endpoint cases were observed in the PPE and HN-TS populations from Month 12 throughout Month 54 in the qHPV vaccine group. As shown in the post-marketing follow-up studies, the protective efficacy of qHPV against HPV 6-, HPV 11-, HPV 16- and HPV 18-related disease lasts at least 6 years. Taken together, these results suggest that the protective efficacy of 9vHPV against HPV 6-, HPV 11-, HPV 16-, HPV 18-, HPV 31-, HPV 33-, HPV 45-, HPV 52-, and HPV 58-related persistent infection and disease lasts at least 4 years and likely longer.

7.1.8.2 Persistence of Immunogenicity

Per protocol, approximately 20% of the subjects enrolled in Protocol V503-001 were tested for persistence of serum anti-HPV responses during the follow-up period. Table 61 and Table 62 present anti-HPV antibody GMTs and seropositivity rates, respectively, in subjects 16 through 26 years of age at Months 3 (one month after the second dose), 7 (one month after the third dose), 12 and 24.

For both 9vHPV and qHPV recipients, anti-HPV antibody GMTs were highest at Month 7, and at Month 24 anti-HPV antibody GMTs had fallen to 10-20% of Month 7 values regardless of HPV types. Anti-HPV antibody GMTs against the origi-l types (i.e., HPV 6, 11, 16 and 18) were similar between qHPV and 9vHPV recipients at all time points.

Seropositivity rates for all HPV types except HPV 18 and 45 remained >97% in 9vHPV recipients at Month 24. Seropositivity rates for HPV types 18 and 45 among 9vHPV recipients were 86.5% and 87.4%, respectively, at Month 24, meaning that anti-HPV 18 and HPV 45 antibodies were undetectable at Month 24 in >10% of 9vHPV recipients. Similarly, anti-HPV 18 antibodies were undetectable at Month 24 in >10% of qHPV recipients.

Table 61: Persistence of Type-Specific Anti-HPV Antibody GMTs in 16 through 26 Year-old Women in Study V503-001 ([1]PPI Population)

Antibody Assay	**9vHPV n[3]**	**9vHPV (N[2]=6,792) GMT (95%CI)**	**qHPV n[3]**	**qHPV (N[2]=6,795) GMT (95%CI)**

Antibody Assay	9vHPV n[3]	9vHPV (N[2]=6,792) GMT (95%CI)	qHPV n[3]	qHPV (N[2]=6,795) GMT (95%CI)
Anti-HPV 6				
Month 03	788	734 (693, 778)	761	720 (679, 763)
Month 07	3,993	893 (872, 915)	3,975	875 (854, 897)
Month 12	800	331 (312, 350)	781	319 (301, 339)
Month 24	715	209 (196, 223)	689	205 (192, 219)
Anti-HPV 11				
Month 03	790	529 (492, 560)	762	678 (640, 719)
Month 07	3,995	666 (650, 683)	3,982	830 (809, 851)
Month 12	810	212 (200, 226)	788	265 (249, 281)
Month 24	763	123 (116, 131)	734	148 (139, 158)
Anti-HPV 16				
Month 03	794	2,436 (2,304, 2,576)	785	2,475 (2,340, 2,618)
Month 07	4,032	3,131 (3,057, 3,207)	4,062	3,157 (3,082, 3,233)
Month 12	819	1,042 (980, 1,107)	805	1,032 (970, 1,097)
Month 24	778	521 (485, 559)	758	507 (472, 546)
Anti-HPV 18				
Month 03	908	471 (443, 501)	877	371 (350, 395)
Month 07	4,539	805 (783, 827)	4,541	679 (660, 680)
Month 12	972	199 (185, 213)	901	160 (149, 172)
Month 24	886	86 (79, 94)	846	68 (62, 74)
Anti-HPV 31				
Month 03	881	438 (407, 471)	838	6 (6, 7)
Month 07	4,466	658 (637, 681)	4,377	10 (9, 10)
Month 12	909	197 (184, 210)	858	4 (<4, 4)
Month 24	863	102 (95, 110)	804	<4 (<4, <4)
Anti-HPV 33				
Month 03	937	288 (2739, 304)	910	<4 (<4, <4)
Month 07	4,702	416 (406, 426)	4,750	<4 (<4, <4)
Month 12	958	126 (120, 133)	937	<4 (<4, <4)
Month 24	909	65 (62, 69)	881	<4 (<4, <4)
Anti-HPV 45				
Month 03	956	160 (152, 170)	910	<3 (<3, <3)
Month 07	4,792	253 (246, 260)	4,750	<3 (<3, <3)
Month 12	976	69 (65, 73)	937	<3 (<3, <3)
Month 24	928	33 (31, 35)	881	<3 (<3, <3)
Anti-HPV 52				
Month 03	895	241 (230, 253)	835	<3 (<3, <3)
Month 07	4,455	380 (372, 388)	4,335	<3 (<3, <3)
Month 12	916	119 (113, 125)	857	<3 (<3, <3)
Month 24	867	58 (55, 61)	808	<3 (<3, <3)
Anti-HPV 58				
Month 03	884	281 (265, 298)	863	<4 (<4, <4)
Month 07	4,486	483 (470, 495)	4,446	<4 (<4, <4)
Month 12	905	153 (146, 162)	883	<4 (<4, <4)
Month 24	852	80 (76, 85)	834	<4 (<4, <4)

Source: Adapted from STN 125508/0, Module 2.7.3_Table 2.7.3-hpvdiseases:138 (p407-408).
[1]PPI population consisted of all individuals who received all 3 doses of 9vHPV, did not have major protocol deviations, and were naïve (PCR negative and seronegative) to the relevant HPV types prior to dose 1 and through 1 month after dose 3.
[2]N=Number of subjects who received at least 1 injection.
[3]n=Number of subjects who contributed to the analysis.

Table 62: Persistence of HPV Type-Specific Seropositivity Rates in 16 through 26 Year-old Women in Study V503-001 ([1]PPI Population)

Antibody Assay	9vHPV n[3]	9vHPV (N[2]=6,792) SPR (95%CI)	qHPV n[3]	qHPV (N[2]=6,795) SPR (95%CI)
Anti-HPV 6				
Month 03	788	99.5% (98.7%, 99.9%)	761	99.9% (99.3%, 100%)
Month 07	3,993	99.8% (99.6%, 99.9%)	3,975	99.8% (99.7%, 99.9%)
Month 12	800	99.3% (98.4%, 99.7%)	781	99.2% (98.3%, 99.7%)
Month 24	715	98.0% (96.7%, 98.9%)	689	97.4% (95.9%, 98.4%)
Anti-HPV 11				
Month 03	790	100% (99.5%, 100%)	762	100% (99.5%, 100%)
Month 07	3,995	100% (99.9%, 100%)	3,982	99.9% (99.8%, 100%)
Month 12	810	99.8% (99.1%, 100%)	788	99.9% (99.3%, 100%)
Month 24	763	98.7% (97.6%, 99.4%)	734	98.6% (97.5%, 99.3%)
Anti-HPV 16				
Month 03	794	100% (99.5%, 100%)	785	100% (99.5%, 100%)
Month 07	4,032	100% (99.9%, 100%)	4,062	100% (99.8%, 100%)
Month 12	819	99.9% (99.3%, 100%)	805	100% (99.5%, 100%)
Month 24	778	99.9% (99.3%, 100%)	758	99.2% (98.3%, 99.7%)
Anti-HPV 18				
Month 03	908	99.7% (99.0%, 99.9%)	877	99.1% (98.2%, 99.6%)
Month 07	4,539	99.8% (99.7%, 99.9%)	4,541	99.7% (99.5%, 99.8%)
Month 12	972	97.6% (96.4%, 98.5%)	901	94.6% (92.9%, 95.9%)
Month 24	886	86.5% (84.0%, 88.6%)	846	81.0% (78.2%, 83.6%)
Anti-HPV 31				
Month 03	881	99.8% (99.2%, 100%)	838	33.4% (30.2%, 36.7%)
Month 07	4,466	99.8% (99.6%, 99.9%)	4,377	50.1% (48.7%, 51.6%)
Month 12	909	99.3% (98.6%, 99.8%)	858	20.2% (17.5%, 23.0%)
Month 24	863	97.2% (95.9%, 98.2%)	804	14.4% (12.1%, 17.0%)
Anti-HPV 33				
Month 03	937	99.7% (99.1%, 99.9%)	910	9.2% (7.4%, 11.3%)
Month 07	4,702	99.7% (99.5%, 99.9%)	4,750	12.7% (11.8%, 13.7%)
Month 12	958	99.7% (99.1%, 99.9%)	937	6.8% (5.3%, 8.7%)
Month 24	909	98.6% (97.6%, 99.2%)	881	7.5% (5.8%, 9.5%)
Anti-HPV 45				
Month 03	956	99.4% (98.6%, 99.8%)	910	4.9% (3.6%, 6.6%)
Month 07	4,792	99.6% (99.4%, 99.8%)	4,750	9.2% (8.4%, 10.0%)
Month 12	976	96.9% (95.6%, 97.9%)	937	3.1% (2.1%, 4.4%)
Month 24	928	87.4% (85.1%, 89.5%)	881	1.9% (1.1%, 3.1%)
Anti-HPV 52				
Month 03	895	99.7% (99.0%, 99.9%)	835	3.4% (2.2%, 4.8%)
Month 07	4,455	99.8% (99.6%, 99.9%)	4,335	2.6% (2.2%, 3.1%)
Month 12	916	99.5% (98.7%, 99.8%)	857	1.9% (1.1%, 3.0%)
Month 24	867	98.3% (97.2%, 99.0%)	808	3.8% (2.6%, 5.4%)
Anti-HPV 58				
Month 03	884	99.8% (99.2%, 100%)	863	15.3% (13.0%, 17.9%)
Month 07	4,486	99.8% (99.6%, 99.9%)	4,446	20.4% (19.2%, 21.6%)
Month 12	905	99.6% (98.9%, 99.9%)	883	5.7% (4.2%, 7.4%)
Month 24	852	98.1% (97.0%, 98.9%)	834	8.5% (6.7%, 10.6%)

Source: Adapted from STN 125508/0, Module 2.7.3_Table 2.7.3-hpvdiseases:139 (p409-413).
[1]PPI population consisted of all individuals who received all 3 doses of 9vHPV, did not have major protocol deviations, and were naïve (PCR negative and seronegative) to the relevant HPV types prior to dose 1 and through 1 month after dose 3.
[2]N=Number of subjects received at least 1 injection.
[3]n=Number of subjects contributed to the analysis.
SPR=Seropositivity rate

Reviewer's notes: *Data from later visits (Month 36 and Month 42) are not available for this submission.*

Persistence of anti-HPV antibodies against the original HPV types in this submission for both 9vHPV and qHPV was similar to that observed in the Gardasil program. In the Gardasil program, anti-HPV 6, 11 and 16 antibodies remained detectable in a high percentage of subjects at least 9 years after dose 3, while anti-HPV 18 antibodies became undetectable in approximately one-third of vaccinees several years after vaccination. The Applicant speculated that this was likely due to the limits of the immunoassay sensitivity, as clinical protection against disease associated with all four HPV types persisted despite this loss of detectable antibodies. In long-term follow-up studies in the Gardasil program there has been no breakthrough case of HPV-related disease in the PPE population through at least 6 years post-dose 3, even though many vaccine recipients who originally seroconverted for HPV type 18 no longer had measurable anti-HPV 18 antibody by cLIA. In addition, HPV 18 antibodies remained measurable using two other HPV immunological assays, a total IgG assay and a ----------(b)(4)----------. These results suggest either that anamnestic responses may be protective in subjects who have become seronegative or that the protective antibody level is below the cLIA limit of detection.

Longer-term follow-up is required to definitively evaluate the duration of antibody persistence for each component of 9vHPV and to determine whether loss of detectable antibodies by cLIA correlates with loss of clinical efficacy or persistence of efficacy (as has been observed with Gardasil).

7.1.9 Product-Product Interactions

7.1.9.1 Concomitant Administration with Menactra and Adacel (Study V503-005, Designed as Study 5 in the Draft Package Insert)

Protocol Title: A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity and Tolerability of V503 (A Multivalent Human Papillomavirus L1 Virus-Like Particle Vaccine) Given Concomitantly with Menactra and Adacel in Preadolescents and Adolescents 11 to 15 Years Old

Study Sites: 41 sites; 34 sites in the U.S. and 7 sites in Latin America (Chile, Colombia, Mexico, and Peru).

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

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

The primary immunogenicity objectives were to demonstrate that the first dose of 9vHPV could be administered concomitantly with Menactra and Adacel without impairing the antibody responses to HPV types in 9vHPV -or to *N. meningitidis* serogroups A, C, Y, and W-135, and diphtheria, tetanus, and pertussis. The primary safety objective of the study was to demonstrated whether concomitant administration of 9vHPV with Menactra and Adacel would increase reactogenicity,

Summary of Results

The baseline demographics were similar for the concomitant and non-concomitant groups. The median age in each vaccination group at enrollment was 12.0 years. All subjects were between 11 and 15 years of age, with 310 boys and 311 girls assigned to the concomitant group, and 310 boys and 310 girls assigned to the non-concomitant group. Approximately 56% of subjects were from North America, and approximately 43% from Latin America. The race distribution of the study subjects was as follows: 47.4% White; 35.0% Multiracial; 9.6% American Indian or Alaska Native; 6.4% Black; 1.1% Asian; and 0.6% Native Hawaiian or Other Pacific Islander.

Responses to 9vHPV Vaccine

The results of the immunogenicity analysis demonstrated non-inferior antibody GMTs and seroconversion rates for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post-dose 3 when comparing concomitant vs. non-concomitant administration of the first dose of 9vHPV with Menactra and Adacel (data not shown in this review).

Responses to Menactra and Adacel

Antibody responses to Menactra and Adacel administered concomitantly with each other and 9vHPV were also non-inferior to those resulting from concomitant administration of Menactra and Adacel alone (data not shown in this review). Antibody responses to Menactra and Adacel were measured by:

- The percentage of subjects who achieved a tetanus and diphtheria titer ≥ 0.1 IU/ml at four weeks after vaccination with Adacel
- The anti-pertussis toxin (PT), anti-filamentous hemagglutinin (FHA), anti-pertectin (PRN), and anti-fimbrial aggrutinogens (FIM) GMTs at four weeks after vaccination with Adacel
- The percentage of subjects with a 4-fold or greater rise in antibody titers against *N. meningitidis* serogroups A, C, Y, and W-135 at four weeks after vaccination with Menactra

7.1.9.2 Interaction with Hormonal Contraceptive Use

Table 63 presents Month 7 anti-HPV antibody responses among all female subjects 16 through 26 years of age in the pooled PPI population who received 9vHPV with or without use of hormonal contraceptive from Day 1 through Month 7. In general, type specific anti-HPV antibody GMTs were statistically significantly higher in subjects with use of hormonal contraceptives compared with subjects without use of hormonal contraceptives. The clinical significance is unknown.

Table 63: Month 7 Anti-HPV Antibody GMTs among 16 through 26 Year Old Female Recipients of 9vHPV Vaccine by Status of Hormonal Contraceptive Use from Day 1 through Month 7 (PPI, Protocols 001 and 002)

Antibody Assay	Subjects with Hormonal Contraceptive Use(N=5,474) n	GMT (95% CI)	Subjects without Hormonal Contraceptive Use(N=1,778) n	GMT (95% CI)
Anti-HPV 6	3,251	912 (888, 936)	1,069	841 (803, 880)
Anti-HPV 11	3,253	685 (667, 704)	1,073	623 (594, 654)
Anti-HPV 16	3,247	3,240 (3,157, 3,326)	1,113	2,933 (2,805, 3,067)
Anti-HPV 18	3,674	824 (799, 848)	1,209	770 (731, 811)
Anti-HPV 31	3,610	677 (657, 698)	1,195	628 (596, 663)
Anti-HPV 33	3,819	425 (414, 436)	1,236	402 (384, 422)
Anti-HPV 45	3,901	261 (252, 269)	1,258	235 (222, 249)
Anti-HPV 52	3,631	397 (385, 408)	1,160	342 (325, 359)
Anti-HPV 58	3,657	496 (482, 510)	1,160	468 (446, 492)

Source: Adapted from STN 125508/0.43_Module 1.11.3_Table 29(p75)
N=Number of females who were randomized and belonged to the respective contraceptive use group and received at least 1 injection of 9vHPV Vaccine and had any contraceptive use data from Day 1 through Month 7.
n=Number of subjects evaluable.

7.1.9.3 Interaction with Steroids or Other Immunosuppressants

Table 64 summarizes Month 7 anti-HPV antibody GMTs among all 9vHPV recipients in the pooled PPI population who reported use of steroids or other immunosuppressive medications from Day 1 through Month 7. Based on the data presented in the table, the Applicant concluded that there was no evidence of interference with Month 7 antibody responses associated from the use of steroids or other immunosuppressants from Day 1 through Month 7.

Table 64: Month 7 Anti-HPV Antibody GMTs Among 9vHPV Recipients by Status of Steroid or Immunosuppressive Use from Day 1 through Month 7 (PPI Population regardless of Steroid and Immunosuppressive Use from Protocols 001, 002, 005, 007 and 009)

Antibody Assay	Subjects with Immuno-suppressant (N=13) n	GMT (95% CI)	Subjects without Immuno-suppressant (N=11216) n	GMT (95% CI)
Anti-HPV 6	7	1806 (939, 3475)	7660	1225 (1201, 1,250)
Anti-HPV 11	7	1373 (705, 2673)	7667	906 (889, 925)
Anti-HPV 16	7	5618 (2874, 10983)	7776	4628 (4536, 4722)
Anti-HPV 18	7	1551 (707, 3507)	8311	1,232 (1204, 1261)
Anti-HPV 31	7	1051 (469, 2352)	8208	1,044 (1,02, 1,069)
Anti-HPV 33	6	902 (418, 1945)	84582	602 (590, 615)
Anti-HPV 45	7	674 (279, 1626)	8601	394 (385, 405)
Anti-HPV 52	7	692 (326, 1467)	8227	573 (561, 586)
Anti-HPV 58	6	1175 (524, 2631)	8221	752 (736, 768)

Source: Adapted from STN 125508/0.43_Module 1.11.3_Table 30 (p76)

N=Number of females who were randomized and belonged to the respective contraceptive use group and received at least 1 injection of 9vHPV Vaccine and had any contraceptive use data from Day 1 through Month 7.
n=Number of subjects evaluable.
For 005 and 007, only subjects from the non-concomitant groups are included.

Reviewer's comments: *Effects of steroids and immunosuppressants on immune responses depend on the doses and classes of immunosuppressnants. Based on the limited information presented in this submission and the very limited number of subjects who received immnosupressants during the vaccination period, no definitive conclusion can be reached regarding whether use of an immunosuppressant interferes with anti-HPV immune responses induced by 9vHPV.*

7.1.11 Efficacy Conclusions

7.1.11.1 Prevention of Cervical, Vulvar, Vaginal Disease Related to HPV 31, 33, 45, 52, and 58

1. Administration of a 3-dose regimen of 9vHPV vaccine to females, 16 through 26 years of age, is effective in preventing the development of following:
    a. HPV 31-, 33-, 45-, 52-, 58-related high-grade cervical, vulvar, vaginal disease (CIN 2 or worse, VIN 2/3 or worse, VaIN 2/3 or worse, and AIN 2/4 or worse)
    b. HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar, and vaginal disease (any grade)
    c. HPV 31-, 33-, 45-, 52-, and 58-related persistent infection
    d. HPV 31-, 33-, 45-, 52-, and HPV 58-related cytological abnormalities.

   Effectiveness against cervical, vulval, and vaginal disease was demonstrated by efficacy analyses of histopathological endpoints comparing 9vHPV to qHPV, whereas effectiveness against anal disease is inferred through similar pathophysiology and preventative efficacy of qHPV against anal disease endpoints in clinical trials. The protective efficacy induced by the 9vHPV is durable through at least 4 years post-vaccination with respect to persistent infection and disease related to the HPV vaccine types. Please refer to Section 6.1 for details.

2. Administration of a 3-dose regimen of 9vHPV vaccine to females 9 through 15 years of age is protective against cervical, vulvar, vaginal, and anal infection and disease caused by HPV types 31, 33, 45, 52, and 58.

3. Administration of a 3-dose regimen of 9vHPV vaccine to males 9 through 15 years of age is protective against anogenital infection and disease caused by HPV types 31, 33, 45, 52, and 58.

   The conclusions for both males and females 9 through 15 years of age are inferred from non-inferior anti-HPV 31, 33, 45, 52, and 58 antibody responses induced by 9vHPV in these populations compared with 16 through 26 year-old females, the population used to establish clinical efficacy. Please refer to Section 6.2 and Section 7.1.5.

7.1.11.2 Prevention of Cervical, Vulvar, Vaginal, and Anal Disease Related to HPV 6, 11, 16, and 18

1. Administration of a 3-dose regimen of 9vHPV vaccine to females 16 through 26 years of age is protective against cervical, vaginal, vulvar, and anal infection and disease caused by HPV types 6, 11, 16, and 18.

This conclusion is inferred from non-inferior anti-HPV 6, 11, 16, and 18 antibody responses induced by 9vHPV compared with qHPV, which supports bridging the efficacy findings in the Gardasil Program to 9vHPV. The conclusion is further supported by efficacy of 9vHPV in preventing infection and disease related to HPV types 6, 11, 16, and 18, as assessed by vaccine efficacy relative to the historical placebo control in the Gardasil Program.

2. Administration of a 3-dose regimen of 9vHPV vaccine to females 9 through 15 years of age is protective against cervical, vaginal, vulvar, -and anal infection and disease caused by HPV types 6, 11, 16, and 18.

3. Administration of a 3-dose regimen of 9vHPV vaccine to males 9 through 15 years of age is protective against anogenital infection and disease caused by HPV types 6, 11, 16, and 18.

The conclusion for 9 through 15 year-old boys and girls is based on numerically superior and statistically non-inferior anti-HPV 6, 11, 16, and 18 antibody responses induced by 9vHPV in these populations compared with 16 through 26 year-old females.

7.1.11.3 Overall Prevention of Cervical, Vulvar, and Vaginal Disease, Pap Test Abnormalities, and Cervical and External Genital Procedures

Administration of a 3-dose regimen of 9vHPV to 16 through 26 year-old females also reduced their:

- Overall risk for development of CIN, VIN and VaIN disease;
- Risk of having an abnormal Pap test, particularly a Pap test that is predictive for CIN 2/3 and, therefore, requires colposcopic follow-up; and
- Risk of undergoing cervical and external genital diagnostic and therapeutic procedures, especially definitive therapy procedures.

7.1.11.4 Persistence of Immunogenicity, Lot-consistency and Interaction with Other Vaccines

- The 9vHPV vaccine induced robust anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses through at least 1.5 years post-vaccination.
- The final manufacturing process of 9vHPV vaccine produced lots that generated consistent anti-HPV responses as measured at Month 7
- Concomitant administration of a 3-dose regimen of 9vHPV with Menactra and Adacel did not adversely affect immune responses to any of the three vaccines.
- Administration of a 3-dose regimen of 9vHPV to 12 to 26 year-old females who were previously administered a 3-dose regimen of qHPV induced robust antibody responses to HPV types 6, 11, 16 and 18 as well as high seroconversion rates for HPV types 31, 33, 45, 52, and 58. The magnitude of anti-HPV 6, 11, 16, and 18 antibody responses was higher in prior qHPV recipients compared to HPV vaccine naïve subjects, while the magnitude of anti-HPV 31, 33, 45, 52 and 58

antibody responses in prior qHPV recipients was statistically significantly lower than in HPV vaccine naïve subjects. However, the clinical significance is unknown.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

In all clinical trials conducted during the clinical development of the 9vHPV vaccine, safety was evaluated using VRC-aided surveillance during Days 1 through 15 after each study vaccination to collect injection site and systemic adverse reactions, as well as SAEs. SAEs and new onset clinical conditions (including potential autoimmune disorders) were also collected throughout the study periods.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Six studies collectively contributed to the pooled 9vHPV safety database and included female subjects 9 to 26 years of age and male subjects 9 through 15 years of age at enrollment. The data presented in this Summary of Clinical Safety were collected from over 13,000 9vHPV recipients that adequately represent the indicated population. In total, 5307 children 9 through 15 years of age and 8053 young women 16 through 26 years of age received at least one dose of the 9vHPV vaccine. Over 97% of subjects received all three doses of the 9vHPV vaccine. A listing of the clinical trials used to support the safety of 9vHPV is shown in Section 5.3.

The pooled safety population -excludes subjects who received the low-dose or high-dose formulation of 9vHPV in Part A of Protocol V503-001 because the dose levels of 9vHPV were different. Safety analyses in these subjects are presented in Section 8.5.1. Prior qHPV vaccine recipients who received saline placebo in Protocol V503-006 are also excluded from the pooled safety population.

Some analyses presented in Section 8 cover the “Entire Study Period.” For Protocol V503-001, the entire study period varies by subject enrollment date and includes Day 1 through the visit cut-off date of April 10, 2013. For Protocol V503-002, the entire study period includes Day 1 through Month 12. For Protocols V503-005, V503-006, V503-007, and V503-009/GDS01C, the entire study period includes Day 1 through Month 7.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 20,751 subjects were vaccinated in 6 clinical trials. A total of 13,360 subjects received at least 1 dose of 9vHPV vaccine, and 7391 subjects received at least 1 dose of qHPV vaccine.

A summary of the numbers of subjects from the six clinical trials who were vaccinated with 9vHPV and completed Month 7 follow-up or discontinued prior to Month 7 is shown in Table 65. Protocols V503-001 and -002 are ongoing (extended follow-up). Protocols V503-005, -006, -007, and -009 are completed. Among the 13,360 vaccinated subjects, a total of 328 subjects (2.5%) discontinued study vaccinations. Most subjects who discontinued were either lost to follow-up or withdrew consent. Fifteen subjects

discontinued study vaccinations due to an adverse experience, and seven subjects discontinued study vaccinations due to a protocol violation.

Table 65: Disposition and Demographics of Subjects Who Received 9vHPV Vaccine (Protocols 001, 002, 005, 006, 007, and 009) (Day 1 through Month 7[1])

Disposition and Subgroup	9vHPV N (%)
Subjects in Population	13285
Vaccinated at	
Vaccination 1	13285 (100.0)
Vaccination 2	13102 (98.6)
Vaccination 3	12959 (97.5)
Completed	12843 (96.7)
Discontinued	409 (3.1)
Adverse Event	12 (0.1)
Lost To Follow-Up	198 (1.5)
Physician Decision	4 (< 0.1)
Pregnancy	1 (<0.1)
Protocol Violation	5 (<0.1)
Withdrawal By Subject	189 (1.4)
Unknown[2]	33 (0.2)
Gender	
Male	1784 (13.4)
Female	11501 (86.6)
Age (Years)	
9 to 15	5237 (39.4)
16 to 17	301 (2.3)
18 to 26	7747 (58.3)
Mean	17.9
SD	5.3
Median	19.0
Range	9 to 26
Race	
Asian	1889 (14.2)
Black	575 (4.3)
Other	3046 (22.9)
White	7775 (58.5)
Ethnicity	
Hispanic Or Latino	4290 (32.3)
Not Hispanic Or Latino	8994 (67.7)
Null	1 (<0.1)
Region	
Africa	165 (1.2)
Asia-Pacific	1738 (13.1)
Europe	4773 (35.9)
Latin America	3642 (27.4)
North America	2967 (22.3)

Source: Adapted from STN125508/0.43_Module 1.11.3., Table 31 and 32 (p77-78)
[1]For Protocol 002 the disposition records were collected at Month 12. For 005 and 007, only subjects from the non-concomitant groups are included and the study medication disposition is based on both the 9vHPV vaccine and other study vaccine.
[2]A disposition record did not exit at the time of reporting.

The race distribution of the integrated safety population for 9vHPV was similar when stratified by age to 16 through 26 year-old women (56.2% White; 25.4% Other Races or Multiracial; 14.7% Asian; 3.7% Black) and 9 through 15 year-old girls and boys (61.2% White; 18.9% Other Races or Multiracial; 14.6% Asian; 5.3% Black) [Data source: STN125508/0_Module 2.7.4_Appendix 2.7.4: 3 and 4, p162-165].

The race distribution of the safety population for qHPV was similar to the integrated safety population for 9vHPV. Please refer to Section 6.1.10.1.1 for details.

The race distribution of the safety population for Study V503-009 was different from the race distribution of 9 through 15 year-olds in the integrated safety population since V503-009 was conducted only in Europe. However, the race distributions for 9vHPV and qHPV in this study were similar. Please refer to Section 6.3.10.1.1 for details.

8.2.3 Categorization of Adverse Events

All verbatim terms for reported AE were coded using the Medical Dictionary for Regulatory Activities version 16 (MedDRA v16), and the resulting system organ class (SOC) and preferred terms (PTs) were used for tabulation of rates.

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

The only study to include a placebo-controlled arm was V503-006, a small study to investigate the safety and immunogenicity of 9vHPV in prior qHPV recipients. The pivotal study, V503-001, had an active comparator control, qHPV. Therefore, the category and frequency of the adverse events observed in the historical AAHS placebo controls in the previous Gardasil vaccine program were used as a reference for safety assessment. However, the safety surveillance of the Gardasil vaccine program was different from that of the 9vHPV vaccine program. For the Gardasil vaccine program, SAEs were collected from Day 1 to 15 following any vaccination and fetal loss was not collected as an SAE. For the 9vHPV vaccine program, SAEs were collected for much longer period for Studies V503-001 and V503-002 (at least for 6 months after last vaccination), and fetal loss was collected as an SAE. In addition, in the 9vHPV program, all subjects were evaluated for safety using VRC-aided surveillance. In contrast, in the Gardasil vaccine program, only a subset of subjects was evaluated using VRC-aided surveillance. All of these factors limit comparison of safety data for 9vHPV to historical safety data for AAHS placebo control collected in the Gardasil vaccine program.

In addition, the majority of 9 through 15 year-old subjects were enrolled in open label studies (V503-002, -005, and -007). Consequently, there was potential for observation bias for safety assessments (see also Reviewer's comments in Section 8.4.7).

Reviewer's comments: *Safety analyses of the only one qHPV controlled study, V503-001, are presented in Section 6.1.12. The population of the placebo controlled study, V503-006, was subjects who were previously vaccinated with qHPV and were different from that of other five clinical trials. In addition, the remaining four clinical trials were open label studies. Therefore, this section only presents the integrated safety analyses of the database for 9vHPV recipients.*

8.4 Safety Results

8.4.1 Deaths

A total of 5 subjects who received 9vHPV died during the entire study period; all of them occurred in Study V503-001. Of the 5 deaths, one each was due to trauma (road traffic accident); completed suicide; cancer (acute lymphocytic leukemia); hypovolemic and septic shock; and sudden death. None of the deaths were considered related to the 9vHPV by the investigators or this clinical reviewer. Please refer to Section 6.1.12.3 for details.

8.4.2 Nonfatal Serious Adverse Events

Among the 13,309 subjects who received 9vHPV, 305 (2.3%) experienced non-fatal SAEs during the entire study period. Per protocol, fetal loss was also considered to be a 'non-fatal SAE' if a fetal loss occurred during Day 1 through six months post dose 3. Overall, the most frequent SAEs were elective abortion (79 cases, or 0.6% of the study population) and other fetal loss (64 cases, of which, 37 were spontaneous abortion). Rates of spontaneous abortions are discussed separately in Section 9.1.1.1. Infections and infestations were the most frequent SAEs not related to fetal loss (61 cases, of which 21 were appendicitis).

Of the 162 SAEs not related to fetal loss, 66 occurred within 28 days after any vacci-tion. Table 66 lists the SAEs within 28 days following any 9vHPV vaccination in Studies V503-005, 006, 007 and 009. For Studies V503-001 and -002, please refer to Section 6.1.12.4 and Section 6.2.12.4 for the subjects who experienced SAEs within 28 days following any vaccination with 9vHPV or qHPV.

Table 66: Non-fatal SAEs (Excluding Events of Fetal Loss) Reported from Day 1 through Day 28 after Any Vaccination with 9vHPV (Protocols 005, 006, 007 and 009)

Protocol	Subject Number	SAE	Dose	Day of Onset	Related	Outcome
V503-005						
	34107	Appendicitis	2	27	N	Resolved
	34090	Seroma	1	9	N	Resolved
	34475	Affective disorder	2	1	N	Resolved
	35254	Gastroenteritis	1	6	N	Resolved
	34260	Testicular torsion	3	8	N	Resolved
V503-006					N	Resolved
	37083	Syncope	2	14	N	Resolved
	37801	Tonsillitis	1	2	Y	Resolved
V503-007						
	39147	Non-cardiac chest pain	1	8	N	Resolved
	40212	Thermal burn	1	24	N	Resolved
	40105	Appendiceal abscess	3	9	N	Resolved
	39203	Forearm fracture	1	7	N	Resolved
	39318	Appendicitis	1	20	N	Resolved
	40567	Appendicitis	3	9	N	Resolved
	40424	Pyelonephritis	1	22	N	Resolved
	40515	Eating disorder	1	23	N	Resolved

Protocol	Subject Number	SAE	Dose	Day of Onset	Related	Outcome
	40230	Viral pharyngitis	3	1	N	Resolved
V503-009						Resolved
	51204	Anemia	2	9	N	Resolved
	51204	Pulmonary vasculitis	2	9	N	Resolved

Source: Generated by the clinical review from information in STN 125508/0_Module 2.7.4_Appendix 2.7.4:41 (p402-475) and Appendix 2.7.4:42 (p476-517)

***Reviewer's comment**: This reviewer reviewed the narratives of all the SAEs including those that occurred outside the 28-day window of vaccination in this submission and concurs with the investigator's assessment of causality.*

8.4.3 Study Dropouts/Discontinuations

A total of 15 9vHPV recipients (0.1%) discontinued study vaccinations due to a clinical adverse experience. Among them, 12 subjects (0.1%: 6 subjects in V503-001, 1 in V503-002, 2 in V503-005 and 3 in V503-006) discontinued due to a vaccine related adverse experience. The vaccine-related adverse events that led to discontinuation in Study V503-001 were allergy, headache, fatigue, injection-site pain, injection-site swelling, and rash; in V503-002 asthma crisis; in V503-005 pyrexia and pain in extremity; and in V503-006 abdominal pain, injection-site swelling and swelling tongue. Please refer to the individual studies for additional details.

8.4.4 Common Adverse Events

- The most common (≥10%) local and systemic adverse reactions in females 16 through 26 years of age were injection-site pain (89.7%), injection-site swelling (40.2%), injection-site erythema (34.3%) and headache (14.7%).
- The most common (≥10%) local and systemic reactions in girls 9 through 15 years of age were injection-site pain (82.5%), injection-site swelling (37.3%), injection-site erythema (30.3%) and headache (12.9%).
- The most common (≥10%) local and systemic reactions in boys 9 through 15 years of age were injection-site pain (72.4%), injection-site swelling (28.2%), injection-site erythema (24.2%) and headache (12.5%).

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Please refer to Sections 8.4.6 and 8.4.7 for details.

8.4.5 Clinical Test Results

No routine clinical laboratory evaluations were conducted in any of the studies.

8.4.6 Systemic Adverse Events

8.4.6.1 Summary of Common Systemic Adverse Events

The numbers and percentages of 9vHPV recipients with systemic adverse experiences within 15 days following any vaccination visit (reported by ≥1% of subjects) are listed in Table 67 by system organ class. The most common (≥ 10%) vaccine-related systemic adverse event was headache.

Table 67: Systemic Adverse Events within 15 Days Following Any 9vHPV Vaccination (Rate ≥ 1%) by System Organ Class and Relationship to Vaccination (Protocols 001, 002, 005, 006, 007, and 009)

Population and Adverse Event Classification	Overall N (%)	Vaccine-Related N (%)
Subjects in population with follow-up	13234	13234
with one or more systemic adverse events	7136 (53.9)	3735 (28.2)
with no systemic adverse events	6098 (46.1)	9499 (71.8)
Ear and labyrinth disorders	**133 (1.0)**	**34 (0.3)**
Gastrointestinal disorders	**2019 (15.3)**	**809 (6.1)**
Abdominal pain	291 (2.2)	92 (0.7)
Abdominal pain upper	383 (2.9)	123 (0.9)
Diarrhea	372 (2.8)	122 (0.9)
Nausea	750 (5.7)	457 (3.5)
Vomiting	292 (2.2)	104 (0.8)
General disorders and administration site conditions	**1968 (14.8)**	**1,353 (10.2)**
Fatigue	376 (2.8)	258 (1.9)
Malaise	159 (1.2)	113 (0.9)
Pyrexia	1198 (9.1)	882 (6.7)
Infections and infestations	**2090 (15.8)**	**284 (2.1)**
Influenza	396 (3.0)	86 (0.6)
Nasopharyngitis	659 (5.0)	96 (0.7)
Upper respiratory tract infection	256 (1.9)	23 (0.2)
Injury, poisoning and procedural complications	**249 (1.9)**	**4 (0.0)**
Musculoskeletal and connective tissue Disorders	**868 (6.6)**	**295 (2.2)**
Back pain	186 (1.4)	41 (0.3)
Myalgia	207 (1.6)	103 (0.8)
Pain in extremity	189 (1.4)	49 (0.4)
Nervous system disorders	**3637 (27.5)**	**2099 (15.9)**
Dizziness	522 (3.9)	321 (2.4)
Headache	3,230 (24.4)	1,845 (13.9)
Migraine	129 (1.0)	38 (0.3)
Reproductive system and breast disorders	**572 (4.3)**	**55 (0.4)**
Dysmenorrhoea	343 (2.6)	22 (0.2)
Respiratory, thoracic and mediastinal Disorders	**1,063 (8.0)**	**195 (1.5)**
Cough	269 (2.0)	34 (0.3)
Nasal congestion	127 (1.0)	21 (0.2)
Oropharyngeal pain	594 (4.5)	117 (0.9)
Skin and subcutaneous tissue disorders	**426 (3.2)**	**146 (1.1)**

Source: Adapted from STN 125508/0.43_Module 1.11.3_Table 33 (p80-81)

8.4.6.2 Summary of Vaccine-Related Systemic Adverse Events

Table 68 presents by age and gender the numbers and proportions of vaccine-related systemic adverse reactions observed Day 1 through Day 15 following any 9vHPV vaccination.

Table 68: Vaccine-Related Systemic Adverse Reactions within 5 Days Following Any 9vHPV Vaccination (Rate ≥ 1% in One or More Vaccination Groups) by Age and Gender across All Studies[1]

Adverse Experiences	16 to 26 Year-old Women (N^2=8022) n^3 (%)	9 to 15 Year-old Girls and Boys (N^2=5212) n^3 (%)	9 to 15 Year-old Girls (N^2=3436) n^3 (%)	9 to 15 Year-old Boys (N^2=1776) n^3 (%)
Headache	1,177 (14.7)	668 (12.8)	444 (12.9)	224 (12.5)
Pyrexia	413 (5.1)	470 (8.9)	281 (8.1)	189 (10.5)
Nausea	340 (4.2)	117 (2.2)	79 (2.3)	38 (2.1)
Dizziness	234 (2.9)	87 (1.6)	65 (1.9)	22 (1.2)
Fatigue	188 (2.3)	70 (1.3)	44 (1.3)	26 (1.4)
Diarrhea	94 (1.2)	28 (0.5)	17 (0.5)	11 (0.6)
Oropharyngeal Pain	77 (1.0)	40 (0.8)	29 (0.8)	11 (0.6)
Abdominal Pain Upper	57 (0.7)	66 (1.3)	46 (1.3)	20 (1.1)

Source: Adapted from STN125508/0.43_Module 1.11.3_Table 34(p82-83) and Table 35 (p84-88)
[1]Data for 16 through 26 year-old women were from Protocols 001, 002 and 006. Data for 9 through 15 year-olds were from Protocols 002, 005, 006, 007 and 009.
[2]N=Subjects in population with follow-up.
[3]n=Subjects with one or more corresponding adverse reactions.

8.4.6.3 Solicited Systemic Adverse Reactions

Temperature was solicited using VRC-aided surveillance for 5 days after each vaccination. Table 69 shows by severity grade percentages of subjects with an increased temperature within 5 days following each dose of 9vHPV.

Table 69: Distribution of Maximum Temperatures within 5 Days Following Each and Any Vaccination among 9vHPV Recipients across All Studies (Protocols 001, 002, 005, 006, 007 and 009)

Temperatures	**Dose 1 N (%)**	**Dose 2 N (%)**	**Dose 3 N (%)**	**Any Dose N (%)**
Subjects in population	13285	13102	12959	13285
Without temperature data	184	262	290	134
With temperature data	13101	12840	12669	13151
Temperature (Oral or Oral Equivalent)				
< 37.8°C	12691(96.9)	12498 (97.3)	12251(96.7)	12101 (92.0)
≥ 37.8°C < 38.9°C	350 (2.7)	292 (2.3)	338 (2.7)	866 (6.6)
≥ 38.9°C < 39.9°C	50 (0.4)	41 (0.3)	70 (0.6)	156 (1.2)
≥ 39.9°C < 40.9°C	8 (0.1)	8 (0.1)	8 (0.1)	23 (0.2)
≥ 40.9 °C	2 (0.0)	1 (0.0)	2 (0.0)	5 (0.0)

Source: STN125508/0.43_Module 1.11.3_Tables 36-39(p89-92).
Note: Percentages are calculated based on the number of subjects with temperature data.

8.4.7 Local Reactogenicity

8.4.7.1 Summary of Injection Site Reactogenicity

Table 70 presents the numbers and percentages of subjects with injection-site adverse reactions (rate ≥1% in one or more vaccination groups) reported across the studies within 5 days following any 9vHPV vaccination. The proportions of subjects reporting an

injection site adverse reaction were approximately equal post-dose 1 (67.6%), post-dose 2 (67.7%), and post-dose 3 (68.0%). Among subjects who received 9vHPV vaccine, the rates of injection-site pain was approximately equal (65.6%, 65.4% and 65.5%) across the 3 reporting time periods. However, the rates of injection-site swelling (12.3%, 20.9% and 26.2% post dose 1, 2 and 3 respectively) and injection-site erythema (9.8%, 16.5% and 20.5% post dose 1, 2 and 3 respectively) increased following each successive dose of 9vHPV.

The majority of injection site adverse reactions were mild and moderate in intensity. Most of the severe adverse reactions were injection site pain. Among the severe injection site adverse reactions, the proportion accounted for by pain was 96.2% (332 out of 345) for 16 through 26 year-old women, 98.2% (162 out of 165) for 9 through 15 year-old females and 93.8% (30 out of 32) for 9 through 15 year-old males.

Table 70: Injection Site Adverse Reactions within 5 Days Following Any 9vHPV Vaccination (Rate ≥ 1% in One or More Vaccination Groups) by Age and Gender across All Studies[1]

Adverse Reactions	16 to 26 Year-old Women (N^2=8022) n^3 (%)	9 to 15 Year-old Girls and Boys (N^2=5212) n^3 (%)	9 to 15 Year-old Girls (N^2=3436) n^3 (%)	9 to 15 Year-old Boys (N^2=1776) n^3 (%)
Total AEs	7219 (90.0)	4153 (79.7)	2850 (82.9)	1303 (73.4)
Mild	4222 (52.6)	2512 (48.2)	1617 (47.1)	895 (50.4)
Moderate	2652 (33.1)	1444 (27.7)	1068 (31.1)	376 (21.2)
Severe	345 (4.3)	197 (3.8)	165 (4.8)	32 (1.8)
Pain	7193 (89.7)	4131 (79.3)	2836 (82.5)	1295 (72.9)
Swelling	3225 (40.2)	1783 (34.2)	1282 (37.3)	501 (28.2)
Erythema	2750 (34.3)	1470(28.2)	1041 (30.3)	429 (24.2)
Pruritus	447 (5.6)	138 (2.6)	109 (3.1)	29 (1.6)
Bruising	137 (1.7)	2 (0.0)	2 (0.1)	0 (0.0)
Hematoma	106 (1.3)	103 (2.0)	75 (2.2)	28 (1.6)
Mass	97 (1.2)	13 (0.2)	10 (0.3)	3 (0.2)
Hemorrhage	76 (0.9)	51 (1.0)	35 (1.0)	16 (0.9)
Induration	58 (0.7)	57 (1.1)	37 (1.1)	20 (1.1)

Source: Adapted from STN125508/0.43_Module 1.11.3_Tables 40-41(p93-96) and Tables 42-43 (p97-01)

[1]Data for 16 through 26 year-old women were from Protocols 001, 002 and 006. Data for 9 through 15 year-olds were from Protocols 002, 005, 006, 007 and 009.

[2]N=Subjects in population with follow-up.

[3]n=Subjects with one or more corresponding adverse reactions.

Reviewer's comments: *Injection site adverse reactions were collected for 15 days after each vaccination, but only the adverse reactions with onset in the first 5 days after each vaccination are reported in the draft package insert. The same approach was used for the approved Gardasil package insert. In addition, there was no significant difference in the frequencies of injection site adverse reactions between the first 5 days and the first 15 days-. In the six studies, the frequencies of injection site adverse reactions within the first 15 days post dose 1, 2 and 3 were 72.3%, 67.7% and 68.1%, respectively, while the those within the first 5 days post dose 1, 2 and 3 were 67.6%, 67.5% and 68.0%, respectively [Data source: STN125508/0_Module 2.7.4_Appendixes 2.7.4: 22-27 (p359-364)].*

The frequencies of both injection site reactions and systemic adverse experiences in 9 through 15 year-olds in general were numerically lower than those in 16 through 26 year-olds. Since the study design for 9 through 15 year-olds clinical trials (V503-002, 005, 007 and 009) was open label, and the study design for 16 through 26 year-old females (V503-001) was randomized and double-blind, it is possible that this difference was caused in part by observation bias. However, there were similar observations in the placebo controlled studies in the Gardasil program, with numerically lower rates of adverse reactions among younger subjects compared with older subjects. For example, the rates of injection-site reactions in 10 to 15 year-old males, 10 to 15 year-old females and 16 to 23 year-old females were 74.0%, 80.4% and 87.5%, respectively..

8.4.7.2 Severity of Solicited Injection Site Reactions

Table 71 presents the numbers and percentages by severity grade of subjects in all studies with solicited injection-site reactions within 5 days following any vaccination.

Table 71: Solicited Injection Site Adverse Reactions within 5 Days Following Each and Any 9vHPV Vaccination by Intensity across the Studies (Protocols 001, 002, 005, 006, 007 and 009)

	Dose 1 N (%)	**Dose 2 N (%)**	**Dose 3 N (%)**	**Any Dose N (%)**
Subjects in population	13231	13069	12933	13234
Adverse Reactions				
Pain				
Mild	7093 (53.6)	6249 (47.8)	5892 (45.6)	6778 (51.2)
Moderate	1526 (11.5)	2131 (16.3)	2319 (17.9)	4032 (30.4)
Severe	89 (0.7)	205 (1.6)	303 (2.3)	524 (4.0)
Swelling				
Mild	1280 (9.6)	2,010 (15.4)	2408 (18.6)	3,384 (25.6)
Moderate	242 (1.8)	506 (3.9)	639 (4.9)	1,042 (7.8)
Severe	110 (0.8)	229 (1.7)	346 (2.7)	574 (4.3)
Erythema				
Mild	1141 (8.6)	1832 (14.0)	2159 (16.7)	3358 (25.4)
Moderate	125 (0.9)	262 (2.0)	347 (2.7)	617 (4.7)
Severe	30 (0.2)	65 (0.5)	152 (1.2)	232 (1.7)

Source: STN125508/0.43_Module 1.11.3_Table 44-51(p102-110).
Note: Percentages are calculated based on the number of subjects with temperature data.

8.4.8 Adverse Events of Special Interest

The potential autoimmune disorders observed in the 9vHPV and the qHPV groups in general are balanced by preferred term except MS, type 1 diabetes mellitus, and Raynaud's disease. The overall the number of reported cases of type 1 diabetes mellitus (3 cases in 9vHPV vs. no case in qHPV), Raynaud's phenomenon (2 cases in 9vHPV vs. no case in qHPV) and MS (5 cases in 9vHPVvs. 2 cases in qHPV) were small, and the clinical relevance of the imbalance between treatment groups is unclear.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

The safety profile of the 3 dose formulations (termed low, mid and high dose formulation) was assessed in Part A of Protocol V503-001. Approximately 1240 female subjects 16 through 26 years of age were equally randomized to one of the 3 dose formulations of

9vHPV vaccine or qHPV vaccine (approximately 310 subjects per group). The 3 dose formulations had essentially the same safety profile.

8.5.2 Product-Demographic Interactions

The adverse experience profile of 9vHPV was assessed by age, gender and racial/ethnic grouping. The following racial categories were evaluated: White, Black, Asian, and Other. The ethnic categories included only Hispanic/non-Hispanic. Subjects were included in specific categories based on the subjects' own identification of their racial/ethnic group. Analysis of adverse experiences by race/ethnicity also indirectly assessed the impact of region of origin: most subjects of Asian descent were enrolled in Asia, most Hispanic-Americans were enrolled in Latin America, most subjects of African descent were enrolled in the Americas and Africa, and subjects of "Other Races" were generally enrolled in Latin America (i.e., mixed Black, White, and/or Native American descent). Please also refer to Section 8.4.6 and Section 8.4.7 for subgroup analyses by age and gender.

8.5.3.1 Injection Site Reaction Subgroup Analyses by Race and Ethnicity

For each race or ethnic group, the rates of solicited injection-site reactions (erythema, pain and swelling) in boys and girls 9 through 15 years of age were numerically lower compared with those among the young women 16 through 26 years of age in the corresponding race and ethnic group. In general, the rates of injection-site reactions were comparable among race and ethnic groups. The rates of injection-site reactions in Blacks for both age groups were numerically lower compared with those among other race and ethnic groups in the corresponding age group. Table 72 presents the rates of solicited injection site reactions among 16 through 26 year-old female subjects and 9 through 15 year-old boys and girls by race and ethnicity groups.

Table 72: Solicited Injection Site Reactions within 5 Days Following Any 9vHPV Vaccination by Race and Ethnicity across Studies (Protocols 001, 002, and 006)

Adverse Events	White n (%)	Black n (%)	Asian n (%)	Other Race n (%)	Hispanic n (%)	Non-Hispanic n (%)
16-26 Year-olds						
Subjects with Follow-up	4,514	291	1,180	2,037	2,736	5,285
Subjects with one or more AE	4,190 (92.8)	239 (82.1)	1,019 (86.4)	1,816 (89.2)	2,447 (89.4)	4,816 (91.0)
Erythema	1,785 (39.5)	63 (21.6)	364 (30.8)	538 (26.4)	727 (26.6)	2,023 (38.3)
Pain	4,155 (92.0)	237 (81.4)	999 (84.7)	1,802 (88.5)	2,430 (88.8)	4,762 (90.1)
Swelling	1,923 (42.6)	117 (40.2)	470 (39.8)	715 (35.1)	994 (36.3)	2,231 (42.2)
9-15 Year-olds						
Subjects with Follow-up	3,230	280	701	1,001	1,541	3,671
Subjects with one or more AE	2,768 (85.7)	187 (66.8)	548 (78.2)	736 (73.5)	1,173 (76.1)	3,066 (83.5)
Erythema	1,055 (32.7)	50 (17.9)	136 (19.4)	229 (22.9)	400 (26.0)	1,070 (29.1)
Pain	2,696 (83.5)	180 (64.3)	530 (75.6)	725 (72.4)	1,155 (75.0)	2,976 (81.1)
Swelling	1,199 (37.1)	91 (32.5)	195 (27.8)	298 (29.8)	488 (31.7)	1,295 (35.3)

Source: Generated by CBER reviewer from STN125508/0.43_Module 1.11.3_Tables 52-63: 81 (p111-124).

8.5.3.2 Systemic Adverse Reactions: Subgroup Analyses by Race and Ethnicity

The rates of subjects with one or more systemic adverse reactions among each race and ethnic group were comparable in women 16 through 26 years of age. Table 73

presents for 16 through 26 year-old females the rates across all studies of systemic adverse reactions within 15 days following any 9vHPV vaccination (Rate ≥ 1%), regardless of causality and by system organ class and preferred term.

Table 73: Systemic Adverse Events within 15 Days Following Any 9vHPV Vaccination Regardless of Causality and by System Organ Class and Preferred Term (Rate ≥ 1%) among 16 through 26 Year-Old Females (Protocols 001, 002, and 006)

Adverse Events	White n (%)	Black n (%)	Asian n (%)	Other Races n (%)	Hispanic n (%)	Non-Hispanic n (%)
Subjects in population with follow-up	4514	291	1180	2037	2736	5285
with one or more systemic adverse events	2552 (56.5)	177 (60.8)	549 (46.3)	1233 (60.5)	1679 (61.4)	2832 (53.6)
Ear and labyrinth disorders	**47 (1.0)**	**3 (1.0)**	--*	--*	--*	--*
Gastrointestinal disorders	**802 (17.8)**	**41 (14.1)**	**144 (12.2)**	**348 (17.1)**	**467 (17.1)**	**868 (16.4)**
Abdominal pain	87 (1.9)	10 (3.4)	15 (1.3)	74 (3.6)	99 (3.6)	87 (1.6)
Abdominal pain upper	125 (2.8)	7 (2.4)	28 (2.4)	44 (2.2)	56 (2.0)	148 (2.8)
Diarrhea	146 (3.2)	9 (3.1)	37 (3.1)	68 (3.3)	95 (3.5)	165 (3.1)
Nausea	409 (9.1)	10 (3.4)	48 (4.1)	104 (5.1)	146 (5.3)	425 (8.0)
Vomiting	101 (2.2)	--*	--*	47 (2.3)	60 (2.2)	99 (1.9)
General disorders and administration site conditions	**551 (12.2)**	**59 (20.3)**	**161 (1 3.6)**	**297 (14.6)**	**404 (1 4.8)**	**664 (12.6)**
Fatigue or Malaise	206 (4.6)	10 (3.4)	37 (3.1)	71 (3.5)	84 (3.1)	245 (4.6)
Pyrexia	240 (5.3)	39 (13.4)	99 (8.4)	167 (8.2)	238 (8.7)	307 (5.8)
Infections and infestations	**688 (15.2)**	**37 (12.7)**	**141 (11.9)**	**405 (19.9)**	**535 (19.6)**	**736 (13.9)**
Influenza	134 (3.0)	14 (4.8)	--*	172 (8.4)	217 (7.9)	114 (2.2)
Nasopharyngitis	285 (6.3)	8 (2.7)	57 (4 . 8)	110 (5.4)	131 (5.2)	325 (6.1)
Upper respiratory tract infection	--*	3 (1.0)	38 (3 . 2)	--*	--*	61 (1.2)
Injury, poisoning and procedural complications	**60 (1.3)**	**3 (1.0)**	**18 (1.5)**	--*	--*	**75 (1.4)**
Musculoskeletal and connective tissue Disorders	**378 (8.4)**	**19 (6.5)**	**67 (5.7)**	**154 (7.6)**	**206 (7.5)**	**412 (7.8)**
Arthralgia	52 (1.2)	--*	--*	--*	--*	--*
Back pain	92 (2.0)	6 (2.1)	13 (1.1)	38 (1.9)	55 (2.0)	94 (1.8)
Myalgia	90 (2.0)	4 (1.4)	25 (2.1)	37 (1.8)	54 (2.0)	102 (1.9)
Neck pain	55 (1.2)	--*	--*	--*	--*	57 (1.1)
Pain in extremity	49 (1.1)	4 (1.4)	--*	45 (2.2)	56 (2.0)	--*
Nervous system disorders	**1371 (30.4)**	**109 (37.5)**	**211 (17.9)**	**740 (36.3)**	**1003 (36.7)**	**1428 (27.0)**
Dizziness	213 (4.7)	11 (3.8)	40 (3.4)	123 (6.0)	152 (5.6)	235 (4.4)
Headache	1202 (26.6)	100 (34.4)	172 (14.6)	667 (32.7)	902 (33.0)	1239 (23.4)
Migraine	61 (1.4)	4 (1.4)	--*	32 (1.6)	47 (1.7)	57 (1.1)
Psychiatric disorders	**55 (1.2)**	--*	**12 (1.0)**	**24 (1.2)**	**27 (1.0)**	**64 (1.2)**
Reproductive system and breast disorders	**251 (5.6)**	**30 (10.3)**	**58 (4 .9)**	**156 (7.7)**	**199 (7.3)**	**296 (5.6)**
Dysmenorrhoea	136 (3.0)	21 (7.2)	32 (2.7)	90 (4.4)	117 (4.3)	162 (3.1)
Respiratory, thoracic and mediastinal Disorders	**399 (8.8)**	**21 (7.2)**	**74 (6.3)**	**127 (6.2)**	**164 (6.0)**	**457 (8.6)**
Cough	72 (1.6)	3(1.0)	19 (1.6)	34 (1.7)	41 (1.5)	87 (1.6)
Nasal congestion	54 (1.2)	--*	--*	--*	--*	65 (1.2
Oropharyngeal pain	267 (5.9)	8 (2.7)	41 (3.5)	62 (3.0)	73 (2.7)	305 (5.8)

Adverse Events	White n (%)	Black n (%)	Asian n (%)	Other Races n (%)	Hispanic n (%)	Non-Hispanic n (%)
Skin and subcutaneous tissue disorders	**168 (3.7)**	**5 (1.7)**	**38 (3.2)**	**71 (3.5)**	**89 (3.3)**	**193 (3.7)**

Source: Generated by CBER reviewer from STN125508/0.43_Module 1.11.3_Tables 64-69(p125-136).
*--: no data or the percentage was <1%.

The rates of subjects with one or more systemic adverse reactions among Blacks and Asian were numerically lower (around 30%) compared with those (around 50%) among Whites, Hispanic, Non-Hispanic and other Races in boys and girls 9 through 15 years of age. Table 74 present for 9 through 15 year-old males and females the rates across all studies of systemic adverse events within 15 days following any 9vHPV vaccination (Rate ≥ 1%), regardless of causality and by system organ class and preferred term.

Table 74: Systemic Adverse Events within 15 Days Following Any 9vHPV Vaccination Regardless of Causality and by System Organ Class and Preferred Term (Rate ≥ 1%) among 9 through 15 Year-old Males and Females (Protocols 002, 005, 006, 007 and 009)

Adverse Events	White n (%)	Black n (%)	Asian n (%)	Other Races n (%)	Hispanic n (%)	Non-Hispanic n (%)
Subjects in population with follow-up	3230	280	701	1001	1541	3671
with one or more systemic adverse events	1769 (54.8)	96 (34.3)	236 (33.7)	524 (52.3)	775 (50.3)	1850 (50.4)
Ear and labyrinth disorders	**51 (1.6)**	**1 (0.4)**	--*	**11 (1.1)**	**20 (1.3)**	**45 (1.2)**
Ear pain	31(1.0)	1 (0.4)		10 (1.0)	17 (1.1)	26 (0.7)
Eye disorders	**35 (1.1)**	--*	--*	**9 (0.9)**	-	**38 (1.0)**
Gastrointestinal disorders	**514 (15.9)**	**20 (7.1)**	**40 (5.7)**	**110 (11.0)**	**170 (11.0)**	**514 (14.0)**
Abdominal pain	67 (2.1)	-	7 (1.0)	31 (3.1)	39 (2.5)	66 (1.8)
Abdominal pain upper	157 (4.9)	9 (3.2)	--*	12 (1.2)	21 (1.4)	158 (4.3)
Diarrhea	73 (2.3)	6 (2.1)	10 (1.4)	23 (2.3)	35 (2.3)	77 (2.1)
Nausea	157 (4.9)	3 (1.1)	--*	17 (1.7)	37 (2.4)	142 (3.9)
Vomiting	93 (2.9)	--*	10 (1.4)	27 (2.7)	40 (2.6)	93 (2.5)
General disorders and administration site conditions	**552 (17.1)**	**40 (14.3)**	**92 (13.1)**	**211 (21.1)**	**290 (18.8)**	**605 (16.5)**
Fatigue or Malaise	94 (2.9)	--*	--*	39 (3.9)	46 (3.0)	116 (3.1)
Pyrexia	364 (11.3)	35 (12.5)	83 (11.8)	171 (17.1)	230 (14.9)	423 (11.5)
Infections and infestations	**532 (16.5)**	**14 (5.0)**	**71 (10.1)**	**202 (20.2)**	**272 (17.7)**	**547 (14.9)**
Gastroenteritis	50 (1.5)	1 (0.4)	--*	29 (2.9)	30 (1.9)	51 (1.4)
Influenza	41 (1.3)	4 (1.4)	--*	20 (2.0)	35 (2.3)	30 (0.8)
Nasopharyngitis	147 (4.6)	3 (1.1)	28 (4.0)	45 (4.5)	75 (4.9)	148 (4.0)
Rhinitis	39 (1.2)	--*	--*	--*	--*	39 (1.1)
Upper respiratory tract infection	109 (3.4)	4 (1.4)	17 (2.4)	56 (5.6)	53 (3.4)	133 (3.6)
Injury, poisoning and procedural complications	**116 (3.6)**	**--***	**13 (1.9)**	**21 (2.1)**	**36 (2.3)**	**115 (3.1)**
Musculoskeletal and connective tissue Disorders	**187 (5.8)**	**9 (3.2)**	**18 (2.6)**	**36 (3.6)**	**64 (4.2)**	**186 (5.1)**
Back pain	32 (1.0)	--*	--*	--*	--*	--*
Myalgia	31 (1.0)	2 (0.7)	6 (0.9)	12 (1.2)	23 (1.5)	--*
Pain in extremity	63 (2.0)	2 (0. 7)	6 (0.9)	12 (1.2)	20 (1.3)	63 (1.7)

Adverse Events	White n (%)	Black n (%)	Asian n (%)	Other Races n (%)	Hispanic n (%)	Non-Hispanic n (%)
Nervous system disorders	**880 (27.2)**	**47 (16.8)**	**71 (10.1)**	**208 (20.8)**	**345 (22.4)**	**861 (23.5)**
Dizziness	90 (2.8)	10 (3.6)	10 (1.4)	25 (2.5)	45 (2.9)	90 (2.5)
Headache	799 (24.7)	43 (15.4)	60 (8.6)	187 (18.7)	307 (19.9)	782 (21.3)
Reproductive system and breast disorders	**61 (1.9)**	**--***	**--***	**12 (1.2)**	**23 (1.5)**	**54 (1.5)**
Dysmenorrhoea	52 (1.6)	--*	--*	9 (0.9)	17 (1.1)	47 (1.3)
Respiratory, thoracic and mediastinal Disorders	**365 (11.3)**	**10 (3.6)**	**20 (2.9)**	**47 (4.7)**	**97 (6.3)**	**345 (9.4)**
Cough	118 (3.7)	4 (1.4)	10 (1.4)	9 (0.9)	32 (2.1)	109 (3.0)
Nasal congestion	48 (1.5)	1 (0.4)	--*	--*	--*	41 (1.1)
Oropharyngeal pain	190 (5.9)	3 (1.1)	--*	19 (1.9)	34 (2.2)	182 (5.0)
Skin and subcutaneous tissue disorders	**99 (3.1)**	**5 (1.8)**	**13 (1.9)**	**27 (2.7)**	**34 (2.2)**	**110 (3.0)**

Source: Generated by CBER reviewer from STN125508/0.43_Module 1.11.3_Tables 70-75(p137-167).
*--sign means no data available or the percentage was <1%.

8.5.5 Product-Product Interactions

8.5.5.1 Concomitant Administration with Menactra and Adacel (Study V503-005)

Overall Adverse Event Summary

The primary safety objective of this open-label, randomized study was to evaluate the tolerability of the concomitant administration of a first dose of 9vHPV with Menactra and Adacel in boys and girls 11 to 15 years of age. Please refer to Section 7.1.9.1 for details of the study design.

The frequency of AEs was generally similar between the concomitant and con-concomitant groups. One subject (0.2%) in each group (1/613 in the concomitant group and, 1/611 in the non-concomitant group) was discontinued due to an AE. Five subjects in each group (5/613 in the concomitant group and 5/611 in the non-concomitant group) (0.8%), reported SAEs over the duration of the study. All the reported SAES were not related to study treatment.

In the concomitant group, one discontinuation (AN 34232) of the study vaccination occurred due to a vaccine-related severe pyrexia that resolved spontaneously after two days on Day 2 following Vaccination 2. This patient continued in the study follow-up. In the non-concomitant group, one discontinuation (AN 34258) of the study vaccination followed by discontinuation from the study occurred due to vaccine-related severe pain in the extremity following dose 1 of 9vHPV, which resolved spontaneously after 4 days.

Comparison of Injection-Site Adverse Reactions

Injection-site reactions were assessed in the concomitant and non-concomitant groups with respect to the numbers and percentages of subjects who reported solicited injection-site reactions at the 9vHPV injection-site (following the first dose) and at the Menactra/Adacel injection-site. Generally, the solicited injection-site reactions at both

9vHPV and Menactra/Adacel injection-sites were similar between concomitant and non-concomitant groups in terms of the frequency and intensity of the reactions.

Summary of Systemic Adverse Experiences

The numbers and percentages of subjects who reported specific systemic clinical AEs within 15 days following Vaccination 1 are compared by system organ class between the concomitant and non-concomitant groups. The proportions of systemic adverse experiences were similar between the two groups. Most of the AEs were mild or moderate. The proportions of severe systemic adverse experiences in the concomitant and non-concomitant groups were 4.7% and 3.8%, respectively.

The solicited systemic adverse reactions and maximum oral temperatures in Days 1 to 5 following Vaccination 1 were also similar between the concomitant and non-concomitant groups (approximately 8% of subjects with temperature ≥ 37.8°C in each group).

Summary of Serious Adverse Events

There were 11 SAEs in 10 subjects reported during this study, all of which were nonfatal. The number of subjects with SAEs in the study was comparable in the two groups, with six in the concomitant group and 5 in the non-concomitant group, all of which resolved. In the concomitant group, two subjects had appendicitis, and one subject each had abdominal wall seroma, mood disorder, and left testicular torsion. In the non-concomitant group, one subject had gastroenteritis and orthostatic hypotension, and one subject each had appendicitis, bronchitis, classic dengue and depression disorder. None was vaccine-related as judged by the investigators. None of the SAEs resulted in discontinuation. No subject died in this study.

SAEs occurring within 28 days following any vaccination are listed in Section 8.4.2.

Reviewer's comments*: This reviewer concurs with the investigators that none of the SAEs were vaccine related.*

Conclusion

The safety profile was generally favorable and similar between the concomitant and non-concomitant groups.

8.5.5.2 Study of 9vHPV in Prior Gardasil Recipients (Study V503-006)

Summary of Overall Clinical Adverse Experiences

The safety profile of 9vHPV was evaluated in a placebo controlled, double-blind trial with females 12 to 26 years of age who previously received a 3-dose regimen of qHPV. A summary of clinical adverse experiences by vaccination group from Day 1 through the end of the study is provided in Table 75.

Table 75: Adverse Event Summary (Day 1 to End of Study) (Study V503-006, All Vaccinated Subjects)

	9vHPV Vaccine n (%)	Placebo n (%)
Subjects in population with follow-up	608	305
Subjection with one or more adverse events	583 (95.9)	229 (75.1)
Subjects with injection-site reactions	554 (91.1)	135 (44.3)
Subjects with non-injection-site reactions	374 (61.5)	177 (58.0)
Subjects with vaccine-related adverse events	566 (93.1)	175 (57.4)
Subjects with vaccine-related injection-site reactions	554 (91.1)	135 (44.3)
Subjects with vaccine-related non-injection-site reactions	186 (30.6)	79 (25.9)
Subjects with SAE	3 (0.5)	3 (1.0)
Subjects with vaccine-related SAE	1 (0.2)	1 (0.3)
Subjects who died	0 (0.0)	0 (0.0)
Subjects who discontinued due to an AE	3 (0.5)	0 (0.0)
Subjects who discontinued due to a vaccine-related AE	3 (0.5)	0 (0.0)
Subjects who discontinued due to an SAE	0 (0.0)	0 (0.0)

Source: Replicated from STN125508/0_Module 5.3.5.1.p006_CSR_Table 12-2 (p140)

Three subjects in the 9vHPV group (3/608 [0.5%]) discontinued study vacci-tion due to an adverse experience. Subject AN37058 experienced abdominal pain and diarrhea 14 days after her second dose. Subject AN37035 experienced a swollen tongue 1 day after her first dose. The third subject (AN 37080) experienced injection-site swelling and erythema 1 day after her first dose of 9vHPV. This subject was the only one with AEs of erythema and swelling with a maximum size >6 and ≤7 inches. All of these adverse experiences resolved after a few days and were judged by the investigators to be vaccine related and non-serious.

A total of 20 subjects (13 in 9vHPV, 7 in qHPV) reported from post-Day 1 through Month 7 an incident condition that was potentially indicative of a systemic autoimmune disorder. In the 9vHPV vaccine group, 13 subjects reported arthralgia. In the placebo group, 4 subjects reported arthralgia, 2 subjects reported goiter, and 1 subject reported hypothyroidism. None of these events was considered to be an autoimmune condition by the reporting investigator.

Reviewer's comments: *This reviewer concurs with the reporting investigators that the arthralgia observed in the 13 subjects vaccinated with 9vHPV was not a systemic autoimmune disorder.*

This was the only placebo controlled study to evaluate the safety profile of the 9vHPV vaccine. However, the study population included subjects who were vaccinated previously with qHPV. Thus, the safety profiled obtained from this population may not be applicable to HPV vaccine naïve population.

Summary of Injection Site Reactions

Table 76 presents the numbers and proportions of subjects who reported at least one injection-site adverse reaction within 5 days of any vaccination. Across both vaccination

groups, the most common injection-site adverse reactions following any vaccination visit were pain, swelling, and erythema.

Table 76: Injection Site Reactions of 9vHPV in 12 to 26 Year-old Females Who were Previously Vaccinated with qHPV (Rate ≥ 1% in Days 1 to 5 Post-vaccination, Study V503-006)

Adverse Events	Intensity Grading	9vHPV N (%)	Saline Placebo N (%)
Population		608	305
Pain	Total	549 (90.3)	116 (38.0)
	Mild	316 (52.0)	105 (34.4)
	Moderate	209 (34.4)	10 (3.3)
	Severe	24 (3.9)	1 (0.3)
Swelling	Total	298 (49.0)	18 (5.9)
	Mild	182 (29.9)	13 (4.3)
	Moderate	65 (10.7)	3 (1.0)
	Severe	46 (7.6)	1 (0.3)
Erythema	Total	257 (42.3)	26 (8.5)
	Mild	190 (31.3)	22 (7.2)
	Moderate	39 (6.4)	0 (0.0)
	Severe	20 (3.3)	1 (0.3)
Pruritus	Total	47 (7.7)	4 (1.3)
	Mild	31 (5.1)	4 (1.3)
	Moderate	14 (2.3)	0 (0.0)
	Severe	2 (0.3)	0 (0.0)
Hematoma	Total	29 (4.8)	7 (2.3)
	Mild	24 (3.9)	6 (2.0)
	Moderate	5 (0.8)	1 (0.3)
Reaction	Total	8 (1.3)	1 (0.3)
	Mild	6 (1.0)	0 (0.0)
	Moderate	2 (0.3)	1 (0.3)
Mass	Total	7 (1.2)	2 (0.7)
	Mild	6 (1.0)	2 (0.7)
	Moderate	1 (0.2)	0 (0.0)

Source: Adapted from STN125508/0_Module 5.3.5.1.p006_CSR_Table 12-6 (p148-9) and Table 12-7 (p150).

Reviewer's comments: *Although the proportions of subjects with overall injection site reactions were similar to those in HPV vaccine naïve females in the other studies, the proportions of injection site swelling and erythema and the corresponding intensities were numerically higher among subjects who were previously vaccinated with qHPV (Please refer to Tables 30, 44 and 73).*

Summary of Systemic Adverse Experiences

Systemic clinical adverse experiences from Day 1 to 15 following any vaccination were analyzed by system organ class. In both vaccination groups, the most common clinical adverse experiences were headache (9vHPV 30.9% vs. placebo 26.6%), fatigue (9vHPV 3.5% vs. placebo 3.6%), and pyrexia (9vHPV 6.7% vs. placebo 3.3%).

The numbers and percentages of subjects who reported specific systemic clinical adverse experiences from Day 1 to 15 following any vaccination were similar between 9vHPV and placebo groups, except for higher frequencies of the following events:

- Abdominal Discomfort: 1.3% (8/608) in the 9vHPV group vs. no case in the placebo group.
- Dizziness: 4.9% (30/608) in the 9vHPV group vs. 2.0% (6/305) in the placebo group.
- Nausea: 8.6% (52/608) in the 9vHPV group vs. 3.9% (12/305) in the placebo group.
- Pyrexia: 6.7% (41/608) in the 9vHPV group vs. 3.3% (10/305) in the placebo group.

Most of the systemic adverse experiences reported by subjects across the two groups were of mild or moderate intensity. The proportion of subjects in the 9vHPV group with severe systemic adverse experiences was 10.4% (63/608), while that for the placebo group was 11.1% (34/305).

Table 77 presents by system organ class the numbers and percentages of subjects with vaccine-related systemic adverse experiences from Day 1 to 15 following any vaccination (rate ≥1% in one or more vaccination groups).

Table 77: Vaccine-Related Systemic Adverse Events within 15 Days Post-Vaccination (Rate ≥1% in One or More Vaccination Groups) Among Females 12 to 26 Years of Age Previously Vaccinated with qHPV (Study V503-006)

Adverse Events	9vHPV N (%)	Saline placebo N (%)
Subjects in population with follow-up with one or more systemic adverse events	608 186 (30.6)	305 79 (25.9)
Gastrointestinal disorders Abdominal pain upper Diarrhea Nausea Vomiting	**44 (7.2)** 9 (1.5) 4 (0.7) 24 (3.9) 6 (1.0)	**12 (3.9)** 2 (0.7) 3 (1.0) 6 (2.0) 3 (1.0)
General disorders and administration site conditions Fatigue Malaise Pyrexia	**50 (8.2)** 11 (1.8) 5 (0.8) 31 (5.1)	**16 (5.2)** 7 (2.3) 3 (1.0) 5 (1.6)
Infections and infestations Influenza	**15 (2.5)** 7 (1.2)	**7 (2.3)** 3 (1.0)
Musculoskeletal and connective tissue Disorders	**11 (1.8)**	**4 (1.3)**
Nervous system disorders Dizziness Headache	**129 (21.2)** 18 (3.0) 119 (19.6)	**61 (20.0)** 5 (1.6) 55 (18.0)
Psychiatric disorders	**7 (1.2)**	**5 (1.6)**
Skin and subcutaneous tissue disorders	**11 (1.8)**	**2 (0.7)**

Source: Adapted from STN125508/0_Module 5.3.5.1.p006_CSR_Table 12-14 (p162).

Summary of Serious Adverse Events

Five subjects reported six non-fatal SAEs (three in the 9vHPV group and three in the placebo group). The three SAEs reported by two subjects in the placebo group were thoracic and lumbar vertebral fraction (both in Subject AN 37897, snowboarding accident) and migraine (resulting in hospitalization, Subject AN 37974). The three SAEs in 9vHPV group are summarized below.

Narrative Summary of SAEs in the 9vHPV Group

Subject AN37083, a 15 year-old white female, was previously vaccinated with Gardasil vaccine in 2007/2008. On December 5, 2010 (13 days post dose 2 of 9vHPV), she had an episode of syncope for about 30 minutes. She was hospitalized for clinical evaluation. Following extensive evaluation, she was diagnosed with dysautonomia. She recovered from the syncope and was discharged. The investigator assessed the syncope as not related to vaccine. She received her third dose of 9vHPV on February 9, 2011, as scheduled without subsequent syncope.

Subject AN 37571, an 18 year old white female, developed appendicitis 75 days after her second dose of 9vHPV. She was hospitalized and underwent laparoscopic appendectomy the same day. She recovered and received her third dose of 9vHPV as scheduled. The SAE was considered by the investigator not to be related to the vaccine.

Subject AN 37801, an 18 year old white female, experienced tonsillitis and fever of 38.2^{o}C on the second day after she received her first dose of 9vHPV. Lymphadenopathy on both sides of the neck was noted. She was hospitalized and treated with drainage of swollen tonsils, IV Penicillin and a 10-day course of Metronidazole and Vepicombin. Tonsil incision or puncture in the following 3 consecutive days produced 1-1.5 ml of purulent fluid. No bacteriological testing was performed. She recovered from tonsillitis 3 days later and was discharged from the hospital with a diagnosis of left peritonsillar abscess. She received her second and third doses of 9vHPV as scheduled. The reporting investigator concluded that tonsillitis was related to 9vHPV**.**

Reviewer's comments: *The symptoms of dysautonomia in Subjects AN 37083 appeared to be consistent with those of postural tachycardia syndrome (POTS). A link between POTS and Gardasil vaccination has been postulated in a recent report (Blitshteyn S. Eur J Neurol, 2014; 21: 135-139), though the mechanism for such an association remains unclear. In this report, six subjects developed symptoms of POTS within 6 days to 2 months after immunization with Gardasil vaccine. Two patients experienced significant symptomatic exacerbation following a subsequent Gardasil injection, suggesting a positive re-challenge result. Since Subject* AN 37083 *received Gardasil vaccination approximately two years ago, and her symptoms of dysautonomia only occurred after the second dose of 9vHPV, it is difficult to determine if the dysautonomia or syncope is related to 9vHPV.*

Conclusion

The overall safety and tolerability profile of 9vHPV was favorable when administered to 12- to 26-year-old females who were previously vaccinated with qHPV. Safety and tolerability findings in that population were generally consistent with those previously reported in HPV-vaccine naïve 9- to 26-year-old -females following administration of a 3-

dose regimen of the qHPV vaccine and in HPV vaccine naïve 9 through 15 year-old males and females and 16 through 26 year-old females following administration of 9vHPV in other studies included in this submission.

8.5.5.3 Concomitant Administration with Repevax (Study V503-007)

The safety and immunogenicity of the 9vHPV vaccine when concomitantly administered with Repevax was investigated, and the study design and clinical evaluation were similar to those of Study V503-005. This reviewer assessed all the immunogenicity and safety data of this trial. Concomitant administration of the 9vHPV with Repevax did not negatively impact on immunogenicity of 9vHPV vaccine and Repevax, as well as the safety profile. Since Repevax is not licensed in the U.S., the evaluation of this trial is not documented in this review. However, the safety data is included in the pooled integrated safety analyses.

8.6 Safety Conclusions

Based on the integrated safety data for 9vHPV, this reviewer concludes that:

- The safety profile of 9vHPV is favorable in female subjects 16 through 26 years of age, as well as in female and male subjects 9 through 15 years of age. The safety profile of 9vHPV is generally similar to that of qHPV among subjects 9 to 26 years of age.
- Use of 9vHPV among subjects 9 to 26 years of age is associated with an increase in injection-site adverse reactions compared with qHPV. However, most of the injection-site adverse reactions in subjects administered 9vHPV are mild or moderate in intensity.
- In general, frequencies and intensities of injection-site adverse reactions are similar following administration of a first, second, and third dose of 9vHPV; however, the frequencies of injection-site erythema and swelling were increased at each consecutive vaccine administration.
- The safety profiles of 9vHPV in males 9 through 15 years of age and females, 9 through 15 years of age are generally similar.
- The safety profile of 9vHPV does not appear to be impacted by racial background, ethnicity, or continent of origin.
- The safety profile of 9vHPV is favorable in females 12 to 26 years of age who previously received a 3-dose regimen of qHPV. However, administration of 9vHPV in prior qHPV recipients is associated with higher proportions of subject with injection-site swelling and erythema than in subjects who are naïve to HPV vaccination. Most of these injection-site adverse reactions are mild in intensity.
- The safety profile of 9vHPV is not impacted by concomitant vaccination with Menactra and Adacel.
- Overall rates of new onset autoimmune disorders were similar between 9vHPV recipients and qHPV recipients and were generally within rates observed in the general population. However, there was an imbalance between 9vHPV and qHPV in small numbers of cases of multiple sclerosis, type 1 diabetes mellitus, and Raynaud's phenomenon with higher rates of each among 9vHPV recipients. The incidence rates for these medical conditions in the 9vHPV group are within the ranges reported in the general population of similar ages.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

9.1.1.1 Pregnancy Outcomes in Clinical Studies

Table 78 presents the pregnancy outcome summary from all studies submitted to the application. Overall, 1213 subjects who received 9vHPV in Protocols V503-001, -002 and 006 experienced 1373 pregnancies. The vast majority of these pregnancies (~98%) occurred in subjects enrolled in Protocol V503-001. An adverse pregnancy outcome was defined as spontaneous abortion (SAB), late fetal death ectopic pregnancy or congenital anomaly. The overall proportion of pregnancies with a known outcome that ended in a fetal loss (excluding elective abortion) was 12.4% (146/1178) for 9vHPV recipients and 14.3% (158/1108) for qHPV recipients

Table 78: Summary of Outcomes for Pregnancies that Occurred from Study Day 1 through Visit Cut-Off Date (All Vaccinated Subjects, Protocols V503-001, -002 and -006)

Population and Pregnancy Outcomes	9vHPV (N=10,105) n (%)	qHPV ((N=7,093) n (%)
Number of Subjects	**10,055**	**7,093**
Subjects with pregnancies	1,213 (12.1)	1,129 (15.9)
Number of pregnancies	**1,373**	**1,300**
Number of pregnancies with known outcome	1,178	1,108
Live Births[1]	**897 (76.1)**	**841 (75.9)**
Infant Outcome		
Normal	868 (96.8)	811 (96.4)
Congenital Anomaly	14 (1.6)	18 (2.1)
Other Abnormality	7 (0.8)	11 (1.3)
Unknown	9 (1.0)	5 (0.6)
Fetal Loss[1]	**281 (23.9)**	**267 (24.1)**
Type of Loss		
Ectopic Pregnancy	13 (1.1)	7 (0.6)
Spontaneous Abortion	122 (10.4)	143 (12.9)
Late Fetal Death	3 (0.3)	4 (0.4)
Elective Abortion	143 (12.1)	113 (10.2)
Fetal outcome		
Normal	54 (19.2)	43 (16.1)
Congenital Anomaly	6 (2.1)	3 (1.1)
Other Abnormality	2 (0.7)	1 (0.4)
Unknown	215 (76.5)	216 (80.9)

Source: Adapted from STN 125508/0.43_Module 1.11.3_Tables 76-77(p168-171).

[1]Percentages of "Live Births", "Fetal Loss" and "Type of Loss-" are calculated based on the number of fetuses/infants with known outcome. Percentages under "Infant Outcome" are calculated based on "Live Births". Percentages under "Fetal Outcome" are calculated based on "Fetal Loss".

N=Number of vaccinated subjects in each vaccination group. n=Number of cases with the respective category. The "Unknown" category reports the number of congenital anomaly outcomes that were reported by the study site as "Unknown".

Reviewer's comments: *The proportions of pregnancies ending in spontaneous abortion, congenital anomaly and late fetal mortality observed in both the 9vHPV and qHPV groups were within the ranges reported in the literature for the general population of women of child-bearing age[(37-39)]. However, the results should be interpreted with caution when compared to literature reports because pregnancy outcomes vary with age, ethnicity and race, and no populations reported in literature exactly match the populations in this study,*

The Applicant provided analyses to evaluate differences in pregnancy outcomes among subjects whose estimated date of conception (EDCn) occurred within 30 days of any 9vHPV vaccination compared with subjects whose EDCn occurred more than 30 days after any 9vHPV vaccination. Table 79 presents the summary of pregnancy outcomes in 9vHPV recipients by EDCn.

Table 79: Summary of Pregnancy Outcomes among 9vHPV Recipients--Comparing Estimated Date of Conception (EDCn) within 30 Days of Any Vaccination vs. Not within 30 Days of Any Vaccination (Protocols 001, 002, and 006, Entire Study Period)

Population and Pregnancy Outcomes	EDCn within 30 Days n (%)	EDCn not within 30 Days n (%)
Number of Subjects with pregnancies	**91**	**1,140**
Number of pregnancies	**92**	**1,281**
Number of pregnancies with known outcome	89	1,089
Live Births[1]	**44 (49.4)**	**853 (78.3)**
Infant Outcome		
Normal	41 (93.2)	827 (97.0)
Congenital Anomaly	0 (0.0)	14 (1.6)
Other Abnormality	1 (2.3)	6 (0.7)
Unknown	2 (4.5)	7 (0.8)
Fetal Loss[1]	**45 (50.6)**	**236 (21.7)**
Type of Loss		
Ectopic Pregnancy	0 (0.0)	13 (1.2)
Spontaneous Abortion	17 (19.1)	105 (9.6)
Late Fetal Death	1 (1.1)	2 (0.2)
Elective Abortion	27 (30.3)	116 (10.7)
Fetal outcome		
Normal	11 (24.4)	43 (18.2)
Congenital Anomaly	0 (0.0)	6 (2.5)
Other Abnormality	0 (0.0)	2 (0.8)
Unknown	34 (75.6)	181 (76.7)

Source: Adapted from STN 125508/0.43_Module 1.11.3 Tables 78 &79(p172-175)).
[1]Percentages of "Live Births", "Fetal Loss" and "Type of Loss-" are calculated based on the number of fetuses/infants with known outcome. Percentages under "Infant Outcome" are calculated based on "Live Births". Percentages under "Fetal Outcome" are calculated based on "Fetal Loss".
N=Number of vaccinated subjects in each vaccination group.
n=Number of cases with the respective category.
The "Unknown" category reports the number of congenital anomaly outcomes that were reported by the study site as "Unknown".

Because of the protocol requirement for the use of effective contraception from Day 1 through Month 7 and the pregnancy testing prior to each vaccination, only approximately 1% of study subjects who received 9vHPV became pregnant within 30 days of a vaccination. Pregnancies within this timeframe represented only 6.7% (89/1373) of all pregnancies reported in subjects who received 9vHPV. Based on the cut-off date for the current analyses, outcomes were available for 1178 pregnancies. The great majority of pregnancies whose outcomes were not available at the time of the visit cut-off date were ongoing (i.e., subjects had not completed their pregnancies). There were no congenital anomalies reported in pregnancies with an EDCn within 30 days of a study vaccination. Twenty congenital anomalies were reported among pregnancies with an EDCn not within 30 days of a study vaccination, including:

- Fourteen congenital anomalies in live infants (including 3 cases that had an intra-uterine diagnosis and 11 cases diagnosed beyond the neonatal period)
- Six congenital anomalies associated with fetal loss (all 6 cases reported were elective abortions based on intra-uterine diagnosis)

The SAB rate among the 9vHPV recipients who became pregnant within 30 days of any vaccination was higher than those who became pregnant not-within 30 days of vaccination (19.1% vs. 9.6%).

Reviewer's comment: *On April 23, 2014, this reviewer requested that the Applicant provide the SAB rate among qHPV recipients who became pregnant within 30 days of any vaccination. The data provided by the Applicant showed that the SAB rate in subjects who received qHPV and became pregnant within 30 days of any vaccination was 8.0% (7 spontaneous abortions out of 88 pregnancies with known outcome). The SAB rate in subjects who received qHPV and had a pregnancy not-within 30 days of any vaccination was 13.3% (136 out of 1020).*

CBER reviewers conducted extensive analyses to explore potential confounding factors that may contribute to the increased SAB rate for pregnancies beginning within 30 days of vaccination with 9vHPV. These factors included age, race, geographic regions, smoking history, previous history of SABs, concomitant medications, history of sexually transmitted diseases, and baseline serostatus of HPV types. Even after adjusting for these potentially confounding factors the imbalance in SAB rates remained.

A similar imbalance in elective abortions was also observed between subjects who became pregnant within 30 days vs. not-within 30 days of vaccination in the 9vHPV group (30.3% vs. 10.7%, Table 79), and in the qHPV group [36% (38/88) within 30 days vs. 7.9% (81/1020) not-within 30 days, data submitted to STN 125508/0.13]. The cause of these imbalances in elective abortions is unknown.

On June 13, 2014, the review team requested that the Applicant provide further assessments and interpretations for the imbalance in SAB rates. Table 80 presents the summary of the Applicant's assessment identifying Latin American region as a potential confounding variable, based on the large proportion of SABs reported from Latin American countries and known social and legal barriers to elective abortion in those countries.

Table 80: Comparison of Spontaneous Abortion Rates between 9vHPV Recipients and qHPV Recipients Based on Proximity of Estimated Date of Conception (EDCn) Relative to Vaccination Dates (Protocols 001, All Study Population and Non-Latin American Population)

Population and Treatment Group	**EDCn within 30 Days of Vaccination n/N (%)**	**EDCn not-within 30 Days of vaccination n/N (%)**	**All SAB n/N (%)**
Entire Population			
9vHPV Group	17/60 (28.3%)	105/960 (10.9%)	121/1012 (12.0%)
qHPV Group	7/55 (12.7%)	136/933 (14.6%)	143/988 (14.5%)
Non-Latin Americans			
9vHPV Group	5/25 (20.0%)	54/591 (9.1%)	58/610 (9.5%)
qHPV Group	1/31 (3.2%)	70/570 (12.3%)	71/601 (11.8%)

Source: The Table is created by the reviewer based on the data submitted to STN 125508/0.13 (Module 1.11.3) and STN 125508/0.25 (Module 1.11.3) per CBER request.
n=number of spontaneous abortions; N=number of subjects with natural pregnancy outcomes (i.e., live births, spontaneous abortions, or late fetal death and excluding those terminating in elective abortion).

As seen in Table 80, even for the Non-Latin American population, the SAB rate among subjects who received the 9vHPV vaccine and became pregnant within 30 days of any vaccination was still higher (20%) compared with the SAB rates among subjects who received the 9vHPV or qHPV vaccine and became pregnant not-within 30 days of vaccination (9.1% and 12.3% respectively). Because of small numbers of SABs in these *post hoc* analyses, it is difficult to determine whether the observed imbalance in SAB represents a real risk. Consequently, the review team recommended a post-marketing assessment of SAB, to be conducted collaboratively by FDA and the Centers for Disease Control and Prevention (CDC) using Vaccine Safety Datalink (VSD).

Reviewer's comments*: Elective abortions are not included in the denominators in Table 80. As a result, the spontaneous rates in Table 80 are different from the corresponding rates in Table 79.*

9.1.2 Use during Lactation

Breastfeeding was not a contraindication to enrollment or vaccination. Administration of 9vHPV or qHPV to nursing mothers in the phase 3 studies was reported and followed for outcome of both the mother and her infant until the infant was weaned.

A total of 86 lactating subjects received 9vHPV in Protocols V503-001 and V503-002 (including 85 subjects in Protocol V503-001 and 1 subject in Protocol V503-002). By comparison, in Protocol V503-001, a total of 87 subjects administered qHPV were lactating during the vaccination period. No subjects who were lactating during the vaccination period were enrolled in Protocols V503-005, -006, -007 and -009.

The adverse experience profile of 9vHPV (injection-site reactions and fever in Day 1 to 5 and systemic adverse events in Day 1 to 15 after each vaccination) in lactating women was generally similar to the adverse experience profile in the overall Safety Population.

A total of 10 SAEs were reported by 10 lactating 9vHPV recipients. Seven SAEs were related to pregnancy (e.g., spontaneous abortion, premature labor), and the remaining three were elective abortion, hemorrhagic fever and ependymoma.

There were no SAEs reported in breastfed infants -9vHPV or qHPV recipients. No safety signals of clinical concern were identified among these infants.

9.1.3 Pediatric Use and PREA Considerations

The investigational vaccine has been adequately studied in children 9 years of age and older.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups. The Applicant requested a partial waiver from the requirements of PREA for children 0-8 years of age. CBER agreed to grant the waiver request because initiating vaccination prior to age 8 does not represent a meaningful therapeutic benefit over initiating vaccination at 9 years of age and older, and Gardasil 9 is not likely to be used in a substantial number of children in this age group because the objective of immunization with this vaccine is to prevent diseases that occur following exposure to HPV.

9.1.4 Immunocompromised Patients

The safety and effectiveness of 9vHPV have not been formally evaluated in immunocompromised patient populations. Small numbers of subjects were vaccinated concomitantly with immunosuppressive therapies, and the immunogenicity of 9vHPV in these subjects compared to the general study population is discussed in detail in Section 7.1.9.4.

9.1.5 Geriatric Use

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

9.2 Safety Update Reports

9.2.1 Safety Update Report Four Months after the Submission of the BLA

The Applicant submitted a Safety Update Report to STN 125508/0.9 on April 10, 2014. The safety update included data from three completed clinical trials (V503-005, V503-007, and V503-009) and three extension studies of completed clinical trials (V503-001, V503-002, and V503-006).

In this report, the same investigator from Denmark reported three SAEs assessed as vaccine-related: one subject (AN 19756) experienced hypersomnia at more than four years after the third dose of 9vHPV, and two subjects (AN 71508 and AN 71686) experienced postural tachycardia syndrome (POTS) at more than three years after the third dose of 9vHPV and qHPV, respectively.

The safety update also reported rates of spontaneous abortions that occurred during the extended reporting period: 9.4% (128 spontaneous abortions out of 1364 pregnancies

with known outcomes) in 9vHPV recipients, and 11.7% (156 out of 1334) in qHPV recipients.

***Reviewer's comments**: A recent study (Blitshteyn S. Postural tachycardia syndrome following human papillomavirus vaccination, Eur J Neurol, 2014; 21: 135-9) reported that six patients developed new onset POTS 6 days to 2 months following Gardasil vaccination, suggesting a causal association between POTS and HPV vaccines. Given the lack of temporal association with vaccination of the events reported in the safety update, these events were unlikely related to vaccination.*

Based on the safety update provided, the conclusions regarding the safety of 9vHPV is unchanged.

10. CONCLUSIONS

10.1 Efficacy and Immunogenicity

- Administration of a 3-dose regimen of 9vHPV vaccine to females 16 through 26 years of age induced statistically non-inferior anti-HPV 6, 11, 16, and 18 antibody responses compared with qHPV vaccine, supporting the bridging of the protective efficacy of the qHPV vaccine in preventing cervical, vaginal, vulvar, external genital and anal infection and disease caused by HPV types 6, 11, 16, and 18 to the 9vHPV vaccine.
- Administration of a 3-dose regimen of 9vHPV vaccine to female 16 through 26 years of age was effective in preventing the primary endpoint of HPV 31/33/45/52/58-related, high-grade cervical, vulvar, and vaginal disease (CIN 2 or worse, VIN 2/3 or worse, VaIN 2/3 or worse), the secondary endpoint of the five new HPV type related persistent infection, and the exploratory endpoint of invasive procedures (genital biopsy and definitive therapy). Effectiveness in preventing anal disease caused by these five new HPV types is inferred by similar disease pathophysiology and immunogenicity of 9vHPV with respect to these HPV types.
- Administration of a 3-dose regimen of 9vHPV vaccine to pre-adolescents and adolescents 9 through 15 years of age induced statistically non-inferior anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 antibody responses compared with anti-HPV responses induced in females 16 through 26 years of age, supporting inference in the pediatric population of 9vHPV protective efficacy in preventing ano-gential diseases due to the vaccine HPV types.
- The 9vHPV vaccine induced robust anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 antibody responses through at least 1.5 years post-vaccination.
- The final manufacturing process of the 9vHPV vaccine produced materials that generated consistent Month 7 anti-HPV cLIA responses.
- Concomitant administration of a 3-dose regimen of 9vHPV vaccine with Menactra and Adacel did not interfere with antibody responses to any of the three vaccines.
- Administration of a 3-dose regimen of 9vHPV vaccine in females 12 to 26 years of age who were previously administered a 3-dose regimen of qHPV vaccine induced higher anti-HPV 6, 11, 16 and 18, and lower anti-HPV 31, 33, 45, 52 and 58 responses compared with females 12 to 26 years of age who were naïve to

HPV vaccines. The clinical significance of the reduced responses to the five new HPV types is unclear.

10.2 Safety conclusion:

- The safety profile of the 9vHPV vaccine was favorable and generally similar to that of the qHPV vaccine among subjects 9 to 26 years of age. Use of 9vHPV vaccine among subjects 9 to 26 years of age was associated with an increased frequency of injection-site adverse reactions compared with qHPV vaccine. However, most of the injection-site adverse reactions in subjects administered 9vHPV vaccine were mild or moderate in intensity.
- In general, across the 3-dose series of vaccine administration, injection-site adverse experiences were reported in similar frequencies following administration of a first, second, and third dose of 9vHPV vaccine; however, the frequencies of the adverse reactions of injection-site erythema and injection site swelling were increased at each consecutive vaccine administration.
- The adverse experience profiles of 9vHPV vaccine in males and females 9 through 15 years of age were similar to each other and to the adverse experience profile in females 16 through 26 years of age.
- The adverse experience profile of 9vHPV vaccine was not impacted by racial background, ethnicity, or continent of origin.
- The 9vHPV vaccine was generally tolerated in prior qHPV vaccine recipients. No safety issues were identified following administration of 9vHPV to nursing mothers, and vaccination did not appear to impact the health of breastfeeding infants of mothers who received 9vHPV vaccine.
- The rates of new onset of medical conditions of potential autoimmune disorders were similar between the 9vHPV and qHPV treatment groups except for small numerical imbalances in cases of multiple sclerosis. Women 16 through 26 years of age who received the 9vHPV vaccine reported more cases than women who received the qHPV vaccine. However, the rate of multiple sclerosis in the 9vHPV group was within the range reported in the general population of similar ages.
- The spontaneous abortion rate among women who received the 9vHPV vaccine was similar to rate among women who received qHPV. However in a *post-hoc* subanalysis the spontaneous abortion rate among women who received the 9vHPV vaccine and became pregnant within 30 days of any vaccination was also numerically higher than the corresponding rate in women who were immunized with the qHPV vaccine. The clinical significance of this imbalance is unknown.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

A comparison of the risks and benefits of licensure of the 9vHPV vaccine for use in the indicated populations is presented in Table 81.

Table 81: Risk-Benefit Assessment of the 9vHPV Vaccine

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 anogenital dysplasias, and eventually to anogenital cancers. • Treatment for anogenital 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.	• Anogenital cancers are progressive, life-threatening diseases. • Anogenital dysplasias are serious conditions, 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	• Gardasil and Cervarix prevent approximately 70% of cervical cancer caused by HPV 16 and 18 and are marketed worldwide. Nearly 100% of cervical and a-l cancers are caused by oncogenic HPV types. Neither vaccine provides protection against anogenital cancers caused by HPV types other than HPV 16 and 18. • 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.	• There is a need for effective prevention of HPV infection or ano-genital cancers caused by other oncogenic HPV types such as HPV 31, 33, 45, 52 and 58, which are included in the 9vHPV vaccine. • The 9vHPV vaccine has a potential to prevent approximately 90% of cervical cancer caused by oncogenic HPV types.
Clinical Benefit	• The Applicant submitted results from one well-controlled clinical efficacy trial in women 16 through 26 years of age that demonstrated protection against high-grade and low-grade genital lesions, genital warts, persistent infections, Pap abnormalities, and invasive procedures associated with the five new HPV types in 9vHPV and also demonstrated non-inferiority of antibody responses to the four original HPV types compared to qHPV. An immunogenicity bridging trial demonstrated non-inferior antibody responses to 9vHPV among males and females 9 through 15 years of age compared to females 16 through 26 years of age. • Compared to historical data from placebo recipients in the qHPV program, the efficacy study demonstrated 9vHPV protective efficacy against HPV-associated genital disease endpoints regardless of HPV type -among females naïve to HPV infection. • The point estimates of 9vHPV prophylactic efficacy against high-grade	• Based on direct evidence of efficacy and inference from immunogenicity endpoints, the 9vHPV vaccine is effective in preventing pre-cancerous genital lesions and genital warts associated with the nine vaccine HPV types among males 9 through 15 years of age and females 9 to 26 years of age. • Effectiveness against genital cancers is inferred from the efficacy demonstrated against pre-cancerous lesions and pathophysiology of HPV-associated cancers. • Compared with qHPV, 9vHPV offers approximately additional 20% coverage of cervical, vulvar and vaginal high grade intraepithelial neoplasia and cancers caused by the oncogenic HPV types. • Although efficacy of 9vHPV against a-l lesions was not assessed, it is inferred through highly similar pathophysiology to HPV-associated genital disease, prevention of HPV 16 and 18-related

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	genital disease related to the five new HPV types are consistent across the subgroups investigated. • Efficacy of 9vHPV against anal lesions associated with the five new HPV types was not assessed in this submission because of infeasibility.	anal lesions by qHPV, prevention of HPV 31, 33, 45, 52 and 58-related persistent infection by 9vHPV.
Risk	• The most common adverse reactions from 9vHPV vaccination are the injection site reactions such as erythema, swelling, and pain. However, most injection site reactions are mild or moderate in severity, and they resolve relatively quickly without sequelae. • Severe allergic reactions that led to study discontinuation were observed in two subjects • Syncope or fainting occurred in some subjects following injection, although no syncope with fall resulted in injury. • There was a numerically higher rate of spontaneous abortions among subjects who became pregnant within 30 days of any vaccination with 9vHPV, compared with subjects who became pregnant within 30 days of any vaccination with qHPV and subjects who became pregnant not-within 30 days of any study vaccination. • There was a numerically higher case rate of multiple sclerosis in the 9vHPV t group compared to qHPV control.	• All the evidence indicates that the population-based benefit of vaccination with 9vHPV outweighs the risk associated with vaccine-related adverse outcomes. • Although 9vHPV may cause an anaphylaxis and syncope, these adverse reactions are rare and manageable. • Numerically higher rates of spontaneous abortion and multiple sclerosis associated with the 9vHPV vaccination are of uncertain clinical significance and warrant further evaluation in in post-marketing assessments.
Risk Management	• It is uncertain whether numerically higher rates of spontaneous abortion and multiple sclerosis are related to 9vHPV. • Any risk associated with 9vHPV vaccination within 30 days of conception would be applicable to a very small percentage of 9vHPV recipients.	• The Applicant has proposed a pregnancy registry for post-marketing assessment of pregnancy outcomes. • Post-market assessment for multiple sclerosis and autoimmune disorders in general may be conducted via Mini-Sentinel. • Post-marketing assessment of spontaneous abortion may be conducted via Vaccine Safety Datalink

11.2 Risk-Benefit Summary and Assessment

As detailed in the table above, the benefit/risk balance for 9vHPV vaccine is favorable among females 9 to 26 years of age and males 9 through 15 years of age. On the basis of the data from this submission, 9vHPV is effective in preventing (1) HPV 16, 18, 31, 33, 45, 52, and 58-related cervical, vulvar, vaginal, and anal cancers, and the high-grade pre-cancers that immediately precede them; and (2) HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58-related CIN, VIN, VaIN, AIN, and genital warts, and persistent infection. The proposed indication for 9vHPV is supported by the data presented in this application.

The most common adverse reactions observed with 9vHPV in the proposed population are injection site reactions (pain, swelling and erythema), headache, pyrexia, nausea, dizziness and fatigue. These adverse reactions are typically mild to moderate, and resolve within several days. Allergic reactions are rare and manageable.

Although numerically higher rates of spontaneous abortions and multiple sclerosis were associated with the 9vHPV vaccination, the relatedness and clinical significance are uncertain. These safety concerns could be addressed by post-marketing assessments.

Currently there is no available vaccine licensed for prevention of anogenital cancers caused by HPV types other than HPV 16 and 18. The new HPV types in the 9vHPV vaccine have a potential to prevent approximately 20% cervical cancer. Consequently, licensure of the 9vHPV vaccine would fill an unmet medical need. In the opinion of this reviewer, the substantial benefit offered by the 9vHPV outweighs its risks.

11.3 Discussion of Regulatory Options

In the opinion of this reviewer, the clinical data support traditional approval of this BLA.

11.4 Recommendations on Regulatory Actions

In the opinion of this reviewer, the clinical efficacy, immunogenicity and safety data submitted in this application support approval of this BLA to license Gardasil 9 for use in females 9 to 26 years of age and males 9 through 15 years of age.

11.5 Labeling Review and Recommendations

At the time this review was finalizing, labeling negotiations with the Applicant were ongoing. The initial comments and suggestions for package insert revision were sent to the Applicant on November 10, 2014. We proposed the following labeling revisions:

- Including a statement that the efficacy of Gardasil 9 against anal disease was not assessed in this submission.
- Including a statement that safety and effectiveness of Gardasil 9 has not been assessed in women older than 26 years of age.
- Revising Section 8.1 of the proposed PI to include information regarding spontaneous abortions.
- Deleting the post hoc analysis results comparing efficacy of 9vHPV with historical placebo control in the Gardasil program.
- Including a statement about the lower immune responses for the five new HPV types observed among subjects who were previously immunized with qHPV.

The Applicant submitted its initial responses on November 17, 2014 and accepted CBER's proposed labeling revisions.

11.6 Recommendations on Postmarketing Actions

This reviewer recommends that post-marketing assessments be conducted to further evaluate the rates of spontaneous abortions and new onset of selected auto-immune conditions following vaccination with 9vHPV. The assessment of new onset auto-immune conditions will be conducted by the FDA using Mini-Sentinel, while the assessment of spontaneous abortions will involve a collaboration between FDA and CDC using Vaccine Safety Datalink

In addition, the Applicant also committed to conduct the following post-marketing assessments:

- Long-term immunogenicity, efficacy, and safety of Gardasil 9 through an extension of Protocol V503-002: The proposed observational study will extend the base study up to Month 126 for girls and boys between the ages of 9 through 15 years at randomization.
- Long-term efficacy and safety study in collaboration with the Nordic Region countries of Denmark, Norway and Sweden through the extension of Protocol V503-001: The observational study will include up to 4453 women 16 through 26 years of age enrolled and vaccinated in these countries during the original clinical trial who with follow up for up to 12 years
- Pregnancy registry in the U.S. to collect data on spontaneously-reported exposures to HPV9 during pregnancy: Data in this registry will be used to assess risks relevant to pregnancy, including pregnancy outcomes of live births, congenital anomalies, spontaneous abortions, and late fetal deaths.
- Immunogenicity bridging study (V503-003) to support use Gardasil 9 in males 16 through 26 years of age: This study is designed to evaluate the immunogenicity and safety of V503 in young men in comparison to young women 16 through 26 years of age.