sBLA Clinical Review Memorandum

Application Type	sBLA
STN	125508/868
CBER Received Date	13 December 2019
PDUFA Goal Date	12 June 2020
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Alexandra Yonts, MD
Review Completion Date / Stamped Date	22 May 2020/ 9 June 2020
Supervisory Concurrence	Rebecca Reindel, MD, Team Leader, CRB2 Andrea Hulse, MD, Branch Chief, CRB2
Applicant	Merck Sharpe & Dohme Corp.
Established Name	9-valent human papillomavirus (type 6, 11, 16, 18, 31, 33, 45, 52, 58)
(Proposed) Trade Name	GARDASIL 9
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	A dose (0.5 mL) contains recombinant virus-like proteins (VLPs) of the major capsid (L1) proteins of HPV types 6,11,16,18,31,33,45,52 and 58 (30 µg/ 40 µg /60 µg /40 µg /20 µg /20 µg /20 µg /20 µg /20 µg of the 9 types, respectively) adsorbed on preformed aluminum containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS)
Dosage Form(s) and Route(s) of Administration	0.5mL suspension for intramuscular injection as a single-dose vial and prefilled syringe
Dosing Regimen(s)	• Three-dose regimen (0,2 and 6 months) approved for use in individuals 9 through 45 years of age (STN 125508/0 and 125508/493)

	• Two-dose regimen (0 and 6-12 months) approved for use in individuals 9 through 14 years of age (STN 125508/153)
Indication(s) and Intended Population(s)	The BLA supplement proposes to extend the indications to include the prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine in men and women 9 through 45 years of age. GARDASIL 9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases: • Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58 • Genital warts (condyloma acuminata) caused by HPV types 6 and 11 And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: • Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS) • Cervical intraepithelial neoplasia (CIN) grade 1 • Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3 • Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3 • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

	GARDASIL 9 is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases: • Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58 • Genital warts (condyloma acuminata) caused by HPV types 6 and 11 And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: • Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3
Orphan Designated (Yes/No)	No

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GLOSSARY

9vHPV	9-valent Human Papillomavirus Vaccine
AE	adverse event
AIS	adenocarcinoma *in situ*
AIN	anal intraepithelial neoplasia
BLA	biologics license application
CFR	Code of Federal Regulations
CIN	cervical intraepithelial neoplasia
CMC	chemistry, manufacturing, and controls
CR	complete response
CRMTS	CBER Regulatory Meeting Tracking System
eCTD	electronic Common Technical Document
(b) (4)	
ES	Executive Summary
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act of 2007
HIV	Human Immunodeficiency Virus
HM	heterosexual men
HNC	Head and Neck Cancer
HNRT	Human Papillomavirus-Naïve to the Relevant Type
HPV	Human Papillomavirus
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
iPSP	initial pediatric study plan
ITT	intention-to-treat
mITT	modified-intention-to-treat
MSM	men who have sex with men
OBE	Office of Biostatistics and Epidemiology
OPSCC	Oropharyngeal Squamous Cell Carcinoma
PD	pharmacodynamics
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PIN	penile intraepithelial neoplasia
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPE	Per-Protocol Efficacy
PREA	Pediatric Research Equity Act
PVP	pharmacovigilance plan
qHPV	quadrivalent Human Papillomavirus vaccine
REMS	risk evaluation and mitigation strategy
RMS/BLA	regulatory management system for the biologics license application
sBLA	supplemental Biologics License Application
SAE	serious adverse event
VaIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia
VLP	virus like particle

1. EXECUTIVE SUMMARY

GARDASIL 9 [Human Papillomavirus 9-valent Vaccine] is a recombinant 9-valent vaccine prepared from purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. GARDASIL 9 was licensed in 2014 (STN 125508/0) for the prevention of vaccine type HPV-related anogenital lesions and cervical, vaginal, vulvar and anal cancers in females 9 through 26 years of age and anogenital lesions and anal cancers in males 9 through 15 years of age. In 2015 this indication was expanded to include males 16 through 26 years of age (STN 125508/15) and in 2018 it was expanded to include both males and females 27 through 45 years of age (STN 125508/793). With the current Biologics License Application supplement (sBLA), the Applicant proposes to expand the indication for GARDASIL 9 to include prevention of vaccine type HPV-related oropharyngeal and other head and neck cancers via the Accelerated Approval licensure pathway. Accelerated approval would be based on the biologic plausibility, further supported by epidemiologic and pharmacologic data, that the surrogate endpoint of prevention of HPV-related anogenital persistent infection and disease by GARDASIL 9 is reasonably likely to predict its effectiveness in preventing HPV-related persistent oral infection and disease.

This application includes study summaries for and references to the pivotal efficacy trials of both GARDASIL (the quadrivalent HPV vaccine) and GARDASIL 9, as studies conducted with GARDASIL are relevant to GARDASIL 9 due to similarities in manufacturing and components of these two vaccines (both manufactured by Merck). These trials are outlined in more detail in Section 5.1. In summary, 8 major studies contributed to the body of efficacy data for GARDASIL (“qHPV”):

- Study V501-005 demonstrated efficacy of a monovalent precursor HPV-16 vaccine against HPV-16 persistent infection (100%, 95% CI 90.9, 100) and cervical intraepithelial neoplasia (CIN) (100%, 95% CI 51, 100) in 16 to 25-year-old women.
- Study V501-007 demonstrated efficacy (89.5%, 95%CI 70.7, 97.3) of qHPV against HPV 6/11/16/18-related persistent infection, CIN, vaginal intraepithelial neoplasia (VaIN), vulvar intraepithelial neoplasia (VIN) and warts in 16 to 23-year-old women.
- Study V501-013 demonstrated efficacy of qHPV against HPV 6/11/16/18-related CIN, VIN, VaIN, warts (100%, 95% CI 87.4, 100) and persistent infection (100%, 95% CI 88.4, 100) in 16 to 23-year-old women.
- Study V501-015 re-demonstrated efficacy (100%, 95% CI 75.8, 100) of qHPV against HPV 6/11/16/18-related CIN, VIN, VaIN and warts in over 12,000 women 16 through 26 years of age.
- Study V501-19 demonstrated efficacy (88.7%, 95% CI 78.0, 95.0) of qHPV against HPV 6/11/16/18 related persistent infection, CIN, VIN, VaIN and warts in 27 through 45-year-old women.
- Study V501-020 demonstrated efficacy of qHPV against HPV-6/11/16/18 related genital warts, penile intraepithelial neoplasia (PIN) and external genital persistent infection (90.6%, 95% CI 77.0, 91.3) in men 16 through 26 years of age, as well as against anal intraepithelial neoplasia (77.5%, (95% CI 39.6, 93.3) and intra-anal persistent infection in a subset of men who have sex with men (MSM).

- Extension studies V501-020-010 and V501-019-021 demonstrated long term (>10 years) immunogenicity and effectiveness of qHPV in decreasing the incidence of HPV 6/11/16/18-related external genital lesions in men and CIN, VIN, VaIN, warts and persistent infection in women due newly acquired HPV-types.

There was a single pivotal efficacy study conducted for licensure of GARDASIL 9 ("9vHPV"), Study V503-001, which demonstrated vaccine efficacy of the 9vHPV (in comparison to qHPV) of 96.7% (95% CI 80.9, 99.8) against CIN, VIN, VaIN, warts and persistent infection due to the 5 novel HPV types contained in 9vHPV (types 31, 33, 45, 52 and 58) in over 14,000 women ages 16 through 26 years.

Vaccine efficacy in boys and girls ages 9 through 15 years (both for qHPV and 9vHPV), men 16 through 26 years (9vHPV only) and men ages 27 through 45 years (qHPV only) was inferred from immunogenicity data that demonstrated non-inferior anti-vaccine type (6/11/16/18/31/33/45/52/58) HPV antibody responses in these populations. The Applicant also conducted immunogenicity studies to confirm non-inferior HPV-type 6/11/16/18 antibody responses in women 16 through 26 to after vaccination with 9vHPV compared with qHPV.

In addition to references to previous trials conducted during the GARDASIL and GARDASIL 9 clinical development programs, the Applicant cited lines of evidence from the scientific literature supporting vaccine effectiveness against oral HPV infection in vaccinated adolescents and young adults. Persistent oral infection (> 6 months) with oncogenic HPV types has already been scientifically established as an intermediate endpoint for prevention of HPV related cancers, including those of the head and neck. A randomized, placebo-controlled clinical trial, conducted in mid-adult, HIV-infected men, found the efficacy of qHPV to be 88% (95% CI 2, 98) against persistent oral HPV infection as a secondary endpoint. However, this study was not specifically designed to evaluate qHPV efficacy against oral persistent infection and, in fact, the study failed to meet its primary endpoint of protection against anal persistent infection and AIN. Two small cross-sectional studies demonstrated decreased prevalence of oral infection with some HPV types after subjects had received at least two doses of vaccine. One large cross-sectional study, which analyzed data from the National Health and Nutrition Examination Surveys (NHANES) database coupled with oral HPV swab data, noted a significant decrease in prevalence of oral HPV infection in vaccinated individuals compared to those who had not received qHPV. This effect was especially notable in men, who typically have higher rates of oral HPV infection, as well as HPV-related head and neck cancer, compared to women. Finally, a population level analysis of NHANES data, which was conducted to assess the impact of herd immunity through mass HPV vaccination on oral HPV infection, demonstrated a decrease in prevalence over time of vaccine type oral HPV infection in men, despite low vaccine uptake, which was suggestive of a herd immunity effect from rising rates of HPV vaccination of girls and adolescent females over the past decade.

Overall, the demonstration of vaccine efficacy against the clinical endpoints of persistent infection, precancerous lesions, and cancers in the anogenital region are the most relevant to the proposed indication to prevent HPV-related oropharyngeal and other head and neck cancers. CBER agrees with the

Applicant's proposal that these clinical endpoints are surrogates which are reasonably likely to predict protection at other mucosal sites. While the pathophysiology of HPV-related transformation of squamous epithelial cells is thought to be the same regardless of the mucosal site of infection, there are not currently any easily identifiable precancerous lesions in the oropharynx, larynx or oral cavity which are analogous to CIN, VIN, VaIN or AIN. As this sBLA was submitted under the Accelerated Approval pathway, the Applicant agreed to conduct a post-approval, randomized, double-blind, placebo-controlled confirmatory trial to study vaccine efficacy against 6-month persistent oral infection of the 9 HPV types covered by GARDASIL 9 (6/11/16/18/31/33/45/52/58) in 20 through 45-year-old previously unvaccinated men. This study, V503-049, is currently recruiting subjects and the study completion is anticipated in late 2025.

As no new clinical studies were conducted in support of this BLA supplement, no new safety data was submitted for review. However, previous clinical trials of 9vHPV, submitted and reviewed under STN 125508/0, STN 125508/15 and 125508/493, demonstrate that the vaccine is safe and generally well tolerated, with the most commonly reported adverse events being injection site reaction, allergic reaction and syncope. A pregnancy registry for 9vHPV was opened in 2015 and continues to enroll women exposed to 9vHPV during pregnancy and will collect pregnancy outcomes data in these women. Additional post-marketing safety studies were either recently completed and are under review (V503-028-00) or are ongoing (V503-002-20, V503-021-01). Preliminary review of the final and interim reports of these studies, as well as periodic queries to the Applicant's safety database and VAERS, have not revealed any new safety signals since initial licensure of 9vHPV. Merck's existing pharmacovigilance plan, including post-marketing commitment (PMC) safety studies, remains adequate as there are no changes to the vaccine dose, components or target population and no new safety concerns associated with this sBLA for the proposed expanded indication.

Global epidemiology studies show that HPV-related head and neck cancers disproportionately affect white, male, non-smokers in North America and Europe. Therefore, it is important to note that studies of efficacy, immunogenicity and safety of qHPV and 9vHPV have included subjects from this population (Studies V501-020, V501-108 and V503-003) and have not revealed any safety or efficacy concerns in this population specifically. Studies which demonstrated the durability of immune response and effectiveness are especially important for the proposed new indication, as the average age of presentation of HPV-related head and neck cancers is 61 years, which is older than the average age of cervical cancer diagnosis (~50) and represents a longer interval since time of vaccination.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C 355c), this sBLA was required to contain an assessment of the safety and effectiveness of the product for the proposed expanded indication of prevention of vaccine type HPV-related oropharyngeal and other head and neck cancers in all pediatric age groups. As the Applicant's rationale for expansion of indication for vaccination with 9vHPV was based on the principals of biological plausibility, analogous pathophysiology and mechanisms of protection against HPV infection at all mucosal sites,

previous demonstration of vaccine efficacy in the anogenital region and assessments of immunogenicity in children 9 years of age and older as performed in past clinical trials were applied to this submission. As with previous submissions, a partial waiver from the requirements of PREA in children 0 through 8 years of age was requested. CBER granted the waiver request for this age group as initiation of vaccination before 9 years of age does not represent a meaningful therapeutic benefit over initiation at 9 years or older in terms of prevention of HPV-related head and neck cancers and GARDASIL 9 is unlikely to be used in a substantial number of children in this age group.

In summary, previously demonstrated efficacy and effectiveness of qHPV and 9vHPV vaccination against persistent HPV infection and disease at anogenital sites serving as a surrogate of protection against HPV infection and disease at head and neck mucosal sites, coupled with additional evidence supporting small and large population level impact of HPV vaccination on prevalence of oral HPV infection, supports the proposed indication for 9vHPV use as prevention for vaccine type HPV-related oropharyngeal and other head and neck cancers. Safety data from past BLA submissions, as well as post-marketing safety data indicate that the safety profile of 9vHPV remains favorable without emergence of new safety signals in the decade since initial licensure.

In conclusion, this reviewer recommends approval of the proposed indication of GARDASIL 9 for the prevention of vaccine-type HPV-related oropharyngeal and other head and neck cancers in males and females 9 through 45 years of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

No new clinical trials were conducted to support the proposed new indication for prevention of HPV-related head and neck cancers. A summary of demographic information from subjects enrolled in pivotal clinical trials for GARDASIL (qHPV) and in the clinical development program for GARDASIL9 (9vHPV) is provided below.

1.1.1 qHPV Pivotal Trial Demographic Information

In the original pivotal efficacy studies (V501-005, 007, 013, 015) for qHPV, a total of 20,887 women ages 16 through 26 years were enrolled: 9,087 received qHPV, 1,508 received the HPV-16 vaccine as a control and 10,292 received placebo. Overall, average age was 20 years and the majority of subjects were White (n=14,700, 70.4%), followed by Hispanic American (n =2,554, 12.2%), “Other” (n=1,837, 8.8%), Black (N=957, 4.6%), Asian (N=789, 3.8%) and Native American (n= 50, 0.2%). These demographic characteristics were similar across treatment groups.

In clinical efficacy and immunogenicity studies to support efficacy of qHPV in men and boys (V501-020, V501-016, V501-018) a total of 4,065 (N= 2,032 qHPV, N= 2,033 Placebo) men ages 16 through 26 years were enrolled, as well as 1,352 boys ages 9 through 15 years. In the main efficacy study (V501-020), the average age was 20.5 years, and the majority of subjects were identified as White (N=1,431, 35.2%), followed by Hispanic American (N= 835, 20.5%), Black (N=805, 19.8%), “Other” (n= 585, 14.4%), Asian (n= 406, 10%) and Native American (N=3, 0.1%). Most of these men had never smoked cigarettes (N=2,263, 55.7%), though a large percentage were current smokers

(n= 1,477, 36.3%). Most men reported having had 1-3 lifetime sexual partners at the time of study enrollment (N=2,532, 62.3%) and a very low proportion reported having more than 5 lifetime sexual partners (n= 8, 0.2%).

Two major clinical studies were conducted to support efficacy and effectiveness in men and women ages 27 through 45 years (V501-020 with extension V501-108, V501-19-021). There were 1,336 mid-adult women (ages 24 through 45 years) enrolled in the long-term follow-up efficacy study of qHPV (V501-19-021), which was conducted in Colombia. The mean age of subjects in the base study at the time of enrollment was 36 years. The majority of these women identified as Hispanic (99.5%, N= 1,329). There were 150 mid-adult men (ages 27 through 45) enrolled in the immunogenicity study of qHPV (V501-108), which was conducted in the US and Mexico. The average age in this study was 34.8 years. Men were primarily White (N= 68, 45.3%) or Native American/Alaskan (N= 65, 43.3%).

1.1.2 9vHPV Clinical Development Program Demographic Information

The key immunogenicity studies supporting licensure of 9vHPV (STN 125508/0) enrolled three different study populations. In these studies (V503-001, -002, -005, -007, and -009) there were 7,264 women ages 16 through 26 years (mean 22 years), 2,764 girls ages 9 through 15 years (mean 12 years) and 1,218 boys ages 9 through 15 years (mean 12 years). Overall, subjects were mostly White (N= 6,418, 57.0%) and of non-Hispanic/Latino ethnicity (N= 7,588, 67.4%); 4.65% (N= 523) were Black, 15.4% (N= 1732) were Asian and 22.9% (N= 2573) identified as “Other” race. The ethnic and racial composition was similar among the study populations.

Study V503-003, a phase 3, open label, non-inferiority immunobridging study of 9vHPV, enrolled 1,000 healthy heterosexual men (HM) 16 through 26 years of age. This study also enrolled a sub-population of 300 men who have sex with men (MSM). In both study populations (HM and MSM), the majority of subjects were White (N= 701, 63.4% HM, N= 178, 56.9% MSM) and roughly one-third were of Hispanic/Latino ethnicity (N= 314, 28.4% HM, N= 98, 31.3% MSM). Most men in the study had never smoked cigarettes or other tobacco products (N= 815, 73.7% HM, N= 203, 64.9% MSM).

Reviewer Comment: As HPV-related head and neck cancer disproportionately affects white, male, non-smokers,[1,2] of median age 61 years,[3] and prevalence of oral HPV infection increases with the number of lifetime sexual partners (7.4% prevalence in individuals with > 5 lifetime sexual partners),[4,5] it is important to note that immunogenicity and efficacy against anogenital disease has been previously examined and demonstrated in populations that are considered at increased risk of future HPV-related head and neck cancer specifically white, male, non-smokers.

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1.2 Patient Experience Data

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	

		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.			

No prior patient experience data exist and no new clinical studies or data, including patient experience data were submitted to support this BLA supplement.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

HPV infections are common in the general population and cause both benign and malignant epithelial lesions of the skin and mucous membranes throughout the body.[6] Though most HPV infections are self-limited and resolve within 6-12 months, persistent oral infection does occur. If immune clearance of HPV infection does not occur in a timely fashion, overexpression of viral oncoproteins E6 and E7, which causes deregulation of host cell p53 and pRb regulatory mechanisms, can lead to squamous cell dysplasia and the development of precancerous and malignant lesions between 10 to 30 years after initial infection.[7] This pathophysiology has been well studied in HPV-related cervical and anogenital cancer, and a similar mechanism of oncologic transformation following persistent infection occurs in other HPV-infected mucosal sites, including other anogenital regions, the oral cavity, pharynx and larynx.

The oncogenic potential of high-risk HPV types (16, 18, 31, 33, 45, 52 and 58) has been well established in cervical cancer, as well as cancers of the vulva, vagina and anus, providing justification for the development and licensure of HPV vaccines, including 9vHPV, as a preventative strategy for men and women ages 9-45. The association between head and neck cancers (HNC), especially oropharyngeal squamous cell carcinoma (OPSCC), and HPV infection has only been identified more recently, as there are no established pre-malignant disorders for oral squamous cell carcinomas, such as

cervical intraepithelial neoplasia (CIN) in cervical cancer, during which HPV infection could clearly be identified. Routine screening for oropharyngeal cancer and its risk factors is not currently recommended.[8]

In the United States, the current estimated incidence of HNC is ~65,000 cases per year, accounting for 3% of all malignancies, with a significantly higher proportion of those cancers occurring in men compared to women (48,000 vs 17,000). It is also estimated that approximately 14,500 people die from HNC in the United States every year, with a 5-year relative survival rate between 48-67%, depending on factors such as race.[9] Examination and early detection of many HNC is difficult due to the internal or relatively obstructed location of the lesions (posterior oropharynx) and rapid progression to invasive disease within the lymphoid tissues, which results in the majority of patients (>80%) being diagnosed after the disease has spread to the regional lymphatic system or beyond.[10]

HPV DNA is detected in approximately one-quarter of all HNC cases, with significant variance in the proportion of cases attributed to HPV among the various types of HNC.[11] The most commonly detected high-risk HPV type involved in head and neck cancer is HPV-16, which is present in ~90% of HPV-related OPSCC[1], followed by HPV types 33, 35 and 58.[7] Rates of HPV association are lower in non-oropharyngeal cancers (between 2.4-16% for oral cavity, nasopharynx, hypopharynx, unspecified pharynx and larynx sites).[7] It is currently estimated that 18-70% of OPSCC are associated with HPV in North America, depending on the case definition. To distinguish HPV-related OPSCC from unrelated OPSCC with coincidental transient oral HPV infection, evidence of viral biological activity is required in the form of E6/E7 mRNA and/or $p16^{INK4a}$, in addition to the presence of HPV DNA.[7]

Rates of OPSCC have been steadily increasing over the past two decades and, as of 2013-2014, the incidence of HPV-related OPSCC in the United States was 4.62 per 100,000 persons.[12] HPV-related OPSCC is now the most common HPV-related malignancy in the United States.[13] In contrast, incidence of HPV-negative OPSCC during this same time period was 1.82 per 100,000 persons. The median age at diagnosis for a patient with HPV-positive OPSCC is 58 years.[14] HPV-positive OPSCC appears to disproportionately affect white, non-Hispanic, male, non-smokers under the age of 64 and is now the sixth most common non-skin solid cancer in this subpopulation.[12] Other risk factors for HPV-positive OPSCC include a higher number of lifetime sexual partners (including those engaged in activities such as open mouth kissing and oral sex), marijuana use and history of cervical HPV infection.[15] Rates of survival for patients with HPV-related OPSCC are higher than those with non-HPV-related OPSCC, with a 28-74% reduction in risk of cancer-related death.[16,17] However, 20% of HPV-OPSCC patients have a poor prognosis with high stage tumor invasion and lymph node involvement.

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

2.2.1 Prevention of Oral HPV Infection and Disease

As HPV is transmitted through mutual contact of infected body fluids and epithelialized or mucosal surfaces, typically during deep kissing or sexual intercourse, abstinence from

these activities is the only completely effective method for prevention of transmission. The use of barrier methods, such as condoms or dental dams during oral sex,[18] and limiting the number of kissing or sexual partners may decrease the likelihood of transmission of HPV.

There are currently no reliable or widely feasible methods for screening for head and neck cancer, as no easily identifiable pre-cancerous lesions have been identified for HPV-related head and neck cancer.

2.2.2. Treatment of HPV-related Head and Neck Cancers

Current treatment of HPV-related head and neck cancers varies by stage at the time of diagnosis. Early (Stage I or II), localized squamous cell carcinomas of the head and neck, regardless of etiology (HPV or non-HPV related), may be treated by definitive radiation therapy or surgical resection, depending on the location. Minimally invasive surgical techniques, such as laser microsurgery or robotic surgery from a transoral approach, have minimized the morbidity associated with surgical resection. However, most HNC, particularly HPV-related OPSCC, are not detected until disease has spread to regional lymph nodes, necessitating additional therapeutic modalities.[10]

Treatment of all advanced OPSCC disease (Stage III and above) typically includes surgical resection of the primary tumor (if feasible), as well as affected regional lymph nodes, followed by a combination of radiation and chemotherapy. Organ-sparing (non-surgical) approaches are often considered to preserve functionality and minimize negative cosmetic impact, however advanced resection is sometimes required, which can lead to disfigurement and loss of important functions such as speech and swallowing. Acute and long-term effects of radiation and chemotherapy in these patients include mucositis, accelerated dental decay and disease, xerostomia, dysgeusia, dysphagia, fibrosis, speech difficulties, persistent nausea and vomiting, and occasionally osteonecrosis of the jaw.[19] Given the comparatively younger age at diagnosis for patients with HPV-related HNC, the potential impact of loss of functionality is higher than for patients diagnosed with cancers which typically develop later in life.

The detrimental effects of HNC on patient quality of life are not limited to the direct physical effects of the tumor or treatments. Patients and survivors of head and neck cancer are at increased risk for adjustment disorder and depression, and as such, increased risk for additional psychological complications, including suicidality. Survivors of head and neck cancer are almost twice as likely to die of suicide compared to survivors of other cancers,[20] though it is unclear what impact potential confounding factors such as younger age at diagnosis, male gender and substance use may contribute to the risk of suicidal ideation in this population.

2.3 Safety and Efficacy of Pharmacologically Related Products

Three vaccines have been licensed in the United States for the indication of prevention of anogenital HPV infection, genital warts and HPV-related dysplastic lesions and cancer: quadrivalent (HPV types 6, 11, 16, 18) GARDASIL (Merck) in 2006, bivalent (16/18) CERVARIX (GlaxoSmithKline) in 2009 and nonavalent (6, 11, 16, 18, 31, 33, 45,

52, 58) GARDASIL9 (Merck) in 2014. All three vaccines have a similar mechanism of action, as they contain recombinant VLPs of the L1 protein of specific HPV types, however they vary in the breadth of HPV types targeted, L1 protein dose per type and type of adjuvant used, as described in **Table 1**.

Table 1: Component Comparison of Cervarix, GARDASIL and GARDASIL9

Component	Cervarix	GARDASIL (qHPV)	GARDASIL9 (9vHPV)
HPV type 6 L1	0 µg	20 µg	30 µg
HPV type 11 L1	0 µg	40 µg	40 µg
HPV type 16 L1	20 µg	40 µg	60 µg
HPV type 18 L1	20 µg	30 µg	40 µg
HPV type 31 L1	0 µg	0 µg	20 µg
HPV type 33 L1	0 µg	0 µg	20 µg
HPV type 45 L1	0 µg	0 µg	20 µg
HPV type 52 L1	0 µg	0 µg	20 µg
HPV type 58 L1	0 µg	0 µg	20 µg
AS04[a] adjuvant	50 µg / 500 µg	0 µg	0 µg
AAHS[b] adjuvant	0 µg	225 µg	500 µg

[a] contains 50 µg of monophosphoryl lipid A and 500 µg of aluminum hydroxide
[b] Amorphous aluminum hydroxyphosphate sulfate

Clinical trials demonstrated comparable efficacy for GARDASIL and CERVARIX for cervical endpoints, specifically protection against HPV 16/18-related persistent infection and CIN 2 + in women 16 through 26 years of age who were naïve to HPV type 16 and 18. As both GARDASIL and GARDASIL 9 are similarly manufactured and have similar composition for the most prevalent HPV-types, efficacy data from studies supporting licensure of GARDASIL are relevant to GARDASIL 9 and are discussed in more detail in Section 2.4.1.

The safety of CERVARIX and GARDASIL were thoroughly assessed through randomized, controlled trials, as well as extensive post-licensure studies, and are both generally regarded as safe, with similar safety profiles. High rates of transient injection site reactions, compared to placebo, were reported, as well as lower rates of mild self-limited systemic reactions and post-vaccination syncope.

Distribution of both CERVARIX and GARDASIL were discontinued in the United States in 2016, following licensure of GARDASIL 9, but continue to be distributed globally.

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

GARDASIL9 is the only licensed HPV vaccine currently available in the United States and is approved for the indications of prevention of cervical, vulvar, and vaginal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, precancerous or dysplastic lesions (cervical intraepithelial neoplasia [CIN] 1-3, cervical adenocarcinoma *in situ* [AIS], vulvar intraepithelial neoplasia [VIN] 2-3, vaginal intraepithelial neoplasia [VaIN] grade 2-3) caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 in women 9 through 45 years of age, as well as the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, 58, anal intraepithelial neoplasia [AIN] 1-3 caused by HPV types 6, 11, 16, 18, 31,

33, 45, 52, 58 and genital warts caused by HPV types 6, 11 in both men and women ages 9 through 45.
The efficacy and effectiveness of GARDASIL (qHPV) is relevant to GARDASIL 9 (9vHPV), since the two vaccines are manufactured similarly and contain the same VLPs (in slightly different amounts) for HPV-types 6, 11, 16, 18. As such, efficacy, immunogenicity and safety data which was previously used to support licensure for both vaccines are summarized below.

2.4.1 Previous Clinical Experience with qHPV

2.4.1.1 Clinical Studies Supporting Initial Licensure of qHPV

The quadrivalent HPV vaccine, GARDASIL, was initially licensed in June 2008 under STN 125126/0, with the indication of prevention of cervical cancer, genital warts and genital precancerous/dysplastic lesions (including CIN, VaIN, VIN, AIS) due to HPV-types 6, 11, 16 and 18 in females 9 through 26 years of age. In multiple clinical studies (V501-005, V501-007, V501-013, V501-015), which enrolled over 20,000 women ages 16 through 26 years, qHPV was demonstrated to be more than 94% effective in preventing the development all HPV type 6/11/16/18-related disease endpoints (including CIN, VaIN2+, VIN2+, condyloma acuminata, and AIS). These same studies also demonstrated vaccine efficacy of 85.5-96.0% against 6-month persistent infection of the cervix, vulva and vagina. The indication for prevention of vaginal and vulvar cancer were approved in September 2008 (STN 125126/419), when final close out data regarding cancer endpoints from V501-013 and V501-013 were available. Protection against VIN 2+ and VaIN 2+ were originally demonstrated and approved as an indication with initial licensure as a part of a composite endpoint as described above. Vaccine efficacy against HPV 16/18 VIN2+ and VaIN2+, as surrogates for vaginal and vulvar cancer, in the modified-intention-to-treat population was 84.2% (95%CI 46.2, 97). See Section 5.1 for a tabular summary of the demographics, endpoints and results for each of the studies used to support initial licensure of qHPV in women 16 through 26 years of age.

While efficacy was clearly demonstrated in women who were naïve to HPV infection at the time of vaccination, efficacy was not observed in women who were PCR positive at the time of enrollment, indicating concurrent infection, or in women who had previously been infected with HPV-types contained in the vaccine (6/11/16/18). A higher number of cases of CIN2+ due to HPV 16/18 were noted in women in the qHPV group (versus placebo) in post-hoc pooled analyses of qHPV efficacy data included in STN 125126/0, as outlined in **Table 2** below. This effect was especially pronounced in subjects who were PCR+/Serology+ for relevant HPV types at baseline (79/473 [16.7%] cases in qHPV versus 69/499 [9.8%] cases in placebo), suggesting the possibility of enhanced risk of cervical dysplasia in vaccinated individuals who had past and current HPV infection with HPV types covered by the vaccine. These findings were presented to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) on May 18, 2006. As a result, a post-marketing, long-term follow-up study (V501-015-021) was recommended at the time of approval of GARDASIL to further evaluate long term vaccine effectiveness and potential impact of enhanced disease. This study was primarily designed to evaluate the long-term effectiveness of qHPV against HPV 16/18 high grade dysplasia and cervical cancer, but also included the evaluation of potential viral-type replacement in the setting of vaccination, which would result in higher rates of

non-vaccine type HPV infection and related disease, as a secondary endpoint. Vaccine effectiveness based on history of previous vaccine-type HPV infection and/or vaccine-type HPV infection on Day 1 of vaccination was also evaluated as an exploratory endpoint.

Table 2: Pooled Efficacy Against HPV 6/11/16/18 Related CIN 2+ and AIS (Protocols 005, 007, 013, 015)

Day 1 Status	qHPV (N)	qHPV # cases	qHPV incidence	Placebo (N)	Placebo # cases	Placebo Incidence	Efficacy (95% CI)
Overall MITT[a]	9831	122	0.7	9896	201	0.9	39.0% (23.3, 51.7)
PCR-/Sero -	9342	1	0.6	9400	81	0.4	98.8% (92.9, 100.0)
PCR -/Sero+	853	0	0.0	910	4	0.2	100% (-63.6, 100.0)
PCR +/ Sero -	661	42	3.2	626	57	4.6	31.2% (-4.5, 54.9)
PCR +/ Sero +	473	79	9.1	499	69	7.3	-25.8 (-76.4, 10.1)

[a]MITT= modified-intention-to-treat; subjects received at least 1 vaccination and had at least one follow-up visit after dose 1
Adapted from VRBPAC Presentation, May 18, 2006.

During the 14-year study period of V501-015, also known as the FUTURE II trial (and the extension follow-up study V501-015-021; final report submitted in 2018), there was one case of CIN1 due to HPV-type 6/11/16/18 in the fully vaccinated, HPV-negative, per protocol efficacy (PPE) population, translating to 100% vaccine effectiveness (95% CI 92, 100) and there was one additional case (n=2 total; incidence= 0.067 cases per 1,000 person years) of CIN3+ in the HPV-Naïve to the Relevant Type (HNRT) population, which was well below the expected background rate of CIN2+ in this population. In subjects who had a history of previous vaccine-type HPV infection but were PCR negative at time of vaccination, there were no cases of HPV 6/11/16/18 CIN, vulvar, vaginal or cervical cancer. However, as was observed in the pooled analysis from the original efficacy studies, therapeutic efficacy was not demonstrated in women who had prevalent infection (were PCR +) at the time of vaccination, as incidence was significantly higher than that observed in the HNRT: three cases (0.918 cases per 1000 person-years) of CIN or cancer were observed in the PCR+/Serology- cohort and thirteen cases (4.917 per 1000 person-years) were observed in the PCR+/Serology+ cohort (**Table 3**). These data further demonstrate that the HPV vaccine has no effect on existing HPV infection. The overall incidence of HPV-related disease in both PCR+ cohorts was still lower, however, than the incidence observed in placebo groups in the base study, where 40 cases per person-year and 62 cases per person-year were observed in PCR +/Sero – and PCR+/Sero + women cohorts respectively. This suggests that there is some degree of overall vaccine effectiveness over placebo even with prevalent infection at the time of vaccination.

Table 3: Incidence of HPV 6/11/16/18 CIN (any grade) in Subjects With and Without Evidence of Previous or Prevalent HPV Infection in Long Term Follow-Up Study (V501-019-021)

HPV Status	# Cases	Total # Subjects	Incidence (per 1000-person years)
PCR-/Serology – (HNRT[a])	2	2328	0.067
PCR-/Serology +	0	337	0.0
PCR +/Serology –	3	274	0.918
PCR +/Serology +	13	220	4.917

[a]HNRT= HPV-Naïve to the Relevant Type group; subjects had to have received at least 1 dose of qHPV, had any follow-up visit in the long-term follow-up study and were PCR negative and seronegative for the appropriate HPV type prior to vaccination
Adapted from Tables 11-8, 11-9, 14.2-17 and 14.2-18 in CSR for V501-015-021 in STN 125126/3335.0

As a secondary endpoint, the number of cases of CIN2+ due to non-vaccine HPV types was also assessed. There were 47 cases of non-vaccine type CIN2+, resulting in an incidence of 0.2 per 100 person-years. This is well below the incidence of any CIN2+, regardless of vaccine type, of 5.22 per 1000 person-years, which was observed in the unvaccinated population in the base study (V501-015) and other studies in the initial clinical development plan (V501-013), supporting that there is no type replacement phenomenon.

Immunobridging studies were performed to demonstrate efficacy of qHPV in girls ages 9 through 15 years due to infeasibility of conducting the invasive genital examinations required to conduct efficacy studies in children.

Reviewer Comment: While the data from these studies continue to suggest that there is lack of effectiveness against CIN2 in women with prevalent vaccine type infection prior to vaccination, it is worth highlighting the overall decrease in incidence in CIN2+ in previously and concurrently HPV-infected women who received the HPV vaccine compared to the unvaccinated population. To address these concerns, the current package inserts for GARDASIL/GARDASIL 9 contain language in the "Limitations of Use and Effectiveness" stating that qHPV/9vHPV have not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity and that these vaccines are not for treatment of external genital lesions, cervical, vulvar, vaginal and anal cancers.

2.4.1.2 Clinical Data Supporting the Expansion of qHPV Indication to Include Prevention of External Genital Lesions and Anal Cancer in Men and Boys 9 through 26 years of age

The indication for vaccination was expanded to include males 9 through 26 years of age, initially for the prevention of external genital lesions due to HPV types 6 and 11, in September 2009 (STN 125126/1297). As with girls ages 9 through 15, data from immunogenicity studies were used to infer efficacy in boys ages 9 through 15 due to the infeasibility of anogenital exams in this population.

In Study V501-020, a randomized, double-blind, placebo-controlled trial of over 4,000 men ages 16 through 26, qHPV was demonstrated to be 90.6% (95% CI 70.1, 98.2) effective in preventing external genital lesions due to HPV 6/11/16/18 in the per-protocol population, as well as 85.5% (95% CI 77.0, 91.3) effective in preventing external genital persistent infection with HPV 6/11/16/18. A placebo controlled sub-study within V501-

020, which included ~600 men who have sex with men (MSM), later demonstrated efficacy of qHPV against anal intraepithelial neoplasia (AIN) and anal cancer, with a vaccine efficacy of 77.5% (95% CI 39.6, 93.9), for any HPV 6/11/16/18-related AIN. Efficacy (VE= 94.9%, 95%CI 80.4, 99.4) was also demonstrated against intra-anal persistent infection due to HPV 6/11/16/18. Data from this study, in combination with immunogenicity data, were also used to infer similar protection against AIN and anal cancer in women 16 through 26 years of age through the principles of biological plausibility of a similar pathogenic process and immune response at all mucosal sites of infection. The addition of the indication for prevention of AIN and anal cancers due to HPV 6/11/16/18 in males and females 9 through 26 years of age was approved in February 2010 (125126/1895). Long term vaccine effectiveness in decreasing the incidence of AIN and anal cancer was also demonstrated in men 16 through 26 years of age in an extension study (V501-020-021) of this cohort (STN 125126/3320). Vaccine efficacy and effectiveness in this population has been demonstrated to persist for ≥ 10 years.

As was noted in the initial qHPV studies in women, vaccine efficacy against HPV 6/11-related genital warts, as well as HPV 6/11/16/18- related AIN and anal cancer in MSM, was decreased or absent in men who were PCR or Serology + for vaccine HPV-types at baseline, including in the PPE population, further supporting that there the HPV vaccine does not have any therapeutic efficacy. No reverse case split was noted in this study population.

2.4.1.3 Clinical Data Supporting the Expansion of qHPV Indication to Include Women and Men 27 through 45 Years of Age

A BLA supplement (STN 125126/773) was submitted in January 2008 for the purpose of expanding the indication to include prevention of high grade cervical dysplasia in women 27 through 45 years of age, which included data from the base study, V501-019, a randomized, double-blind, amorphous aluminum hydroxyphosphate sulfate (AAHS)-controlled trial, which enrolled ~3,800 women 27-45 years of age, who were randomized 1:1 to receive either qHPV or AAHS control. The primary endpoint for efficacy in this study was a composite of persistent infection, any grade of cervical or vulvovaginal dysplasia or genital warts caused by HPV 6/11/16/18. Vaccine efficacy in women (in the Per Protocol Efficacy group) who were naïve to HPV 6/11/16/18 at baseline in this study was similar to that seen in younger women, with vaccine efficacy of 82.6% (95% CI 70, 91).

For the general FAS study population (including women with history of HPV infection prior to vaccination), vaccine efficacy was also demonstrated for the primary endpoint, with a notably lower point estimate (47.2%, 95% CI 34, 58). The vast majority of cases meeting the endpoint in both the qHPV and control groups were persistent infection (110 out of 116 in qHPV, 211 of 214 in control). Given the increased likelihood of latent HPV infection and reactivation in this population, the uncertainty of evidence supporting persistent cervical infection as a surrogate for protection against high grade dysplasia in mid-adult women, and the relatively low number of high-grade dysplasia cases detected during the study (N= 21/1910 in qHPV, N= 27/1907 in control, VE= 22.4%, 95% CI -43, 58), efficacy was not able to be established for prevention of high-grade dysplasia due to HPV 16/18 in this population.

Furthermore, the review team raised concerns again regarding a reverse case split for high grade dysplasia due to any HPV (vaccine and non-vaccine) type in the FAS population. A higher number of cases of CIN2+ related to any HPV type were reported in the qHPV group (n= 62) than in the AAHS control group (n= 51); the majority of these cases were caused by the 10 HPV-types not included in the qHPV vaccine (40 qHPV vs 25 in control). The review team was concerned about a possible viral type replacement phenomenon following vaccination, resulting in increased risk of progression of non-vaccine type disease from pre-existing or newly acquired infection. However, upon further investigation by the review team, an imbalance was discovered in non-vaccine type HPV prevalent infection at baseline (n=25 qHPV vs 17 control). The scientific literature at the time did not provide strong epidemiological or virologic evidence that there is competition among HPV types. Notably, this reverse case-split was not observed in the PPE population, in which women received all three recommended doses of qHPV but also excluded women who had evidence of previous or concurrent HPV infection.

As a result of the aforementioned review team findings, including lack of efficacy against high-grade dysplasia due to HPV 16/18 and possible non-vaccine-type HPV replacement, the indication for 27 through 45-year-old women was not approved with sBLA 125126/773. Specific efficacy data (HNRT population analysis, prevention of any-grade CIN and prevention of genital warts), immunogenicity and safety data from V501-019 were added to the package insert. Additionally, CBER did not discourage the continuation of the Applicant's pre-planned, long-term follow-up extension phase of V501-019 to evaluate the effectiveness of qHPV against high-grade cervical dysplasia in mid-adult women.

In the 10-year long-term follow-up, extension study of V501-019 (V501-019-021), the incidence of CIN2+ due to HPV 16/18 in women 27 through 45 years of age decreased over time in subjects who received qHPV. Few cases were reported (2 cases out of 851 subjects from years 4-8 post vaccination and 1 case out of 551 subjects from year 6 to 10 of vaccination) from the group of women who were initially vaccinated (the early vaccination group or EVG), all from the FAS population. Only 2 cases of non-vaccine type CIN2+ were diagnosed in the catch-up vaccine group after 4 years post-vaccination. These data suggest that if there is a vaccine-type replacement phenomenon, that it is short lived and that the limited efficacy demonstrated in the parent study in mid-adult women did not bear out over the decade following vaccination; however, this cannot be stated conclusively as CIN2+ incidence for a placebo-controlled group was not assessed.

A cross-study immunobridging analysis (V501-108) was conducted in men 27 through 45 years of age to infer effectiveness in this population, which demonstrated similar anti-HPV 6/11/16/18 antibody GMTs in this age group compared to 16 through 26-year-old men in the primary efficacy study (V501-020).

Data from both the long-term follow-up study in women 27 through 45 years of age (V501-019-021) and the immunobridging study in men 27 through 45 years of age were submitted as part of an sBLA to support the expansion of indication for the nonavalent HPV vaccine GARDASIL 9 (9vHPV). This sBLA (STN 125508/493) and the expansion of indication to include the prevention of vaccine-type HPV related disease in 27 through 45-year-old men and women was approved in October 2018.

Reviewer Comment: Although an increased incidence of high-grade cervical dysplasia following vaccination in women with recent or concurrent HPV infection arose in multiple studies and populations, long-term vaccine effectiveness studies of qHPV in mid-adult women demonstrated minimal risk of breakthrough disease over a decade (3 cases total HPV 16/18 related CIN2+) following qHPV vaccination, regardless of baseline HPV status, indicating that the overall risk of cancer is likely not increased. Furthermore, increased rates of high-grade dysplasia or cancer were not observed in men with prevalent HPV infection at baseline. This is reassuring and as such this reviewer does not feel that additional long-term evaluation of efficacy for prevention of HPV-related head and neck cancer are necessary.

2.4.2 Clinical Studies Supporting Initial Licensure of 9vHPV

A detailed FDA/CBER clinical review of the key safety and efficacy data submitted to the original BLA (STN 125508/0) is available at https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil-9.

Efficacy

One study (V503-001) in the 9vHPV clinical development program evaluated efficacy of the vaccine against clinical endpoints, specifically the combined proportion of subjects with HPV type 31/33/45/52/58-related CIN/VIN/VaIN 2-3, AIS and vaginal, vulva or cervical cancer. The phase 3 portion of this randomized, double-blind, qHPV controlled study enrolled 14,215 9vHPV vaccine-type specific PCR and serology negative women ages 16 through 26 years, 7,106 of whom received at least 1 dose of 9vHPV and 7,109 of whom received qHPV. Examination and Pap testing were performed on Day 1 (baseline) and at Month 7, 12, 18, 24, 30, 36, 42, 48 and 54. All subjects were followed for development of a clinical endpoint through at least Month 42 of the study.

In the per-protocol group (received all 3 dose of vaccine, had at least one follow-up after Month 7 and were negative for relevant HPV types by serology and PCR at baseline), one subject in the 9vHPV group met the primary endpoint (1 of 6,016; 0.016%) with a case of HPV 58-related CIN2 and 30 subjects in the qHPV group met the primary endpoint (30 of 6,017; 0.49%), resulting in a vaccine efficacy of 96.7% (95% CI 80.9, 99.8; $p<0.0001$). There were no cases of cancer in either group.

This trial also evaluated the immune response to 9vHPV compared to qHPV for the HPV-types contained in both vaccines (6/11/16/18) for non-inferiority. The antibody GMT ratio (9vHPV: qHPV), per HPV type, was considered non-inferior if the LB of the 95% CI was > 0.67 at Month 7. This non-inferiority criterion was satisfied for all four vaccine HPV types, with 9vHPV: qHPV antibody GMT ratios of 1.02 (95% CI 0.99, 1.06), 0.80 (0.77, 0.83), 0.99 (0.96, 1.03), 1.19 (1.14, 1.23) for HPV-types 6, 11, 16 and 18, respectively, in the Per Protocol Immunogenicity population. Similarly, there was no difference in rates of seroconversion by vaccine HPV-type between qHPV and 9vHPV cohorts.

Vaccine efficacy for protection against persistent infection of the cervix, vulva or vagina (both ≥ 6 months and ≥ 12 months) with HPV-types 31/33/45/52/58 was evaluated as a secondary endpoint. Success was demonstrated if the LB of the 95% CI for vaccine efficacy was > 25% for 6-month persistent infection and > 0% for 12-month persistent

infection. Success was met for all 5 new HPV types, with vaccine efficacy ranging between 95.0-98.8% (95% CI LB all ≥ 90.0%) for 6-month persistent infection and 95.9-100% (95% CI LB all ≥ 85.4%) for 12-month persistent infection in the per protocol analysis. Vaccine efficacy and immunogenicity findings were demonstrated to be consistent in all study populations after subgroup analyses of age, race, ethnicity, geographic location and hormonal contraception use status.

As was also seen during pre-licensure studies of qHPV, a reverse case split in high grade disease (CIN2+) was demonstrated in women who were infected with a vaccine type HPV (6/11/16/18/31/33/45/52/58) on Day 1 of the study in the full analysis set cohort only (**Table 3**). This increase in high grade lesions was not demonstrated in the per protocol efficacy (PPE) cohort, from which women who were PCR positive for HPV at baseline were excluded.

Table 4: Efficacy of 9vHPV Against Cervical, Vaginal and Vulvar Disease Related to Vaccine HPV Types (V503-001, FAS[1] Population)

Endpoints	9vHPV (N=7,099)	qHPV (N= 7,105)	Efficacy of 9vHPV (95%CI)
HPV 6/11/16/18 - Related Cervical, Vulvar or Vaginal Disease (Any)	244/7024	230/7022	-6.7 (-28.3, 11.3)
CIN 2 or Worse	138/6882	117/6841	-18.5 (-52.9, 8.1)
HPV 31/3345/52/58- Related Cervical, Vulvar or Vaginal Disease (Any)	208/ 7024	354/ 7022	41.5 (30.8, 51.0)
CIN 2 or Worse	125/6882	149/6871	15.8 (-7.5, 34.1)
All Vaccine Type HPV Related Cervical, Vulvar or Vaginal Disease	384/7024	517/7022	26.0 (15.6, 35.3)
CIN 1	197/6882	290/6871	32.1 (18.4, 43.7)
CIN2	165/ 6882	171/6871	3.1 (-20.7, 22.2)
CIN3	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)
Vaginal/Vulvar Disease	71/ 7021	92/7021	22.6 (-6.0, 43.5)

Source: Adapted from Table 25 in Clinical Review by Sixun Yang, PhD, STN 125508/0
[1]FAS population consisted of individuals who received at least 1 vaccination and had at least 1 follow-up visit after Day 1

Reviewer Comment: V503-001 was not powered to evaluate efficacy in the FAS population. However, as was noted in studies of qHPV, vaccination with currently licensed HPV vaccines do not offer protection against infection or disease from HPV types with which an individual is already infected prior to complete development of an immune response. This further emphasizes the importance of vaccination prior to onset of sexual activity and the associated risk of HPV

transmission. However, despite a lack of efficacy in the short term (within 3 years of vaccination) in previously infected individuals, long term outcomes related to vaccine and non-vaccine type HPV-related disease, as were studied with qHPV in V501-019-021 for licensure of 9vHPV for the 27 through 45-year-old cohort, were not negatively impacted by receipt of an HPV vaccine. This is described in more detail in the Clinical Review for sBLA 125508/493. Therefore, while efficacy in previously infected individuals is questionable at best, this issue does not translate to a safety concern.

Due to low incidence of AIN and anal cancers caused by the 5 newly included HPV types in 9vHPV and infeasibility of performing clinical endpoint studies, vaccine effectiveness against AIN and anal cancer due to HPV-types 31, 33, 45, 52 and 58 were inferred in both men and women on the basis of immunogenicity data for the 5 new HPV types and the biological plausibility of equivalent mechanisms of protection based on similar pathophysiology at all mucosal sites, as well as the preventative efficacy of qHPV against anal disease endpoints demonstrated in clinical trials (V501-020).

Immunogenicity:
Several additional studies evaluated the immunogenicity of 9vHPV in relevant populations:

- V503-002: A phase 3 lot consistency and immunogenicity non-inferiority study comparing vaccine type antibody GMTs in 9 through 15-year-old boys and girls to those in the clinical efficacy reference populations (women ages 16 through 26 years) after 3 doses of 9vHPV. Non-inferiority, defined as GMT ratio (9-15 years:16-26 years) with LB of the 95%CI > 0.67 for each HPV-type, was demonstrated in the 9 through 15-year-old cohort.

- V503-005: A phase 3 immunogenicity vaccine interaction study evaluating the immune response to 3 doses of 9vHPV in 11 through 15-year-old boys and girls with and without concomitant administration of other vaccines recommended in this age group (MENACTRA and ADACEL) with the first dose of 9vHPV. Immune responses to any of the 3 vaccines were not affected by concomitant administration of MENACTRA and ADACEL.

- V503-006: A phase 3 placebo-controlled study comparing vaccine type HPV antibody GMTs and seroconversion rates, by type, in 12 through 26-year-old women who were previously vaccinated with qHPV versus those who were HPV vaccine naïve. Seroconversion rates were similar for all 9 vaccine HPV types in both cohorts, however antibody GMTs for novel vaccine HPV types (31/33/45/52/58) were lower in women who had previously received qHPV.

- V503-007: A phase 3 immunogenicity comparison study of antibody GMTs to vaccine HPV types in 11 through 15-year-old boys and girls who concomitantly received REPEVAX (recombinant Diphtheria, Tetanus, acellular Pertussis and Poliomyelitis vaccine used internationally) with the first dose of 9vHPV versus those who did not. Immune responses to either vaccine were not impacted by concomitant REPEVAX administration.

- V503-009: A phase 3, international (not under IND), qHPV-controlled, non-inferiority immunogenicity study of 9 through 15-year-old girls, comparing HPV type 16/18 antibody GMT responses following 3 doses of HPV vaccine. Non-inferiority was demonstrated if the LB of the 95%CI for GMT ratio (9vHPV: qHPV) was > 0.67 for HPV 16 and 18. Non-inferiority of antibody responses were demonstrated for both high-risk HPV types.

- V503-010: A phase 3 non-inferiority immunogenicity study of two versus three dose regimen of 9vHPV, comparing 9vHPV type (6/11/16/18/31/33/45/52/58) antibody GMTs in 9 through 14 year old boys and girls (receiving both 2 doses, at Day 0 and Month 6 or Day 0 and Month 12) versus 16 through 26 year old women (3 dose only) at 4 weeks after the final vaccine dose. Non-inferiority of HPV-type GMT ratios were met for all comparisons (two dose 9-14 girls Day 0 and Month 6: three dose 16-26 women; two dose 9-14 boys Day 0 and Month 6: three dose 16-26 women; two dose 9-14 boys and girls Day 0 and Month 12: three dose 16-26 women) if the LB of the 95%CI was > 0.67. There was also another comparator group of 9 through 14-year-old boys and girls that received the three-dose regimen. Non-inferiority was demonstrated for all 9 vaccine HPV types in all comparisons; the LB of the 95% CI was > 1.0 in all cases.

- Study V503-003: A phase 3, open label, tolerability and immunogenicity non-inferiority study of the standard three dose regimen of 9vHPV, enrolled ~2,200 healthy men (N=1,106) and women (N=1,101) 16 through 26 years of age. This study also enrolled a sub-population of 300 men who have sex with men (MSM) in the same age range. GMTs of antibodies to vaccine type HPV (6/11/16/18/31/33/45/52/58) at Month 7 (4 weeks after the third dose of 9vHPV) were compared between the male and female cohorts and non-inferiority criteria were met if a lower bound (LB) for the 95% CI of the GMT ratio (Male: Female) was above 0.67. Antibody GMTs for all vaccine HPV types were higher in men than women, with an LB of 95% CI for the GMT ratio > 1.0 in all cases, satisfying non-inferiority criteria.

Safety:

Six studies contributed to the pooled 9vHPV safety database (V503-001, 002, 005, 006, 007 and 009) analyzed in the original BLA submission (125508/0) and a total of 13,360 subjects received at least 1 dose of 9vHPV, including 8,053 women ages 16 through 26 years of age and 5,307 male and female children 9 through 15 years of age. Analysis of adverse event reporting of subjects in these trials, the majority of which were open-label design, except for 001 (qHPV control) and 006 (placebo control), revealed that injection site reactions were very common in all age groups and genders: injection site pain was reported in 72.4-89.7% of subjects, followed by swelling in 24.2-40% and erythema in 24.2-34.3%. Headache was also common, reported in 12.5-14.7% of subjects. A total of 305 subjects (2.3%) reported non-fatal SAEs (including fetal loss) and the most commonly reported non-fatal SAEs were elective abortion (N=79, 0.6%), other fetal loss (N=64 [37 spontaneous abortions (SABs)], 0.5%) and Infections and Infestations (N= 61 [21 cases of appendicitis], 0.5%). Only five of these SAEs were considered at least possibly related to 9vHPV vaccination: pyrexia, allergic reaction, tonsillitis, headache and asthma attack. Five subjects died during the study period and none of these deaths were considered related to 9vHPV per the investigators or original clinical reviewer.

Separate safety analysis of the pivotal efficacy study (V503-001) alone, which was qHPV controlled, did reveal a small numerical imbalance in the number of new cases of multiple sclerosis (2 cases in qHPV and 5 cases in 9vHPV, with symptom onset ranging between a few hours and >14 months after vaccination) observed in the 9vHPV group. Investigator, Applicant and original clinical reviewer assessments were that none of these adverse events were related to HPV vaccination. There was also a notable imbalance in spontaneous abortions when incidental HPV vaccination occurred within 30 days of conception, with 17 cases (28.3%) in the 9vHPV group versus 7 cases (12.7%) in the qHPV group.

Reviewer Comment: CBER reviewers conducted extensive analyses to explore potential confounding factors, including age, race, geographic location, smoking history, history of SABs, concomitant medications, history of sexually transmitted infections and baseline HPV serostatus, and even after adjusting for these factors, the imbalance between 9vHPV and qHPV groups remained. This same imbalance was not seen when the estimated date of conception was outside of 30 days from vaccination. The imbalance appeared to be driven by reports of SABs in Latin American countries where social and legal barriers to elective abortion may have confounded reporting of pregnancy outcomes. The rate of spontaneous abortion for this age group in the general population is estimated to be between 10-20% per The American College of Obstetrics and Gynecology (ACOG). The overall rates of SAB across the 9vHPV development program (19.7% SAB with vaccination within 30 days of conception and 9.7% with vaccination > 30 days prior to conception) remained imbalanced but were within the estimated background rate for the general population. As a result of the observed imbalance in SAB rates, a post-marketing study of rates of SAB in women exposed to 9vHPV was recommended by CBER and is described in more detail in Section 4.6.

Additional safety data regarding the use of 9vHPV in men 16 through 26 years of age was obtained as a part of study V503-003 (described above) and analyzed separately. The vaccine was found to be generally well tolerated in both study cohorts, with mild to moderate injection site reactions being the most commonly reported vaccine related adverse event (N=896, 64.2% men/ N=865, 80.5% women), followed by Nervous System Disorders (N=119, 8.5% men /N=161, 15.0% women), primarily headaches (N=102, 7.3% men / N=138, 12.8% women), general systemic events (fatigue, malaise, pyrexia) (N=71, 5.1% men/ N=78, 7.3% women) and Gastrointestinal Disorders (N=28, 2.0% men/ N=53, 4.9% women).

Study V503-004 was a post-marketing, open-label, phase 3, tolerability and immunogenicity study of the standard regimen of 9vHPV to demonstrate non-inferiority of antibody responses in women 27 through 45 years of age compared to the reference population (16 through 26 years). This study enrolled 1,210 women, 640 subjects ages 27 through 45 and 570 subjects ages 16 through 26. This study was recently completed, and the final study report was submitted as a separate efficacy supplement on 31 October 2019 (STN 125508/(b) (4)), which was under review at this time of this submission. A preliminary review of the study synopsis indicates that antibody responses to the HPV types contained in 9vHPV were non-inferior in women 27 through 45 years of age compared to the reference population. The vaccine appears to be relatively well tolerated in mid-adult women, with similar rates of injection site and systemic reactions, the majority of which were mild-to moderate in severity, in both age

cohorts, 15 SAEs in 14 subjects (1.1%), none of which were considered vaccine related by the study investigators and no deaths during the study.

2.4.3 Post-Licensure Safety of 9vHPV

Since initial approval of GARDASIL 9 in 2014, an estimated 20,019,670 doses of the vaccine have been given worldwide as of 9 June 2019.

In a report published in Pediatrics in December 2019, post-licensure VAERS data for GARDASIL9 vaccination from December 2014 through December 2017 were analyzed. There were 7,244 adverse event (AE) reports, resulting in a crude event reporting rate of 259 per million doses of vaccine. Most reported AEs were considered to be non-serious (97.4%). The most commonly reported reactions, excluding vaccine administration errors, were dizziness, syncope, headache and injection site reactions. Rates of serious adverse events were much lower (N=186), with a crude reporting rate of 7 reports per million doses of vaccine. Of all reported adverse events, syncope was the only term which was reported more frequently than statistically expected.[21] All findings in this study were consistent with pre-licensure clinical trial safety data and current package labeling and are similar to post-licensure safety monitoring data for qHPV and other vaccines routinely administered in this age group (meningococcal vaccine and TDaP).

Currently, there are 5 active or recently completed post-marketing studies to further evaluate the efficacy and safety (V503-004, V503-021-01, V503-002-020, V503-028-00) of 9vHPV, including a pregnancy registry. As of 9 December 2019, enrollment numbers in studies V503-002-020, V503-021-01 and the pregnancy registry were 1,272, ~4,000 and 158 subjects respectively. Additional details on the recently completed V503-028-00 PMC study are provided below.

- Study V503-028-00 (PLOSS study) was a post-licensure, retrospective, observational safety study conducted as a post-marketing commitment (PMC) in the Kaiser Permanente Northern California cohort from 1 October 2015 through 30 September 2017. The objective of the study was to monitor health outcomes and healthcare utilization in the form of ED visits and hospitalizations as a surrogate for adverse events following 9vHPV administration in boys 9 through 15 years of age and girls and women 9 through 26 years of age. There were two cohorts examined: individuals who had only received 9vHPV during the study period and individuals who received 9vHPV and as well as another HPV vaccine during the study period (9vHPV+). Pre-specified analyses were planned for allergic reaction and syncope on Day 0 (day of vaccination). There were 140,628 subjects included in the 9vHPV only cohort and 215,965 in the 9vHPV+ group, with a roughly even spilt between male and female subjects. This study was recently completed, and the final study report was submitted on 10 December 2019 (125508/(b) (4) Office of Biostatistics and Epidemiology (OBE) review at this time of this submission. Preliminary review of the study synopsis revealed signals for safety concerns known to be associated with HPV vaccination and already mentioned in product labeling, specifically headache, injection site reaction, allergic reaction and syncope.

Reviewer Comment: The complete OBE review of V503-028 (b) (4) ***at the time of completion of this clinical review, however this reviewer had a conversation with the OBE reviewer assigned to GARDASIL 9, Dr. Adamma Mba-Jones and her preliminary review of the study reveal did not reveal any new safety signals or concerns. Allergic reaction and syncope continue to be reported after vaccination in a minority of subjects, but these safety concerns are known and these events were reported at rates similar to those in previous post-marketing observational studies of HPV or other vaccines (meningococcal conjugate vaccine or tetanus-diphtheria-acellular pertussis vaccine) administered in this age group.***

Please see section 4.6 for additional information regarding ongoing PMC and safety surveillance studies, including the pregnancy registry, under the applicant's established pharmacovigilance plan.

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

- **December 2014:** GARDASIL 9 was licensed for use in the following populations:
    - In girls and women 9 through 26 years of age with the indications of prevention of:
        - cervical, vulvar, vaginal and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, 58
        - genital warts caused by HPV types 6 and 11
        - precancerous lesions/dysplasia caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58 including CIN 1-3, cervical AIS, VIN 2-3, VaIN 2-3 and AIN 1-3
    - In boys 9 through 15 years of age with the indications of prevention of:
        - of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, 58
        - genital warts caused by HPV types 6 and 11
        - AIN 1-3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58

- **December 2015:** GARDASIL 9 indications were expanded to include the prevention of HPV 6/11/16/18/31/33/45/52/58-related anogenital lesions and HPV 16/18/31/33/45/52/58-related anal cancer in men 16 through 26 years of age (Section 2.4).

- **October 2016**: A two dose regimen of GARDASIL 9 was approved for use in boys and girls 9 through 14 years of age on the basis of non-inferiority immunogenicity data.

- **October 2018**: GARDASIL 9 indications were expanded to include women and men 27 through 45 years of age based on two studies submitted under STN 125508/493 (Section 2.4).

- **April 2019**: Type C meeting with CBER (CRMTS # 11701) to discuss a proposal to add a new indication for the prevention of HPV-related head and neck cancers.
    - CBER agreed to accept the Applicant's proposal (13447/597) to use previous clinical data for the prevention of HPV related anogenital cancer as a surrogate endpoint that is reasonably likely to predict clinical benefit for the

basis for accelerated approval for a BLA supplement to expand the indication to include prevention of certain HPV related head and neck cancers. Additional rationale for accelerated approval included the severity and associated morbidity and mortality with HPV-related HNC and the lack of any existing preventative therapeutics against HPV-related HNC.

- As a part of their request for accelerated approval, the Applicant proposed conducting a double-blind, saline placebo controlled, randomized, confirmatory post-marketing study to confirm clinical efficacy of 9vHPV for protection against 6-month persistent oral HPV infection due to HPV 16/18/31/33/45/52/58 in 20 through 45-year-old men. CBER agreed that persistent oral HPV infection with oncogenic types is an appropriate surrogate for protection against cancer of the head and neck region, as there are no easily detectable, well-established, pre-cancerous dysplastic lesions for these cancers. CBER agreed that the results of this confirmatory study, if successful, could be extrapolated to other populations for which 9vHPV is indicated. CBER found this proposal conceptually acceptable and agreed to review the study protocol under IND 13447 as a part of the proposed BLA supplement for the new indication.

- **July 2019**: Initial Pediatric Study Plan was submitted, which included a request for a partial waiver in children 0 through 8 years of age as the new indication of prevention of HPV-related head and neck cancer does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and is not likely to be used by a substantial number of pediatric patients in that age group. No new pediatric studies were proposed, as the rationale for the expanded indication was based on clinical efficacy demonstrated in previous studies and the biological plausibility of similar pathophysiology and among mucosal sites.
  - The iPSP was reviewed by PeRC in October 2019 with a few recommendations for minor adjustments to the plan and it was ultimately approved as an agreed iPSP in December 2019.

2.6 Other Relevant Background Information

In addition to references to previous efficacy trials and immunogenicity studies conducted during the GARDASIL and GARDASIL 9 clinical development programs, the Applicant cited evidence from the scientific literature supporting vaccine effectiveness against oral HPV infection in vaccinated adolescents and young adults.

Persistent oral infection (> 6 months) with oncogenic HPV types has already been scientifically established as an intermediate endpoint for prevention of HPV related cancers, including those of the head and neck. [22]

ACTG (AIDS Clinical Trial Group) Study A5298 was an NIH-funded, randomized, AAHS or placebo-controlled clinical trial, which was conducted in mid-adult (27-45 years), Human Immunodeficiency Virus (HIV)-infected MSM (and 100 HIV-infected women), with a primary objective of evaluating the efficacy of qHPV vaccination against persistent anal infection and secondary objectives of prevention of AIN and persistent oral HPV infection.[23] This study enrolled 575 subjects who received 3 doses of either qHPV (n=288) or AAHS/NS placebo (n=287) on Day 1, Month 2 and Month 6. Subjects had 2 pre-vaccination anal swabs and an oral mouthwash rinse for baseline HPV DNA typing,

and were re-tested at week 28, week 52 and then every 26 weeks up to 4 years post vaccination. The primary outcome was time to first new persistent anal infection of any newly acquired qHPV type, which was defined as a positive PCR for the same type at 2 consecutive 6 month-assessments. Similar outcomes were evaluated for oral persistent infection and cytology of anal samples was also performed at week 52 or later. A higher proportion of subjects had baseline intra-anal HPV infection (13-33%) with types 6/11/16/18 than oral infection (2-6%), though rates were similar for each type and site between treatment groups. The most frequently detected HPV-type was 16 (31-33% of anal infections, 4-6% of oral infections). The study was ultimately terminated early (at 3 years) due to protocol-defined futility rules for the primary endpoint. While efficacy (defined as VE ~65%, LB 95%CI >0) was not demonstrated for anal persistent infection (VE=21%, 95%CI -61, 61%) or AIN (17%, 95%CI -6,35%) in HIV-infected subjects in this study, efficacy of qHPV against oral persistent infection was demonstrated, with vaccine efficacy of 88% (n= 1 case in qHPV, n= 8 in control; 95%CI 2, 98%) in the modified intention to treat (mITT) group. This effect was not seen in the PPE group, as 5 subjects who had persistent infection in the control group were excluded as they did not receive all 3 doses of vaccine.

Reviewer Comment: These results suggest that qHPV vaccination (and likely 9vHPV) may provide protection against oral persistent infection, however there were a low number of outcomes, leading to a wide confidence interval, and the study was not designed to look at oral persistent infection as the primary outcome.[23]

Two relatively small cross-sectional studies, one conducted in an inner-city adolescent medicine clinic in New York City (N=645, sexually active girls 14-19 years old)[24] and the other in a Colombian high school (N=1784, boys and girls 14-17 years old)[25], examined the impact of HPV vaccination on the prevalence of oral HPV infection. In the New York cohort, 20.5% of patients had never been vaccinated against qHPV before and 50% had completed the 3 dose qHPV vaccine series at the time of enrollment. HPV was detected in 19.6% of oral samples at enrollment; 1.3% were vaccine type (6/11/16/18). Girls who were vaccinated at the time of enrollment had lower odds of oral HPV infection with types 6 and 11 (OR 0.08), though due to low number of oral HPV infections in this population, statistical significance was not reached (p=0.081). Oral infection with high risk types (16 and 18) was extremely rare in this population and was detected in less than 0.5% of samples, regardless of vaccination status.[24] In the Colombian cohort, there were 944 girls (53%) who were fully vaccinated with qHPV versus 95 girls (5.3%) and 745 boys (42%) who had not completed the qHPV series. HPV-16 oral infection was detected significantly more frequently in unvaccinated girls (n=3, 3.16%, χ^2 p-value= 0.021) and unvaccinated boys (n= 17, 2.28%, χ^2 p-value= 0.008) than vaccinated girls (n=7, 0.74%). Students in this study were 72% less likely to have HPV-16 oral infection if they had received at least 2 doses of qHPV (OR 0.28, 95%CI 0.07-0.88).[25] Both of these studies suggest that routine vaccination of adolescents with qHPV results in decreased prevalence of oral HPV-vaccine type infections. Both studies were limited by low overall prevalence of oral HPV infection, are not designed to assess causal relationships and are at high risk of recall bias, as vaccination status, as well as level of sexual activity and other exposure history which may be considered risk factors, were by self-report.

A larger cross-sectional, population-level study, published in the Journal of Clinical Oncology in 2018, used US National Health and Nutrition Examination Surveys (NHANES) data from 2011-2014, coupled with oral HPV swab data, to examine the large

scale impacts of HPV vaccination on prevalence of oral HPV infection in the community.[26] Analyses were restricted to 2,627 individuals who were between 18 and 33 years of age and persons who received at least 1 dose of qHPV vaccine were considered vaccinated. The primary outcome was oral HPV 6/11/16/18 prevalence. Only 18.3% of subjects were vaccinated (more women than men, 29.2% versus 6.9%) and prevalence for oral HPV 6/11/16/18 was significantly reduced in vaccinated individuals compared to the unvaccinated, even after adjusting for potential confounding factors such as age, sex and race (0.11% versus 1.61%, p= 0.008). This difference represents an 88.2% (95%CI 5.7,98.5) reduction in qHPV type oral infections. This effect was most evident in men, in which there were 0 cases in 102 vaccinated and 23 cases in 1,226 unvaccinated (p=0.007), which is consistent with epidemiologic data which demonstrate higher rates of oral HPV infection in men.[26] The same group of authors examined an additional 2 cycles of NHANES data (total study period 2009-2016) from an expanded population (13, 676 men and women 18-59 years of age) and noted an association between rising rates of HPV immunization in the population and a decrease in oral HPV infection rates in both vaccinated and unvaccinated men over the study period, suggesting not only direct vaccine effect but also an element of herd immunity from decreased community prevalence.[27]

Reviewer Comment: As with all cross-sectional studies, data from this study cannot be used to establish a causal relationship between variables. Furthermore, due to a low prevalence of oral HPV infection, sub-group analyses assessing the impact of number of vaccine doses, age at vaccination and time since vaccination could not be conducted.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Submission Integrity

As the rationale for expansion of the GARDASIL9 indication to include prevention of HPV-related head and neck cancer is based entirely on extrapolation of previously conducted studies, it is important to note that concerns with Good Clinical Practice (GCP) compliance were noted with original submission of these studies. A brief summary of these concerns, any related actions and resolution, is included below. For a detailed description of GCP compliance issues, please refer to STN 125126/0 (clinical review by Nancy Miller, MD and BIMO review by Robert Wesley) and STN 125508/0 (clinical review by Sixun Yang, MD PhD and BIMO review by Erin McDowell).

STN 125126/0:

- BIMO inspection revealed that a laboratory technician, who processed 2.6% of all serum specimens from the Phase III GARDASIL trials did not follow the standard operating procedure. Non-conforming specimens from Day 1 samples in the efficacy protocols (501-007, -013, -015) were retested by the Applicant. Re-analyses of these samples did not have any significant impact on overall efficacy results.

STN 125508/0 and STN 125508/493:

- CBER was made aware that one study site (one which was not chosen for BIMO inspection) was closed by another vaccine manufacturer for multiple violations, including violations of the informed consent process, documentation concerns and lack of principal investigator oversight. This investigator was involved in Study V503-001 (as well in the long-term follow-up study V501-108 in STN 125508/493) and enrolled 247 subjects who received 9vHPV and 248 subjects who received qHPV. An audit was conducted by the Applicant which ultimately showed that all 580 subjects were provided informed consent but that there were violations in the process of obtaining re-consent from some subjects. Following analysis by CBER, it was determined that baseline characteristics, immunogenicity results and adverse event reporting at this site were similar to those at other study sites and that data collected from this site should be included in the clinical assessment.

Two additional study sites, both of which enrolled subjects in Study V503-002, required investigation due to allegations of non-compliance with GCP. Review of medical monitor reports and informed consent documents corroborated these allegations and it was also noted that the rates of injection site reactions and temperature elevation were lower at these sites than reported in the study overall. Data from these two sites were excluded and the package insert, and clinical review, were revised accordingly.

3.3 Financial Disclosures

As the rationale for expansion of the GARDASIL9 indication to include prevention of HPV-related head and neck cancer is based entirely on extrapolation of previously conducted studies, it is important to note that concerns with Financial Disclosures were noted with original submission of these studies. A brief summary of these concerns, any related actions and resolution, is included below. For a detailed description of financial disclosures, please refer to STN 125126/0 (clinical review by Nancy Miller, MD) and STN 125508/0 (clinical review by Sixun Yang, MD PhD).

STN 125126/0:
All financial interests and arrangements with study investigators were appropriately disclosed by the applicant. Fourteen investigators reported receiving payment from the Applicant (Merck). One of these investigators was involved in 3 protocols (005-003, 007-003, 015-004) and was responsible for enrollment of 500 subjects. BIMO inspection of this investigator's sites did not reveal any GCP issues. The applicant reports that bias in these studies was minimized as they were randomized, blinded and placebo (AAHS) controlled.

STN 125508/0:
All financial interests with study investigators were appropriately disclosed by the applicant. Five investigators from 3 studies (V503-001, -002 and 006) received significant payments from the Applicant, in the form of symposia, consultant fees, medical education, research and participation on an advisory board, Per the applicant, studies V503-001 and V503-009 were designed in a way which minimized bias (both were randomized and double blind) and the impact of financial conflicts of interest is negligible. Subjects in Study V503-002 all received 9vHPV, randomized from different vaccine production lots, therefore bias of immunogenicity results was minimized.

However, there remains potential for under-reporting of safety events due to financial incentive, making this a weakness of this study. The clinical reviewer assigned to this file found the Applicant's explanations and clarifications to be acceptable.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

No new CMC concerns have been identified in association with this submission.

4.2 Assay Validation

No new studies were conducted in support of this efficacy supplement.

4.3 Nonclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

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

4.4.1 Mechanism of Action

Pre-clinical data suggest that a protective effect is mediated through IgG neutralizing antibodies directed against the major capsid L1 protein. Clinical trials in mid-adult men demonstrated that detectable anti-HPV vaccine type antibodies are present in the saliva in most subjects (72-93%) within 4 weeks of completion of a 3 dose HPV series, supporting a site-specific immune response.[28] HPV antibodies have been demonstrated to persist in the oral cavity for up to 30 months following HPV vaccination.[29] No correlate of protection has been identified, however, as the protection against new HPV infection appears to persist even among subjects for whom type-specific antibodies are no longer detectable.

4.4.2 Human Pharmacodynamics (PD)

No new pharmacodynamic studies were conducted in support of this efficacy supplement.

4.4.3 Human Pharmacokinetics (PK)

No new pharmacokinetic studies were conducted in support of this efficacy supplement.

4.5 Statistical

As no new studies were conducted in support of this efficacy supplement, no statistical reviewer was assigned. Studies conducted under the original BLA (125508/0) or

supplement for the extension to mid-adult men and women (125508/0) for GARDASIL 9 were reviewed at the time of initial submission and details can be found in the corresponding CBER statistical reviews by Lihan Yan (125508/0) and Sang Ahnn (125508/493).

4.6 Pharmacovigilance

The Applicant did not propose any changes to the pre-existing pharmacovigilance plan (PVP) as a result of this BLA efficacy supplement. The Applicant currently receives routine surveillance reports for adverse events following vaccination with GARDASIL 9 through their global safety database (the Merck Adverse Event Reporting and Review System).

Two post-marketing safety studies for 9vHPV are currently active and have been enrolling patients since December 2014:

- V502-002-20: a 10-year extension study of V503-002 to evaluate the long-term safety, immunogenicity and effectiveness of 9vHPV in boys and girls between 9 and 15 years of age at enrollment. Anticipated study completion date: September 30, 2022

- V503-001-021-00: a 10-year extension study of V503-001 being conducted in a subset of subjects in Denmark, Norway and Sweden to evaluate the long-term safety, immunogenicity and effectiveness of 9vHPV in women 9 through 26 years of age at enrollment; interim safety and effectiveness analyses will be conducted every 2 years until completion in December 2026.

Additionally, a pregnancy registry was established in January 2015 and will continue to prospectively collect GARDASIL9 exposure and birth outcome information until at least August 2020, at which time a 5-year summary report will be submitted to determine whether the registry can be discontinued at that time. The final report will be submitted 18 months after enrollment of the last patient. Following the approval of sBLA 125508/493 in October 2018 (expansion of indication to include men and women up to 45 years of age), this registry was extended for an additional period of time to capture potential safety events in mid-adult women who may be inadvertently exposed to GARDASIL 9 during pregnancy. As of 9 December 2019, 158 women have been enrolled in the pregnancy registry.

Reviewer Comment: Due to technical issues with the registry website, patients were unable to enroll between 1 October 2019 and 7 November 2019.

Reviewer Comment: As no clinical studies or data were submitted with this BLA supplement and no changes to the pharmacovigilance plan were proposed by the Applicant, no OBE/PVP reviewer was assigned to this supplement. However, this reviewer reviewed protocols and updates for open PMCs and discussed the status of post-marketing studies and safety surveillance data with the OBE reviewer assigned to previous and currently active submissions to STN 125508, Dr. Adamma Mba-Jones. Per OBE, no new safety signals have been identified through annual reports (ARs), Periodic Adverse Experience Reports (PAERs) or intermittent inquiries to the VAERS database, as of 9 December 2019.

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

5.1 Review Strategy

No new clinical studies were conducted in support of this efficacy supplement and as such there are no clinical trials to review in Section 6 and no new integrated efficacy or safety data to review in Section 7 or Section 8. The Applicant's proposal to expand GARDSIL9 indications to include the prevention of HPV-related head and neck cancers is based solely on the biological plausibility, epidemiologic and pharmacologic evidence supporting prevention of persistent infection and disease at other anogenital sites as a surrogate that is reasonably likely to predict prevention of HPV-related oral infection and disease. As such, summaries and reports of previously conducted trials (pre and post-licensure) and studies demonstrating the efficacy and effectiveness of GARDASIL9, as well as GARDASIL given the similarities in manufacturing and vaccine contents, were reviewed to assess efficacy of GARDASIL9 in the prevention of persistent HPV infection and disease at anogenital sites and the durability of protection for the populations considered most at risk for HPV-related head and neck cancers. Key efficacy and immunogenicity studies that support vaccine efficacy for all labeled age and gender cohorts were reviewed. These studies are discussed in more detail in Sections 2.3 and 2.4 and are presented in tabular form in Section 5.3 below (**Tables 5-7)**.

Additionally, evidence supporting the impact of HPV vaccination on oral HPV infection from the scientific literature was reviewed. This evidence included several articles summarizing randomized clinical trials, cross-sectional studies and population level survey and surveillance data, which provide additional support of the effectiveness of the HPV vaccine in prevention against oral HPV infection. Summaries and appraisal of this additional evidence is included in Section 2.6.

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

The following regulatory documents, as listed by electronic common technical document (eCTD) module, served as the basis of this review:

- BLA 125508/868
  - Module 1.2 (Cover Letter)
  - Module 1.4.4 (Cross Reference to Previously Submitted Information)
  - Module 1.6.3 (Correspondence Regarding Meetings)
  - Module 1.9.6 (Other Correspondence Regarding Pediatric Exclusivity or Study Plans
  - Module 1.14.1 (Draft Labeling)
  - Module 2.2 (Introduction)
  - Module 2.5 (Clinical Overview)
  - Module 2.7 (Clinical Summary)
  - Module 5.2 (Tabular Listing of All Clinical Studies)

- BLA 125508/868.1 Module 1.14.1 Updated Draft Labeling

- BLA 125508/0
  - Module 1.16 (Risk Management Plan)
  - Module 5.3.5 (Reports of Efficacy and Safety Studies)
  - Clinical Review (Sixun Yang, MD PhD)
  - Statistical Review (Lihan Yan, PhD)

- PVP Review (Adamma Mba-Jones, MD)

- BLA 125508/493
  - Clinical Review (Joohee Lee, MD)
  - Statistical Review (Sang Ahnn)

- BLA 125508/786 (Supplement- Module 2.5 Clinical Overview)

- BLA 125508/(b) (4) (Supplement- Module 5.3.5.4 V503-004 Study Report Synopsis)

- BLA 125508/(b) (4) (PMC Submission- Module 5.3.5.4 PLOSS Study Report)

- BLA 125508/870 (Annual Report- Module 5.3.6 Fourth Annual Report Gardasil 9 Pregnancy Registry Thru 09 Dec 2018)

- BLA 125508/872 (PMC Submission- Module 1.11 Clinical Information Amendment)

- BLA 125126/0
  - Clinical Review (Nancy Miller, MD)
- BLA 125126/419
  - Clinical Review (Nancy Miller, MD)
- BLA 125126/773
  - Clinical Review (Jeff Roberts, MD)
- BLA 125126/1297
  - Module 5.3.5 (Reports of Efficacy and Safety Studies)
  - Clinical Review (Jeff Roberts, MD)
- BLA 125126/1895
  - Module 5.2.5 (Reports of Efficacy and Safety Studies)
  - Clinical Review (Jeff Roberts, MD)
- BLA 125126/3320
  - Module 5.3.5 (Reports of Efficacy and Safety Studies)
  - Clinical Review (Joohee Lee, MD)

- IND 13447/0.610
  - Module 5.3.5 (Reports of Efficacy and Safety Studies)
- IND 13447/0.611
  - Module 1.11.3 (Clinical Information Amendment)

5.3 Table of Studies/Clinical Trials

Table 5: Overview of Relevant Efficacy and Immunogenicity Studies Supporting Licensure of qHPV for Prevention of HPV-related Genital Warts, Cervical, Vaginal and Vulvar Disease in Women 16 through 26 Years of Age

Study ID	V501-005	V501-007	V501-013	V501-015
IND/STN Number	125126/0	125126/0	125126/0	125126/0
NCT Number	NCT00365378	NCT00365716	NCT00092521	NCT00092534
Study Phase	2a	2b	3	3

Study ID	V501-005	V501-007	V501-013	V501-015
Study Design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled, dose ranging	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Study Centers	16 US sites	23 international sites	62 international sites	90 international sites
Participants Enrolled *(received study vaccine)*	2409 (*1204*)	1158 (*276*)	5455 (*2717*)	12,167 (*6082*)
Age Range (years)	16 through 25	13 through 26	16 through 24	16 through 26
Demographics	Females only	Females only	Females only	Females only
Study Drug Regimen	3 doses of IM qHPV 16 vaccine at Day 1, Month 2 and Month 6	3 doses of IM qHPV vaccine at Day 1, Month 2 and Month 6	3 doses of qHPV at Day 1, Month 2 and Month 6	3 doses of IM qHPV on Day 1, Month 2 and Month 6
Comparator	AAHS	AAHS	AAHS or Hepatitis B vaccine	AAHS
Study Duration	48 months	36 months	48 months	48 months
Primary Endpoints	1) Persistent HPV 16 infection 2) Combined HPV-16 related CIN, AIS or cervical cancer	Combined persistent infection, genital warts, VIN, VaIN, CIN and vaginal/vulvar/cervical cancer due to HPV 6/11/16/18	1) Combined genital warts, VIN, VaIN (EGL) and vaginal/vulvar cancer due to HPV 6/11/16/18 2) Combined CIN, AIS or cervical cancer due to HPV 6/11/16/18	Combined CIN (2/3), AIS, warts, VIN, VaIN and genital warts due to HPV 16/18
Major Findings	1) Vaccine efficacy (VE) against persistent infection = 100% (95%CI 90.9, 100) 2) VE against CIN= 100% (95% CI 51, 100)	VE against composite endpoint = 89.5% (95%CI 70.7, 97.3)	1) VE against HPV 6/11/16/18 EGL= 100% (95%CI 87.4, 100) 2) VE against HPV 6/11/16/18 CIN= 100% (95% CI 88.4, 100)	VE against primary combined endpoint = 100% (95%CI 75.8, 100)

Table 6: Overview of Efficacy and Effectiveness Studies Supporting Licensure of qHPV for Prevention of HPV-related Genital Warts, External Genital Lesions and Anal Disease in Men 16 through 26 Years of Age

Study ID	V501-020 (V501-020-021)
IND/STN Number	1251256/1297 (125126/3320)
NCT Number	NCT00090285
Study Phase	3
Study Design	Base Study: Randomized, double-blind, placebo-controlled Extension study: long term, open-label follow-up effectiveness study
Study Centers	71 international sites (46 international sites in extension)
Participants Enrolled	4065 (*2032*) (1803 in extension)

Study ID	**V501-020 (V501-020-021)**
(received study vaccine)	
Age Range (years)	16 through 26
Demographics	Males only: 3464 heterosexual men (HM); 601 MSM in sub-study
Study Drug Regimen	3 doses of IM qHPV on Day 1, Month 2 and Month 6
Comparator	AAHS
Study Duration	36 months (10 years including extension)
Primary Endpoints	Base Study: 1) HPV 6/11/16/18-related warts, penile/perianal/perineal intraepithelial neoplasia (PIN) in HM 2) HPV 6/11/16/18-related AIN or anal cancer in MSM Extension: 1) Comparative incidence of HPV 6/11 related genital warts, HPV 6/11/16/18 external genital lesions (EGL) and HPV 6/11/16/18 AIN/anal cancer (MSM only) in Early Vaccination Group (EVG) versus Catch-Up Vaccination Group (CVG) versus historical incidence in placebo group in base study
Major Findings	Base Study: 1) VE against HPV-related 6/11/16/18 warts and PIN = 90.6% (95%CI 77.0, 91.3) 2) VE against all AIN and anal cancer in MSM= 77.5% (95%CI 39.6, 93.3) Extension Study: Decreased incidence of genital warts, EGL and AIN/anal cancer in both EVG and CVG over a 7-year period compared to placebo group in base study

Table 7: Overview of Relevant Immunogenicity and Effectiveness of qHPV for Prevention of HPV-related Anogenital Disease in Men and Women 27 through 45 Years of Age

Study ID	**V501-020-108**	**V501-019 (V501-019-21)**
STN Number	125508/493	125126/773 (125508/493)
NCT Number	NCT01432574	NCT00090220
Study Phase	2	3
Study Design	Open-label, immunogenicity and safety study	Base study: Randomized, double-blind, placebo-controlled efficacy study Extension study: long term, open-label follow-up effectiveness study
Study Centers	2 sites in United States and Mexico	38 international sites (5 sites in Colombia in extension study)
Participants Enrolled (*received study vaccine*)	150	3,819 (*1910*) (1336 in extension)
Age Range (years)	27 through 45	24 through 45
Demographics	Males only	Females only
Study Drug Regimen	3 doses of IM qHPV on Day 1, Month 2 and Month 6	3 doses of IM qHPV on Day 1, Month 2 and Month 6
Comparator	Immunogenicity data from V501-020	AAHS
Study Duration	7 months	48 months (10 years in extension)
Primary Endpoints	1) Anti-HPV 6/11/16/18 antibody GMT at Month 7 2) % seroconversion	Base Study:

Study ID	V501-020-108	V501-019 (V501-019-21)
		Combined persistent infection, warts, VIN, VaIN, CIN, vaginal,vulvar and cervical cancer due to HPV types 6/11/16/18 Extension: 1) Comparative incidence of HPV 6/11/16/18 warts, CIN and 16/18 CIN2+ in early vaccine group (at 6-10 years post vaccination) versus catch up group (at 3-5 years post vaccination) 2) Antibodies kinetics and stratification by age
Major Findings	1) All GMT slightly lower than 16-26-year-old men; HPV-type specific GMT ratios (27-45 yo: 16-26 yo) between 0.74 and 0.91 2) 100% seroconversion for HPV 6/11/16/18	VE for combined endpoint in base study was 88.7% (95% CI 78.0, 95.0) There was 1 breakthrough case of CIN2 in the early vaccination group and no breakthrough cases of warts or CIN in the catch-up group. Antibody GMTs were comparable between 24-34 vs 35-45-year-old women and antibodies persisted for 10 years.

Table 8: Overview of Relevant Efficacy and Immunogenicity Studies Supporting Licensure of 9vHPV For Existing Indications

Study ID	V503-001	V503-002	V503-003	V503-009
STN Number	125508/0	125508/0	125508/013447	125508/0 (not under IND)
NCT Number	NCT00543543	NCT00943722	NCT01651949	NCT01304498
Study Phase	2b/3	3	3	3
Study Design	Randomized, double-blind, qHPV-controlled dose-ranging and efficacy study	Randomized, open-label lot consistency and immunogenicity study	Open-label, non-inferiority immunogenicity study	qHPV controlled, non-inferiority immunogenicity study
Study Centers	105 international sites	70 international sites	76 international sites	24 European sites
Participants Enrolled (r*eceived study vaccine*)	14,840 (*8020)*	2999	2520	600
Age Range (years)	16 through 26	9 through 26	16 through 26	9 through 15
Demographics	Females only	63.0% 9-15 year-old girls; 21.5% 9-15 year-old boys; 15.5% 16-26 year-old women (comparator group)	56% male (N=1106 HM, 313 MSM); 44% female (N=1101)	Females only
Study Drug Regimen	3 doses of IM 9vHPV on Day 1, Month 2 and Month 6	3 doses of IM 9vHPV on Day 1, Month 2 and Month 6	3 doses of IM 9vHPV on Day 1, Month 2 and Month 6	3 doses of IM 9vHPV on Day 1, Month 2 or Month 6

Study ID	V503-001	V503-002	V503-003	V503-009
Comparator	qHPV (3 doses on Day 1, Month 2 and Month 6)	HPV vaccine type antibody GMTs in 16 through 26-year-old women	HPV vaccine type antibody GMTs in 16 through 26-year-old women	qHPV (3 doses on Day 1, Month 2 or Month 6)
Study Duration	42 months	12 months	7 months	7 months
Primary Endpoints	1) Combined HPV 31/33/45/52/58-related CIN2, VIN2/3, VaIN2/3 or cancer 2) Antibody GMTs for HPV 6/11/16/18	Antibody GMTs for all 9 vaccine HPV types	Non-inferiority of vaccine HPV-type antibody GMT ratio between males and females (LB of 95% CI >0.67)	Antibody GMTs for HPV types 6/11/16/18
Major Findings	1) VE= 96.7% (95% CI 80.9, 99.8) for combined endpoint 2) Non-inferiority of anti-HPV 6/11/16/18 antibodies in 9vHPV recipients versus qHPV	Non-inferiority demonstrated between 9 through 15-year-olds (both boys and girls) and 16 through 26-year-olds for all 9 vaccine HPV types	Antibodies against all 9 vaccine HPV types were noninferior in males compared to females	Non-inferiority was demonstrated between 9vHPV and qHPV for antibodies against HPV 6/11/16/18

5.4 Consultations

No external consultations were sought for this sBLA.

5.4.1 Advisory Committee Meeting

No VRBPAC Meeting was held for this new indication.

5.5 Literature Reviewed (if applicable)

1. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS, Gillison ML. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. Journal of Clinical Oncology. 2011. 29 (32): 4294-4301.

2. D'Souza G, Fakhry C, Sugar EA, Seaberg EC, Weber K, Minkoff HL, Anastos K, Palefsky JM, Gillison ML. Six-month Natural History of Oral versus Cervical Human Papillomavirus Infection. International Journal of Cancer. 2007. 121 (1): 143-150.
CDC. HPV-Associated Cancer Diagnosis by Age.

3. www.cdc.gov/cancer/hpv/statistics/age.htm. Updated 2 August 2019. Accessed 18 March 2020.

4. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R. Distinct Risk Factor Profiles for Human Papillomavirus Type 16 Positive and Human Papillomavirus Type 16 negative Head and Neck Cancers. Journal of the National Cancer Institutes. 2008. 100 (6): 407-420

5. Benard VB, Johnson CJ, Thompson TD, Roland KB, Lai SM, Cokkinides V, Tangka F, Hawkins NA, Lawson H, Weir HK. Examining the Association Between Socioeconomic Status and Potential Human Papillomavirus-Associated Cancers. Cancer. 2008. 113 (10): 2910-2918.

6. Schiller JT, Markowitz LE, Hildesheim A, Lowy DR. Human Papillomavirus Vaccines. In SA Plotkin, WA Orenstein, PA Offit, KM Edwards (Ed). Vaccines (7 h, pp. 430-455). 2018. Philadelphia, PA: Elsevier.

7. Taberna M, Mena M, Pavon MA, Alemany L, Gillison ML, Mesia R. Human Papillomavirus-related Oropharyngeal Cancer. Annals of Oncology. 2017. 28:2386-2398.

8. Olson CM, Burda BU, Beil T, Whitlock EP. Screening for Oral Cancer. In US Preventative Services Task Force Evidence Syntheses. 2013. Rockville, MD: Agency for Healthcare Research and Quality.

9. Siegel R, Miller KD, Jemal A. Cancer Statistics 2020. CA: A Cancer Journal for Clinicians (American Cancer Society). 2020. 70: 7-30.
10. SEER*Explorer [Internet]: Oropharynx and Tonsil Cancer Stage Distribution of SEER Incidence Cases, 2007-2016: By Sex, All Races, All Ages. National Cancer Institute: Bethesda, MD. Updated 15 April 2019. https://seer.cancer.gov/explorer/application.php?site=12&data_type=1&graph_type=4&compareBy=sex&chk_sex_3=3&chk_sex_2=2&chk_race_1=1&chk_age_range_1=1&advopt_precision=1&showDataFor=race_1_and_age_range_1. Accessed 9 March 2020.

11. Joseph AW, D'Souza G. Epidemiology of Human Papillomavirus-Related Head and Neck Cancer. Otolaryngologic Clinics of North America. 2012. 45 (4):739-764.

12. Mahal BA, Catalano PJ, Haddad RI, Hanna GJ, Kass JI, Schoenfeld JD, Tishler RB, Margalit DN. Incidence and Demographic Burden of HPV-associated Oropharyngeal Head and Neck Cancers in the United States. Cancer Epidemiology, Biomarkers & Prevention. 2019.

13. Van Dyne EA, Mona Saraiya SJH, Thomas CC, Markowitz LE, Benard VB. Trends in Human Papillomavirus-Associated Cancers- United States, 1999-2015. 2018. https://www.cdc.gov/mmwr/volumes/67/wr/67/wr. Accessed 9 March 2020.

14. Windon MJ, D'Souza G, Rettig EM, Westra WH, van Zante A, Wang SJ, Ryan WR, Mydlarz WK, Ha PK, Miles BA, Koch W, Gourin C, Eisele DW, Fakhry C. Increasing Prevalence of HPV-Positive Oropharyngeal Cancers Among Older Adults. Cancer. 2019. 124 (14): 2993-2999.

15. Pickard RKL, Xiao W, Broutian TR, He X, Gillison ML. The Prevalence and Incidence of Oral Human Papillomavirus Infection Among Young Men and Women, Aged 18-30 Years. Sexually Transmitted Diseases. 2012. 39 (7): 559-566.

16. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, Zahurak ML, Daniel RW, Viglione M, Symer DE, Shah KV, Sidransky D. Evidence for a Causal Association Between Human Papillomavirus and a Subset of Head and Neck Cancers. Journal of the National Cancer Institute. 2000. 92(9):709-720.

17. Ragin CCR, Taioli E. Survival of Squamous Cell Carcinoma of the Head and Neck in Relation to Human Papillomavirus Infection: Review and Meta-analysis. International Journal of Cancer. 2007. 121 (8): 1813-1820.

18. Beder Ribeiro CM, Ferrer I, Santos de Farias AB, Fonseca DD, Morais Silva IH, Monteiro Gueiros LA, Carvalho AT, Porter SR, Leao JC. Oral and Genital HPV Genotypic Concordance Between Sexual Partners. Clinical Oral Investigations. 2014. 18: 261-268.

19. Timbang MR, Sim MW, Bewley AF, Farwell DG, Mantravadi A, Moore MG. HPV-Related Oropharyngeal Cancer: A Review on Burden of the Disease and Opportunities for Prevention and Early Detection. Human Vaccines & Immunotherapeutics. 2019. 15 (7-8): 1920-1928.

20. Osazuwa- Peters N, Simpson MC, Zhao L, Boakye EA, Olomukoro SI, Deshields T, Loux TM, Varvares MA, Schootman M. Suicide Risk Among Cancer Survivors: Head and Neck Versus Other Cancers. Cancer. 2018. 124 (20): 4072-4079.

21. Shimabukuro TT, Su JR, Marquez PL, Mb-Jones A, Arana JE, Cano MV. Safety of the 9-Valent Human Papillomavirus Vaccine. Pediatrics. 2019. 144 (6): e20191791.

22. IARC HPV Working Group. Primary End-points for Prophylactic HPV Vaccine Trials. Lyon (FR): International Agency for Research on Cancer; 2014.

23 Wilkin TJ, Chen H, Cespedes MS, Leon-Cruz JT, Godfrey C, Chiao EY, Bastow B, Webster-Cyriaque J, Feng Q, Dragavon J, Coombs RW, Presti RM, Saah A, Cranston RD. A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298. Clinical Infectious Diseases. 2018. 67 (9):1339-1346.

24. Schlecht NF, Burk RD, Nucci-Sack A, Shankar V, Peake K, Lorde-Rollins E, Porter R, Linares LO, Rojas M, Strickler HD, Diaz A. Cervical Anal and Oral HPV in an Adolescent Inner-City Health Clinic Providing Free Vaccinations. PLoS ONE. 2012. 7 (5):e37419.

25. Castillo A, Osorio JC, Fernandez A, Mendez F, Alarcon L, Arturo G, Herrero R, Bravo LE. Effect of Vaccination Against Oral HPV-16 Infection in High School Students in the City of Cali, Colombia. Papillomavirus Research. 2019. 7: 112-117.

26. Chaturvedi AK, Graubard BI, Broutian T, Pickard RKL, Tong ZY, Xiao W, Kahle L, Gillison ML. Effect of Prophylactic Human Papillomavirus (HPV) Vaccination on Oral HPV Infections Among Young Adults in the United States. Journal of Clinical Oncology. 2018. 36 (3): 262-267.

27. Chaturvedi AK, Graubard BI, Broutian T, Pickard RKL, Tong ZY, Xiao W, Kahle L, Gillison ML. Prevalence of Oral HPV Infection in Unvaccinated Men and Women in the United States, 2009-2016. Journal of the American Medical Association. 2019. 322 (10):977-979.

28. Pinto LA, Kemp TJ, Torres BN, Isaacs-Soriano K, Ingles D, Abrahamsen M, Pan Y, Lazcano-Ponce E, Salmeron J, Giuliano AR. Quadrivalent Human Papillomavirus (HPV) Vaccine Induces HPV-Specific Antibodies in the Oral Cavity: Results from the Mid-Adult Male Vaccine Trial. Journal of Infectious Diseases. 2016. 214: 1276-1283

29. Parker KH, Kemp TJ, Isaacs-Soriano K, Abrahamsen M, Pan Y, Lazcano-Ponce E, Salmeron J, Pinto LA, Giuliano AR. HPV-specific Antibodies at the Oral Cavity Up to 30 Months After the Start of Vaccination with the Quadrivalent HPV Vaccine Among Mid-Adult Aged Men. Vaccine. 2019. 37: 2864-2869.

6. Discussion of Individual Studies/Clinical Trials

No new clinical trials or studies were conducted in support of this supplement. See section 2.4 for discussion of the relevant previously conducted studies.

7. Integrated Overview of Efficacy

No new clinical trials were conducted in support of this supplement and as such there are no new efficacy data to review or integrate.

8. Integrated Overview of Safety

No new clinical trials were conducted in support of this supplement and as such there are no new safety data to be reviewed in this section or integrated.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No new data pertaining to GARDASIL9 exposure in pregnancy were submitted as a part of this supplement.

9.1.2 Use During Lactation

No new data pertaining to GARDASIL9 and lactation were submitted as a part of this supplement.

9.1.3 Pediatric Use and PREA Considerations

This submission is subject to the Pediatric Research Equity Act (PREA). FDA's Pediatric Review Committee (PeRC) and CBER agreed with the Applicant's request for a waiver

of pediatric assessments for children from birth through 8 years of age as initiation of vaccination before 9 years of age does not represent a meaningful therapeutic benefit over initiation at 9 years or older in terms of prevention of HPV-related head and neck cancers and GARDASIL9 is unlikely to be used in a substantial number of children in this age group (section 5050B(a)(4)(B)(iii) of the Federal Food, Drug and Cosmetic Act).

9.1.4 Immunocompromised Patients

The current package insert (PI) states that immunologic response to GARDASIL9 may be diminished in immunocompromised individuals. No new data pertaining to use of GARDASIL9 in immunocompromised patients was submitted as a part of this supplement.

9.1.5 Geriatric Use

The current PI states that the safety and effectiveness of GARDASIL9 have not been evaluated in a geriatric population, defined as individuals aged 65 years and over. No new data pertaining to use of GARDASIL9 in geriatric patients was submitted as a part of this supplement.

10. CONCLUSIONS

Pre- and post-licensure clinical trial efficacy and immunogenicity data from qHPV and 9vHPV support the efficacy and effectiveness of 9vHPV in prevention of vaccine type HPV-related diseases at multiple mucosal sites, including the external genital region, vulva, vagina, cervix and anus, resulting in previous licensure and approval for these indications for use in 9 through 45-year-old males and females. Efficacy studies also support the prevention of 9vHPV vaccine-type (6/11/16/18/31/33/45/52/58) persistent infection at multiple mucosal sites. On the basis of biological plausibility and epidemiologic data, the prevention of vaccine-type anogenital HPV persistent infections and diseases (including pre-cancerous dysplastic lesions and cancers due to high risk types 16/18/31/33/45/52/58), serve as surrogate endpoints which are reasonably likely to predict prevention of vaccine-type HPV oral persistent infection and cancers of the head and neck. Additional lines of evidence from post-licensure data, consisting of randomized clinical trials, cross-sectional studies and population level data, support the effectiveness and impact of HPV vaccination against oral HPV infection on an individual and community scale. As required for licensure under the Accelerated Approval pathway, efficacy against oral persistent infection with relevant HPV types (16/18/31/33/45/52/58), as an intermediate surrogate endpoint that precedes development of HPV-related head and neck cancer, will be confirmed in a post-marketing, phase 3, placebo-controlled trial in 20 through 45-year-old HPV-vaccine naïve men and confirmation of clinical benefit will be extrapolated to other populations for which 9vHPV is indicated.

Safety data from studies conducted during the clinical development of 9vHPV, as well as post-licensure safety data, indicate that 9vHPV continues to be generally well tolerated. No new safety concerns have arisen specific to the proposed new indication. Concerns have arisen in the past regarding the increased frequency of spontaneous abortions in pregnant women who were exposed to the vaccine within 30 days of conception. This

risk continues to be evaluated by an ongoing pregnancy registry, which is expected to be completed in August 2020. During multiple stages of qHPV and 9vHPV development, concerns arose regarding an increase in non-vaccine type HPV-related disease and a lack of clinical benefit in women who have previously been infected with vaccine type HPV. If validated, these concerns would shift the risk-benefit analysis for vaccination in older women and possibly men. However, long term follow-up effectiveness studies in both men and women do not support a non-vaccine type disease replacement phenomenon nor sustained increased risk of high-grade dysplastic lesions or subsequent cancer development in previously infected women. Current product labeling includes statements which adequately address these previous concerns under the "limitations of use" section stating that 9vHPV has not been demonstrated to provide protection against disease from HPV types to which a person has already been exposed and that 9vHPV is not a treatment for HPV-related diseases.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Please see **Table 9** for details on the risk and benefit considerations.

Table 9: Risk-Benefit Considerations Supporting Approval of the Expanded Indication for Use of 9vHPV to Prevent HPV-related Oropharyngeal and Other Head and Neck Cancers

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HPV infection is nearly universal in sexually active populations. • In individuals infected with oncogenic strains, it has been demonstrated that persistence of infection at mucosal sites, including cervix, vagina, vulva and anus can lead to dysplasia, and eventually to cancer. • Persistent oral infection with HPV is associated with cancer development in the head and neck regions, specifically oropharyngeal, laryngeal and oral cavity cancers. • There are currently no pre-cancerous markers or effective screening methods for head and neck cancer. • Existing treatments for head and neck cancer can result in serious iatrogenic morbidity, including negative cosmetic outcomes, dysphagia, mucositis, dry mouth, loss of taste, speech difficulties, persistent nausea and vomiting and occasionally necrosis of the jaw. • White, male, non-smokers are disproportionately impacted by HPV-related head and neck cancers.	• Head and neck cancers are progressive, life-threatening diseases, often diagnosed after spread beyond primary tumor site due to difficulty with early detection. • Treatment of head and neck cancers are associated with significant morbidity and decreased quality of life.
Unmet Medical Need	• Gardasil 9 is the only currently manufactured HPV vaccine in the United States. • Aside from the HPV vaccines, no other drug or biologic is approved for prevention of HPV infection. Prevention is otherwise limited to use of condoms and other barrier methods (dental dams, which are minimally effective due to infrequent use in oral sex. • Vaccine uptake is especially low in boys and men.	• There is an unmet medical need for a licensed product for the prevention of HPV-related head and neck cancers.
Clinical Benefit	• qHPV and 9vHPV have been previously demonstrated to be effective in preventing vaccine type cervical persistent infection, HPV 6/11 related genital warts and HPV 16/18/31/33/45/52/58-related dysplasia (CIN, VIN, VaIN, AIS) and cervical, vulvar and vaginal cancers in women 16 through 26 years of ageqHPV has previously been demonstrated to be effective in preventing HPV 6/11/16/18 extra-genital and intra-anal persistent infection, HPV 6/11 genital warts, AIN and cancer in men 16 through 26 years of age. • Immunogenicity studies support non-inferior immune responses to qHPV and 9vHPV in children 9 through 15 years of age, from which effectiveness in this population is inferred. • Efficacy in women 27 through 45 years of age was demonstrated against a primary composite endpoint (persistent infection, genital warts and cervical dysplasia) in previous qHPV studies. • Long term effectiveness against high grade cervical dysplasia and genital cancers in women 27 through 45 years of age was also confirmed in previous qHPV studies. • Immunobridging studies support the effectiveness of qHPV in men 27 through 45 years of age • Immunobridging studies support the effectiveness of 9vHPV in men 16 through 26 years of age. • Effectiveness of protection against AIN and anal cancer caused by HPV 16/18 in women and anal disease caused by the additional 5 HPV types in 9vHPV in men and women were inferred on the basis of biological plausibility of similar mechanisms of protection at multiple mucosal sites. • Efficacy and effectives studies performed outside of the qHPV and 9vHPV suggest decreased prevalence of vaccine type oral HPV infection in vaccinated populations.	• Clinical efficacy and effectiveness data supporting licensure of qHPV and 9vHPV for the prevention of HPV-related disease at multiple mucosal sites in the anogenital region in males and females 9 through 45 years of age serves as a surrogate for prevention of HPV-related disease in the head and neck regions. • Epidemiologic evidence provides additional support of the effectiveness of HPV vaccination against oral HPV persistent infection, as a surrogate for head and neck cancer, in a real-world setting.
Risk	• As demonstrated in previous safety studies of qHPV and 9vHPV, the most substantial risks of vaccination with Gardasil 9 are associated with the inflammation produced at the injection site. • Syncope, allergic reactions and headache are the other most commonly reported adverse events. • Spontaneous abortion was detected at a higher rate in women who were exposed to 9vHPV within 30 days of conception compared to those who were exposed to qHPV. • No other new safety signals have been detected since licensure through post-marketing studies or safety surveillance.	• Existing evidence indicates that the risk of vaccination with 9vHPV is transient and minor and remains unchanged in the setting of the new proposed indication. • Evaluation of risk of spontaneous abortion is ongoing through a pregnancy registry.
Risk Management	• The most substantial risks of vaccination with Gardasil 9 are associated with the inflammation produced at the injection site. Erythema, swelling, and pain are very common. However, the most injection site reactions are mild in severity, and they resolve relatively quickly and without sequelae. • Previous concerns regarding potential higher rates of spontaneous abortion in women exposed to 9vHPV continue to be monitored via pregnancy registry.	• No new risk management strategies are needed for this application.

11.2 Risk-Benefit Summary and Assessment

The proposed addition of prevention of vaccine type HPV-related oropharyngeal and other head and neck cancers to the indication for 9vHPV adds additional potential benefit of vaccination in the form of prevention of a serious condition with significant associated morbidity and no current preventative measures. No new risks are anticipated with the proposed expanded indication, as there is no change to the target population, dose, formulation or schedule of vaccination and no new safety signals have been identified in post-marketing studies or safety surveillance data to date. As such, the risk-benefit assessment remains favorable for the use of 9vHPV for the prevention of HPV 16/18/31/33/45/52/58-related oropharyngeal and other head and neck cancers in males and females 9 through 45 years of age.

11.3 Discussion of Regulatory Options

The Applicant is seeking accelerated approval for the additional indication of prevention of oropharyngeal and other head and neck cancers caused by HPV types covered by the vaccine. Accelerated approval of this new indication will require confirmation of clinical benefit in a post-licensure study that is currently underway (see Section 11.6).

11.4 Recommendations on Regulatory Actions

The contents of this application support accelerated approval of this sBLA. HPV-related head and neck cancer is a serious condition with no currently approved preventative agent. The previously demonstrated efficacy and effectiveness of qHPV and 9vHPV against HPV-related anogenital infection and disease serve as an appropriate surrogate that is reasonably likely to predict the prevention of HPV-related oral infection and disease. In the opinion of this reviewer, the contents of this application support accelerated approval of this BLA supplement, as proposed, to expand the 9vHPV indications to include prevention of HPV 16/18/31/33/45/52/58-related oropharyngeal and other head and neck cancers.

11.5 Labeling Review and Recommendations

The Applicant sent a revised patient package insert (PPI) and a package insert (PI) including the expansion of indication to include the prevention of HPV-related oropharyngeal and other head and neck cancers due to HPV types 16/18/31/33/45/52/58 in women and men. CBER and Merck reach concurrence on the revised PI (submitted 14 May 2020). The agreed upon changes included:

- Highlights of Prescribing Information/ Indication and Usage- Revised to document the changes in Section 1
- Section 1
    - In Section 1.1 and 1.2, “oropharyngeal and other head and neck cancers” were added to the cancers prevented by GARADSIL9 for men and women.

    - In Section 1- a paragraph was added to address the accelerated approval for this indication
- Section 14.4-subsection was added, titled “Effectiveness in Prevention of HPV-related Head and Neck Cancers”; a paragraph was added to describe the process and surrogate endpoints used for the accelerated approval of the new indication.

11.6 Recommendations on Postmarketing Actions

To confirm effectiveness of GARDASIL9 against vaccine type HPV-related head and neck cancers, and as a Post-Marketing Requirement (PMR) for Accelerated Approval under subpart H (505b of the FD&C Act), the Applicant is conducting a phase 3, randomized, double-blind, saline placebo-controlled, multicenter, international post-marketing study (V503-049) to evaluate the efficacy of a 3 dose GARDASIL 9 regimen (Day 1, Month 2 and Month 6) against 6-month persistent oral HPV infection with oncogenic HPV types 16/18/31/33/45/52/58 in ~6000 men ages 20 through 45 years. Subjects will be healthy, sexually active men without history or evidence of previous HPV-related infection or disease at any head, neck or anogenital site. Oral HPV infection will be assessed by PCR of oral rinse and gargle samples collected at baseline, Month 7, Month 12 and every 6 months after for a total study duration up to 42 months. Immunogenicity and safety will also be assessed. The study is case driven, and analysis will be planned after 20 cases of 6-month persistent HPV oral infection have been identified. The primary endpoint of this study will be met if the lower bound for the 95% confidence interval of vaccine efficacy against 6-month oral HPV 16/18/31/33/45/52/58 persistent infection is > 20%. This protocol was reviewed under IND 13447/605 and allowed to proceed in mid-February 2020. Enrollment of this study began in February 2020 and study completion is anticipated in late 2025, with a final study report expected in mid-2026. CBER agrees that this postmarketing study, as designed, is appropriate to confirm clinical benefit of 9vHPV against oropharyngeal and other head and neck cancers caused by the HPV types contained in the vaccine.

CBER also agrees that no changes need to be made to the Applicant’s existing pharmacovigilance plan (PVP) or other postmarketing safety and effectiveness studies as a result of this BLA efficacy supplement. The 9vHPV pregnancy registry, which was established in 2015, will continue to collect information regarding vaccine exposures during pregnancy, through August 2020.