Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

From:	Adamma Mba-Jonas Medical Officer, Office of Biostatistics and Epidemiology/Division of Epidemiology/Pharmacovigilance Branch
To:	Haruhiko Murata BLA Chair, OVRR/DVP/LDV
Through:	Manette Niu Acting Chief, OBE/DE/PVB Craig Zinderman Associate Director for Product Safety, OBE/DE
Subject:	Biologics License Application Pharmacovigilance Plan Review
Applicant:	Merck Sharp and Dohme Ltd.
Product:	Gardasil 9 - Nanovalent (Human Papillomavirus 9-valent Vaccine, Recombinant)
Proposed Indication:	Prevention of HPV 6/11/16/18/31/33/45/52/58-related cervical, vulvar, vaginal, and anal cancers, and condyloma acuminata
Submission type/number:	BLA 125508/0
Submission Date:	December 13, 2013
Action Due Date:	December 10, 2014

1. INTRODUCTION

Cervical cancer is the third most common gynecologic cancer diagnosis and cause of death in the United States [1]. The etiologic agent central to the development of cervical neoplasia is human papillomavirus (HPV), which is found in over 99% of all diagnosed cervical cancers [2]. HPV is also implicated in other anogenital cancers and genital warts. Prevention and management of cervical neoplasia has involved screening and early detection, as well as vaccination against types of HPV of high oncogenic risk. Over 40 different types of HPV of varying oncogenic risk are known to infect the anogenital area, including types 16 and 18, to which approximately 70% of cervical cancer is attributable [3]. At present, vaccination against HPV types 16, 18, 6, and 11 is available in the US.

1.1 *- Product Description*

Gardasil 9 is a recombinant vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. When the L1 (major capsid) protein is expressed in recombinant systems, it self-assembles into VLPs, similar in conformation to native virions. Each 0.5-mL dose is formulated to contain 30/40/60/40/20/20/20/20/20 μg of HPV 6/11/16/18/31/33/45/52/58 L1 proteins, respectively. The formulation also includes sodium chloride, L-histidine, polysorbate 80, and sodium borate. The final container is a sterile suspension for intramuscular injection in a single-dose vial or a prefilled syringe, to be administered as a 3-dose regimen 0, 2, and 6 months apart.

The sponsor proposes that the product be indicated in girls and women ages 9 to 26 years for the prevention of:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
- and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
  - Cervical intraepithelial neoplasia (CIN) Grade 2 and 3 and Cervical adenocarcinoma *in situ* (AIS).
  - Cervical intraepithelial neoplasia (CIN) Grade 1.
  - Vulvar intraepithelial neoplasia (VIN) Grade 2 and 3.
  - Vaginal intraepithelial neoplasia (VaIN) Grade 2 and 3.
  - Anal intraepithelial neoplasia (AIN) Grades 1, 2 and 3.

The sponsor proposes that the product indication include boys ages 9 to 15 years for the prevention of external genital lesions and persistent infections and the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.

- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
- Anal intraepithelial neoplasia (AIN) Grades 1, 2 and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

1.2 *– Pertinent Regulatory Information*

Gardasil 9 is not yet marketed anywhere in the world. Its predecessor, Gardasil, is a quadrivalent HPV vaccine that was originally approved in the US in 2006 for girls and women ages 9 to 26 for the prevention of cervical cancer caused by HPV types 16 and 18, precancerous genital lesions caused by HPV types 6, 11, 16, and 18 and genital warts caused by HPV types 6 and 11. Since then, FDA has approved indication expansions to include prevention of vaginal and vulvar cancer caused by HPV types 16 and 18 in girls and women ages 9 to 26 years (2008), prevention of genital warts caused by HPV 6 and 11 in boys and men ages 9 to 26 years (2009), and prevention of anal cancer and associated precancerous lesions due to HPV types 6, 11, 16, and 18 in persons ages 9 to 26 years (2010).

1.3 *- Objectives*

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be approved. Available safety related data for Gardasil 9, including data derived from 6 clinical studies as well as relevant post-market surveillance data for Gardasil, was assessed. The Pharmacovigilance Plan (PVP) included in the Risk Management Plan submitted by Merck was also evaluated. Materials assessed as part of this safety review are listed below.

Table 1 - Materials Reviewed

Source	Document Type	Document
Merck & Co., Inc, 125508/0	Study Report	Base study report for V503-001, BLA section 5.3.5.1
Merck & Co., Inc, 125508/0	Study Report	Base study report for V503-002, BLA section 5.3.5.1
Merck & Co., Inc, 125508/0	Study Report	Complete study report for V503-005, BLA section 5.3.5.1
Merck & Co., Inc, 125508/0	Study Report	Base study report for V503-006, BLA section 5.3.5.1
Merck & Co., Inc, 125508/0	Study Report	Complete study report for V503-007, BLA section 5.3.5.1
Merck & Co., Inc, 125508/0	Study Report	Complete study report for V503-009, BLA section 5.3.5.1

Merck & Co., Inc, 125508/0.8	4 Month Post Submission Safety Update Report	Report of safety information obtained after BLA initial filing, section 2.7.4
Merck & Co., Inc, 125508/0	Periodic Safety Update Report summary, Gardasil	Summary of report of postmarket surveillance, worldwide, 1 Jun 2012 – 31 May 2013, BLA section 5.3.6
Merck & Co., Inc	Periodic Safety Update Report,	Report of postmarket surveillance, worldwide, 1 Jun 2012 – 31 May 2013,
Merck & Co., Inc, 125508/0	Other	Clinical Overview, BLA section 2.5
Merck & Co., Inc, 125508/0	Other	Risk Management Plan, BLA section 1.16
Merck & Co., Inc, 125508/0.3	Other	Clinical Safety Summary, BLA section 2.7.4
Merck & Co., Inc, 125508/0	Product Label	Proposed Labeling Information, BLA section 1.14
Merck & Co., Inc, 125508/0	IR Response	Response to Information Request #5, BLA section 1.11.3
Merck & Co., Inc., 125508/0	IR Response	Response to Information Request #13, BLA section 1.11.3
FDA	Periodic Internal Safety	Monthly safety review memos for Gardasil, January 2012-present
FDA	Gardasil 9 Statistical Review	Statistical review memo for Gardasil 9 BLA, October 3, 2014

2. PHARMACOVIGILANCE PLAN REVIEW: CLINICAL SAFETY DATABASE

The applicant submitted data from 6 clinical studies in support of the application.

Table 2 - Subjects Enrolled in Pre-licensure Studies of Gardasil 9

Protocol ID	V503-001	V503-002	V503-005	V503-006	V503-007	
Study Description	Evaluation of safety, efficacy, and dose-tolerability of Gardasil9 in young women	Comparison of immunogenicity and safety of Gardasil9 in young women, pre-adolescent and adolescent girls, and pre-adolescent and adolescent boys	Evaluation of safety and immunogenicity of Gardasil9 when given concomitantly with Menactra and Adacel*	Evaluation of safety and immunogenicity of Gardasil9 in patients who have already received Gardasil (qHPV)	Evaluation of safety and immunogenicity of Gardasil9 when given concomitantly with Repevax**	Evaluation of safety, efficacy, and dose-tolerability of Gardasil9 in pre-adolescent and adolescent girls
Subjects						
Females 9-15 yrs	0	1932	620	120	528	600
Males 9-15 yrs	0	666	621		526	0
Females 16-26 yrs	14840	468	0	493***		0

*****Includes antigens for tetanus toxoid, diphtheria toxoid, pertussis toxoid, filamentous hemagglutinin, fimbrial agglutinogens, and pertactin **Includes antigens for tetanus toxoid, diphtheria toxoid, pertussis toxoid, filamentous hemagglutinin, fimbrial agglutinogens, pertactin, and polio virus types 1, 2, and 3 ***Includes males and females in this age group

A total of 20,751 subjects were vaccinated in 6 clinical trials, including 13,360 subjects who received at least 1 dose of 9vHPV vaccine and 7391 subjects who received at least 1 dose of qHPV vaccine, the primary control employed in the clinical trial program. Protocols V503-005, V503-006, V503-007, and V503-009 are complete. Extension phases of Protocols V503-001and V503-002 are ongoing, and an extension of Protocol V503-006 is planned. For Protocol V503-001, data from all visits occurring on or before the visit cut-off date of 10 APR 2013 are available for evaluation. For Protocol V503-002 base study, data from all visits occurring on or before 30 APR 2011 (Day 1 through Month 12) are available for evaluation.

2.1 – *Safety data from V503-001*

The design and key results from the V503-001 pivotal trial are summarized in the table below.

Table 3. Summary of Pivotal trial V503-001

Study Title:	A Randomized, International, Double-Blinded (With In-House Blinding), Controlled With Gardasil™, Dose-Ranging, Tolerability, Immunogenicity, And Efficacy Study Of A Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (Vlp) Vaccine Administered To 16- To 26-Year-Old Women
Study Design:	Dose-ranging substudy: Recruited subjects were randomized to receive qHPV or 9vHPV at low-, mid-, or high-dosage at Day 1, Month 2, and Month 6. All subjects were followed for safety Day 1 through Month 7. Subjects were assessed for immunogenicity at Month 7, and the formulation with best tolerability was used in the subsequent substudies. Efficacy/immunogenicity substudies: Recruited subjects were randomized to receive qHPV or 9vHPV at the formulation selected in the dose-ranging substudy. Subjects were followed

	for efficacy through at least Month 42, and followed for immunogenicity (persistence of antibody responses) through Month 42. Subjects who received the selected mid-dosage 9vHPV vaccine formulation during the initial substudy were added to and also assessed as part of the efficacy substudy. All subjects included in the efficacy/immunogenicity substudies were followed for safety for the duration of the trial.			
Eligibility criteria:	Females age 16 to 26 years. 14,840 subjects enrolled.			
Study Duration:	26-SEP-2007 to 10-APR-2013			
Study Status:	Base study complete. Study report submitted. Extension study ongoing.			
Objectives:	o To determine optimal dose formulation for 9vHPV administration o To evaluate overall safety of 9vHPV, superiority of 9vHPV with regards to efficacy/immunogenicity endpoints related to HPV types 31/33/45/52/58, and assess non-inferiority to qHPV with regards to efficacy/immunogenicity endpoints related to HPV types 6/11/16/18			
Safety related endpoints:	Adverse event (AE) and Physical examination (PE) monitoring, documented by subjects on Vaccine Report Card (VRC) within 15 days of any dose, and reported spontaneously by day 180 following final dose			
Study Population:		Dose-Ranging Substudy	Efficacy Substudy	Immunogenicity Substudy
	Total (n):	1,242	14,215	13,598
	Age (years):			
	Mean	21.9	21.9	21.9
	Range	16-26	16-26	16-26
	Race:			
	White	636 (51.2%)	7,851 (55.2%)	7,539 (55.4%)
	Black/AfAm	56 (4.5%)	476 (3.3%)	454 (3.3%)
	Asian	153 (12.3%)	2,028 (14.3%)	1,951 (14.3%)
	Other	395 (31.8%)	3,837 (27.0%)	3,634 (26.7%)
	Unknown	2 (0.2)	23 (0.2)	22 (0.2%)
Key Study Results Relevant to Safety:	Dose-ranging substudy	The number of documented adverse events increased with the dose-range. 3 subjects withdrew due to AE (2 in low-dose and 1 in mid-dose range). 1 subject withdrawal was attributed to 9vHPV. No deaths occurred during the substudy.		
	Efficacy/immunogenicity substudy	The number of acute (within 15 days of vaccination) adverse events, and specifically injection site reactions, was higher in the 9vHPV group. 12 subject withdrawals occurred, including 8 in 9vHPV group (all vaccine-related) and 3 in qHPV group (3 vaccine-related). 416 SAEs were documented (233 in 9vHPV group, 183 in qHPV group). 4 SAEs were attributed to vaccine administration – 2 in each arm. 10 deaths occurred – 5 in each arm; none were attributed to vaccine administration.		

2.1.2 - Safety-related Data from V503-001, Dose-ranging Substudy

Injection-site reactions: The proportion of subjects in this substudy who reported specific injection-site adverse experiences in the first 5 days after vaccination was higher in the low-, mid-, and high-dose 9vHPV vaccine groups (87.7%, 89.1%, and 90.5%, respectively) compared to the qHPV vaccine group (83.8%). The most common injection-site adverse experiences reported in more than 1% of subjects following any vaccination visit were pain, swelling, erythema, and pruritus. Risk differences were calculated for AEs reported on the Vaccine Report Card (VRC), which provided a

method of standardizing subject responses. Proportions of study groups reporting injection-site pain on VRC responses were 86%, 88.8%, 89%, and 80% in the low-dose, mid-dose, high-dose, and control groups, respectively, reflecting a possible dose-dependence. Risk differences between both the mid- and high-dose group and the control group were found to be statistically significant ($p<0.05$). Proportions of study groups reporting injection-site swelling on VRC responses were 32%, 35%, 34%, and 27% in the low-dose, mid-dose, high-dose, and control groups, respectively. Risk differences between the mid-dose group and the control group were found to be statistically significant ($p<0.05$), and the risk difference between the high-dose group and control trended towards significance ($p=0.054$). Risk differences for other injection-site AEs were not found to be statistically significant. Overall, subjects who received 9vHPV were more likely to report severe injection site AEs than control group subjects (7.8 vs 4.4%, p=<0.05).

Systemic adverse events: The most common clinical adverse experiences (incidence >5% in any one treatment group) were headache (range among treatment groups, 19.8%-21.6%), pyrexia (range, 5.8%-9.7%), nausea (range, 5.5%-7.6%), nasopharyngitis (range, 3.2%-6.9%), influenza (range, 3.9%-6.5%), and dizziness (range, 2.3%-5.5%). There was no statistically significant risk difference in overall reporting of systemic adverse events on VRC between the control group and any of the dose-range groups. Influenza-like illness (estimated risk difference between high-dose group and control=1.3%, CI (0.1, 3.3)) and musculoskeletal pain (estimated risk difference between high-dose group and control=-1.3 (-3.3, -0.0)) were observed at statistically different proportions between treatment groups. Risk differences for the >5% incidence AEs were not statistically significant when assessed from VRC; however, a statistically significant risk difference between the high-dose 9vHPV group and control was detected for reports of influenza-like illness on the VRC (estimated risk difference between high-dose group and control= 1.3 (0.1, 3.3) . Intensity of AEs was assessed on VRC. Observed AEs were mostly of mild-moderate intensity, and the level of intensity was not significantly different between 9vHPV and control groups.

Serious adverse events: 18 subjects reported 19 SAEs. None were identified as vaccine-related. The most commonly reported serious adverse experiences were induced abortion (4 across all 9vHPV groups, 4 in control group) and spontaneous abortion (2 across all 9vHPV groups, 1 in control group).

Vaccine-related systemic adverse events: Overall, subjects in 9vHPV groups reported more AEs determined to be vaccine-related by investigators in the first 15 days following vaccination (33.5%, 30.7%, and 29.8%, in the low-dose, mid-dose, and high-dose 9vHPV vaccine groups, respectively) than subjects in control group (29.2%). The most common (frequency ≥2%) vaccine-related systemic clinical adverse experiences were headache, pyrexia, nausea, dizziness, fatigue, abdominal pain upper, diarrhea, and oropharyngeal pain. Within the three 9vHPV vaccine groups, the frequency of subjects who reported vaccine-related adverse experiences did not increase with dose. None were classified as serious.

Deaths and Discontinuations: No deaths were reported. 3 discontinuations due to AE were reported, including 1 due to rash 5 days after dose 1 (low-dose group), 1 due to dysmenorrhea 3 days after dose 2 (low-dose group), and 1 subject from the mid-dose group that will be discussed in

Section 2.1.3 - efficacy substudy. The rash was considered vaccine-related.

Pregnancy outcomes: Pregnancy status was checked via urine test and documented at every visit, and subjects with positive tests were followed for outcomes but otherwise discontinued from further participation. Over the course of the substudy, 5, 3, 12, and 14 pregnancies were documented in the low-dose, mid-dose, high-dose, and control vaccine groups, respectively. Proportions of pregnancies resulting in outcomes such as spontaneous abortion, fetal outcomes, and congenital anomalies are difficult to compare due to low numbers in each group; however, there were no apparent dose-related patterns to reports of outcomes.

2.1.3 - Safety-related Data from V503-001, Efficacy Substudy

Adverse event data from the efficacy substudy is summarized in the table below.

Table 4. Adverse Events documented during V503-001, Efficacy/Immunogenicity substudy (Adapted from table 12-4, p. 750)

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

[†] Determined by the investigator to be related to the vaccine.

[‡] Study medication withdrawn.

Injection site reactions: Subjects in the 9vHPV group reported more injection site reactions than subjects in the control group (6,423 vs 6,024), and a higher proportion of subjects in the 9vHPV group reported severe reactions than control group subjects (7.8% vs 4.4%); this difference was statistically significant. Erythema, pain, and swelling were all reported by a statistically significantly higher proportion of subjects in the 9vHPVgroup.

Systemic adverse events: Of the most commonly reported clinical adverse experiences (incidence >5%), only headache was found to have been reported by a statistically significant different proportion of subjects (risk difference=1.7, CI (0.3, 3.2)). Observed AEs were mostly of mild-moderate intensity, and there was a numerically higher number of AEs assessed as moderate and severe in the 9vHPV group (1,954 and 826) than in the control group (1,864 and 761).

Serious adverse events: 233 subjects (3.3%) in the 9vHPV vaccine group and 183 subjects (2.6%) in the control group reported SAEs. SAEs with imbalances of >1 subject are summarized in the table below.

Table 5. Notable SAEs observed in V503-001, efficacy/immunogenicity studies

Adverse Event	**Number reporting in 9vHPV group**	**Number Reporting in qHPV group**
Appendicitis	9	16
Infectious enteritis	2	0
Joint dislocation	0	2
Multiple injuries	2	0
Malignant melanoma	2	0
Syncope	2	0
Fetal distress syndrome	5	1
Premature rupture of membranes	4	2
Bipolar disorder	3	1
Renal failure	2	0
Cervical dysplasia	5	3
Hypervolemic shock	2	0

Pregnancy related outcomes from this study are discussed in a subsequent section ("Pregnancy Outcomes").

In addition to AEs included in the table, 4 AEs related to the SOC "immune system disorders" occurred, including 1 AE of anaphylaxis, 1 AE of hypersensitivity, 1 AE of allergy to vaccine, and 1 AE of sarcoidosis; each of these AEs occurred in the 9vHPV group.

Vaccine-related AE: Overall, subjects in 9vHPV groups reported more vaccine-related AEs in the first 15 days following vaccination (29.5%) than subjects in control group (27.3%). The most common (frequency ≥2%) vaccine-related systemic clinical adverse experiences were headache, pyrexia, nausea, dizziness, and fatigue.

Table 6. Vaccine-related AEs, V503-001 Efficacy Substudy

	9vHPV Vaccine n	(%)	qHPV Vaccine n	(%)
Subjects in population with follow-up	7,071		7,078	
with one or more systemic adverse events	2,086	(29.5)	1,929	(27.3)
with no systemic adverse events	4,985	(70.5)	5,149	(72.7)
Gastrointestinal disorders	**487**	**(6.9)**	**435**	**(6.1)**
Diarrhoea	87	(1.2)	71	(1.0)
Nausea	311	(4.4)	261	(3.7)
General disorders and administration site conditions	**649**	**(9.2)**	**562**	**(7.9)**
Fatigue	166	(2.3)	150	(2.1)
Pyrexia	357	(5.0)	301	(4.3)
Infections and infestations	**164**	**(2.3)**	**157**	**(2.2)**
Musculoskeletal and connective tissue disorders	**202**	**(2.9)**	**168**	**(2.4)**
Myalgia	69	(1.0)	48	(0.7)
Nervous system disorders	**1,196**	**(16.9)**	**1,124**	**(15.9)**
Dizziness	211	(3.0)	197	(2.8)
Headache	1,031	(14.6)	969	(13.7)
Respiratory, thoracic and mediastinal disorders	**117**	**(1.7)**	**82**	**(1.2)**
Oropharyngeal pain	73	(1.0)	40	(0.6)
Skin and subcutaneous tissue disorders	**84**	**(1.2)**	**86**	**(1.2)**

Among these vaccine-related AEs were 4 AEs classified as serious. 2 occurred in the 9vHPVgroup:

> AN 69495, a 26 year old female from Brazil who developed fever, 11 hours after the administration of her 3rd study vaccination. The subject was treated with paracetamol, but symptoms worsened over the ensuing 12 hours. Assessment of the patient by an infectious disease specialist did not reveal an infectious etiology for the fever. The subject spontaneously recovered the following day.
>
> AN 75481, a 20 year old female from Denmark with a history of asthma who developed a severe allergic reaction following her first vaccination. Symptoms included swelling of the mouth and throat, rhinorrhea, rash over body, and difficulty breathing. The subject self-treated with an inhaled beta-agonist and an anti-urticarial medication. Symptoms resolved 23 hours after onset.

Deaths and discontinuations: 10 subjects died during the course of the substudy, including 5 in the 9vHPV investigational group. All but 1 patient died after receiving the complete dose regimen, during the follow-up period. The exception was subject AN 71972, who died (completed suicide) between the first and second vaccinations. Of the remaining patients who died in the investigational group, 1 subject died of trauma following a road traffic accident. The second subject died 531 days following the last dose. This subject had a history of multiple intra-abdominal surgeries and died of hypovolemic and septic shock after 24 hours of abdominal pain; autopsy revealed diffuse hemorrhage and necrosis of jejunum and ileum, intestinal adhesions, volvulus and intestinal strangulation. The third subject died suddenly in her sleep 678 days following the 3rd dose of vaccine; the cause of death is unknown and no autopsy was performed. The fourth subject became symptomatic with acute lymphoblastic leukemia 90 days following the second vaccine dose and died of the disease approximately 2.5 years following the last dose. None of these

fatalities were attributed to the vaccine by the respective investigators.

12 discontinuations occurred during the visit cut-off period including 8 from the 9vHPV vaccine group (1 of whom was originally enrolled in the dose-ranging substudy) and 4 from the qHPV vaccine group. The most common AEs associated with discontinuation were related to injection site reactions. Clinical data for the subjects in the investigational group is summarized in the table below.

Table 7. 9vHPV Patients discontinued during the visit cut-off period due to AEs, V503-001 Efficacy Substudy (Adapted from Table 12-37, p. 849)

Subject ID	Total number doses received	Time from last dose to AE onset (days)	AE	Serious	Vaccine-related
18464	2	1	Asthenia, dizziness, fatigue, hyperhidrosis	No	Yes
18464	2	1	Injection site pain, nausea, pyrexia	No	Yes
68226	1	1	Injection site pain	No	Yes
10888	1	1	Hypoaesthesia, paraesthesia	No	Yes
71291	1	2	Headache	No	Yes
21275	1	93	Spontaneous abortion	Yes	No
20790	2	1	Injection site swelling	No	Yes
75481	1	1	Allergy to vaccine	Yes	Yes
71972	1	15	Suicide	Yes	No

Pregnancy outcomes: 1,192 subjects in the investigational group and 1,129 subjects in the control group became pregnant during the visit cut-off period, and outcome data was available for 1,161 and 1,108 subjects, respectively. Elective abortion was observed in 137 subjects in the investigational group and 113 subjects in the control group. Nine elective abortions were related to antecedent detection of congenital anomaly in the fetus; all other elective abortions were a result of personal decision by the subject. A total of 20 pregnancies (1.7%) among subjects who received the 9vHPV vaccine were complicated by congenital anomaly. 14 of these pregnancies resulted in live births and 6 pregnancies were electively terminated. Fetal distress was discerned during delivery in 30 pregnancies (2.5%). By comparison, a total of 21 pregnancies (1.9%) among subjects who received the qHPV vaccine were complicated by congenital anomaly. 18 of these pregnancies resulted in live births and 3 pregnancies were electively terminated. Fetal distress was discerned during delivery in 19 pregnancies (1.7%). Spontaneous abortion was observed in 121 subjects (10.4%) in the investigational group and 143 subjects (12.9%) in the control group.

1 subject (AN 21275) withdrew from the study following a spontaneous abortion 93 days after initial vaccination. The subject was a 23 year old Korean woman with history of benign ovarian

cyst. Examination of the adverse event reporting form revealed no additional cause for study withdrawal, and it is unclear if the subject withdrew due to the AE or due to physician recommendation.

New medical history: Data regarding reports of new medical history was assessed. Incident conditions with a notable imbalance in occurrence in the investigational group are summarized in the table below. Conditions with imbalances favoring the investigational group have been omitted.

Table 8. Observed new medical history, incidence<2%, with numerical imbalance >5%

Condition (number reporting occurrence)	**Number of subjects reporting in 9vHPV group (%reporting)**	**Number of subjects reporting in qHPV group (%reporting)**
Insomnia (86)	50 (58%)	36 (42)
Tension headache (27)	17 (63)	10 (37)
Stress (57)	35 (61)	22 (39)
Hypertension (55)	33 (60)	22 (40)
Oral herpes (84)	49 (58)	35 (42)
Hypersensitivity (76)	43 (57)	33 (43)
Rash (76)	47 (62)	29 (38)
Lower respiratory tract infection (20)	16 (80)	4 (20)
Peripheral edema (25)	17 (68)	8 (32)
Alopecia (40)	23 (58)	17 (42)
Hypothyroidism (95)	54 (57)	41 (43)
Diabetes mellitus type 1 (5)	4 (80)	1 (20)
Multiple Sclerosis (6)	5 (60)	2 (40)

Observations of new medical conditions that were documented at greater than 1% incidence were reported by roughly similar proportions of subjects between the 9vHPV and qHPV groups. The implications of imbalances in observations of less commonly reported new medical conditions is unclear, as number of subjects reporting is too small to assess significance.

2.2 – *Safety data from V503-002*

The design and key results from the V503-002 clinical trial are summarized in the table below.

Table 9. Summary of Clinical trial V503-002

Study Title:	A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds)
Study Design:	Multicenter immunogenicity and safety/tolerability study with a target enrollment of 2800 subjects (total enrolled = 3052) in three groups (1924 girls age 9-15 years, 662 boys age 9-15 years, and 466 women aged 16-26 years). Immunogenicity of the vaccine was assessed in girls and boys and compared to

<table>
<tr><td></td><td colspan="4">reference group of young women. Safety was monitored for the duration of the study.</td></tr>
<tr><td>Study Duration:</td><td colspan="4">27-AUG-2009 to 30-MAR-2011</td></tr>
<tr><td>Study Status:</td><td colspan="4">Base study complete. Study report submitted. Extension study through Month 36 underway.</td></tr>
<tr><td>Objectives:</td><td colspan="4">Immunogenicity:
o To evaluate whether the 9-valent HPV vaccine induces noninferior immune responses in preadolescent and adolescent boys and girls 9 to 15 years of age compared to young women 16 to 26 years of age.
Safety:
o To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine in preadolescent and adolescent boys and girls 9 to 15 years of age and young women 16 to 26 years of age.</td></tr>
<tr><td>Safety related endpoints:</td><td colspan="4">Adverse event (AE) and Physical examination (PE) monitoring; VRC used for standardization</td></tr>
<tr><td rowspan="6">Study Population Demographics:</td><td></td><td>Females 9-15 (%)</td><td>Males 9-15 (%)</td><td>Females 16-26 (%)</td></tr>
<tr><td>Race</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>56.0</td><td>43.6</td><td>51.1</td></tr>
<tr><td>Black</td><td>8.3</td><td>5.5</td><td>10.2</td></tr>
<tr><td>Asian</td><td>22.2</td><td>27.8</td><td>27.2</td></tr>
<tr><td>Other</td><td>13.4</td><td>23.0</td><td>11.5</td></tr>
<tr><td>Study Results:</td><td colspan="4">Occurrence of AEs was generally comparable among the investigational groups. 42 serious AE were reported by 34 subjects, including 2 SAEs described as vaccine-related. The most common reported SAE was appendicitis (5 cases) and asthma exacerbation (2 cases). 1 patient withdrawal due to a vaccine-related adverse event occurred (asthma)*. No deaths occurred during the trial.</td></tr>
<tr><td>Conclusion:</td><td colspan="4">No clinically significant safety issues were identified.</td></tr>
</table>

On July 14, 2014, FDA was made aware of potential violations in ethics protocols regarding subject recruitment and data collection at two clinical sites in (b)(3)(b)(4)(b)(7) involved in this study. The review team decided to disregard clinical efficacy and safety data from these sites. These concerns involved less than 2% of clinical data from this study, and removal of this data did not substantively affect the safety assessment.

2.2.2 – Safety related data in V503-002

Adverse events are summarized in the table below.

Table 10. Adverse Events documented during V503-002

	9- to 15-Year-Old Females		9- to 15-Year-Old Males		16- to 26-Year-Old Females	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	1,923		662		466	
with one or more adverse events	1,666	(86.6)	536	(81.0)	420	(90.1)
injection-site	1,577	(82.0)	483	(73.0)	398	(85.4)
non-injection-site	877	(45.6)	284	(42.9)	275	(59.0)
with no adverse event	257	(13.4)	126	(19.0)	46	(9.9)
with vaccine-related† adverse events	1,614	(83.9)	500	(75.5)	406	(87.1)
injection-site	1,577	(82.0)	483	(73.0)	398	(85.4)
non-injection-site	402	(20.9)	144	(21.8)	121	(26.0)
with serious adverse events	16	(0.8)	11	(1.7)	15	(3.2)
with serious vaccine-related adverse events	0	(0.0)	1	(0.2)	1	(0.2)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	1	(0.2)	0	(0.0)
discontinued due to a vaccine-related adverse event	0	(0.0)	1	(0.2)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	1	(0.2)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	1	(0.2)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.

Injection site reactions: Occurrence of injection-site reactions was common in all groups and occurred most commonly in the 16-26 year old females reference group. When injection site AEs were compared between the reference group and both 9-15 year old males and 9-15 year old females, no statistically significant differences in overall risk of injection-site AEs or severity of injection site AEs were observed.

Systemic adverse reactions: The systemic AEs most commonly reported in the first 15 days following any vaccination (>3% in any group) included headache, dysmenorrhea, oropharyngeal pain, pyrexia, nasopharyngitis and upper respiratory tract infection. The percentage of patients reporting these events was not markedly different across the treatment groups.

When compared to the reference group of 16-26 year old females, statistically significant risk differences were found for 9-15 year old females with respect to occurrence of: diarrhea (risk difference relative to reference group= -1.9 (-4.1, -0.4)), toothache (risk difference relative to reference group= 1.2 (-2.8, -0.4)), feeling hot (risk difference relative to reference group= -1.2 (-2.8, -0.4)), Malaise (risk difference relative to reference group= -1.5 (-3.2, -0.5), urinary tract infection (risk difference relative to reference group=-1.0 (-2.4, -0.3)), back pain (risk difference relative to reference group= -1.4 (-3.2, -0.3)), headache (risk difference relative to reference group= -4.2 (-8.6, -0.2)), and dysmenorrhea (risk difference relative to reference group= -2.5 (-4.6, -1.0)). Thus, in each case, the 16-26 year old females were more likely to report the AE than 9-15 year olds.

When compared to the reference group of 16-26 year old females, statistically significant risk differences were found for 9-15 year old males with respect to occurrence of gastroenteritis (risk

difference relative to reference group= 2.0 (0.6, 3.5)), myalgia (risk difference relative to reference group= -0.9 (-2.4, -0.1)), feeling hot (risk difference relative to reference group= -1.4 (-2.9, -0.4)), dizziness (risk difference relative to reference group= -1.9 (-4.0, -0.1)), urinary tract infection (risk difference relative to reference group= -1.1 (-2.5, -0.5)), back pain (risk difference relative to reference group= -1.7 (-3.5, -0.5)), headache (risk difference relative to reference group= -7.7 (-12.5, -3.1)), and dysmenorrhea (risk difference relative to reference group= -3.6 (-5.8, -2.3)). With the exception of gastroenteritis, 16-26 year old females were more likely to report the AE than 9-15 year olds. Young age is a known risk factor for gastroenteritis due to lack of acquired immunity [4], which may explain the observed risk difference for this AE.

Overall, neither 9-15 year old males or females reported moderate or severe AEs more frequently than the reference group.

Serious adverse events: 34 subjects experienced 39 SAEs (excluding fetal loss) over the course of the study. The most common SAEs were appendicitis (5 cases) and asthmatic crisis (2 cases). There was no clustering or pattern of SAEs among the vaccination groups.

Two SAEs were attributed to vaccine administration and will be discussed below.

Vaccine-related AE: Overall, 9-15 year old females and 9-15 year old males receiving 9vHPV vaccine reported fewer vaccine-related AEs in the first 15 days following vaccination (20.9 and 21.8%) than 16-26 year old females (26.0%). The most common (frequency ≥2% in any group) vaccine-related systemic clinical adverse experiences (fatigue (range 0.5-2.6%), headache (range 9.1-9.5%), and pyrexia (range 6.7-8.6%) were similar across treatment groups.

Among these vaccine-related AEs were 2 AEs classified as serious:

> AN 31765 was a 10-year-old male from Peru with a history of seasonal allergic rhinitis and bronchial asthma. One day following dose #1 of 9vHPV, the subject experienced cough, breathing difficulty, and weakness. He was hospitalized for asthma exacerbation and treated with steroids. The investigator determined that the AE of asthma exacerbation was possibly due to vaccination due to temporal association and discontinued him from the study.
>
> AN 33179 was a 21 year old female from Belgium with a history of fatigue, recurrent itching and recurrent fever. On the day of the third 9vHPV dose, the subject experienced neck pain, severe headache, fever and photophobia. Infectious work up did not reveal a source and the subject was hospitalized for 3 days. The subject was discharged with a residual mild headache; other symptoms had resolved. Discharge diagnosis was viral infection vs. AE due to vaccination. Investigator attributed the headache to the vaccine.

Deaths and discontinuations: No subjects died during the study period. The single discontinuation, AN 31765, has been previously discussed.

Pregnancy outcomes: 19 pregnancies occurred during the study period, including 4 in the 9-15 year old female and 15 in the 16-26 year old female group. Outcome data was available for review for 17 pregnancies. Of these, 9 resulted in live births and 8 resulted in fetal loss, including 1 ectopic pregnancy, 1 spontaneous abortion, and 6 elective abortions. No congenital anomalies were observed. 2 subjects experienced SAEs during pregnancy, including incompetent cervix and fetal distress; both were in the 16-26 year old female group. Neither SAE was attributed to the vaccine. Two infant SAEs – gastroenteritis and respiratory distress – were observed in the 16-26 year old female group, and neither SAE was attributed to the vaccine.

2.3 - *Safety data from V503-005*

The design and key results from the V503-005 clinical trial are summarized in the table below.

Table 11. Summary of Clinical trial V503-005

Study Title:	A Phase III Open-Label Clinical Trial to Study the Immunogenicity and Tolerability of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) Given Concomitantly with Menactra™ and Adacel™ in Preadolescents and Adolescents (11 to 15 Year Olds)			
Study Design:	Open-label, randomized, multicenter, comparative study. Healthy, preadolescent and adolescent boys and girls were included. Subjects were stratified by gender (1:1 ratio) and randomly assigned to 1 of 2 vaccination groups in a 1:1 ratio. Subjects in vaccination group 1 (310 males, 311 females) received Menactra, Adacel, and first dose of 9vHPV concomitantly on Day 1, and subjects in vaccination group 2 (310 males, 310 females) received the first dose of 9vHPV vaccine on Day 1 and Menactra and Adacel at Month 1. Safety was monitored for the duration of the study.			
Study Duration:	22-OCT-2009 to 22-FEB-2011			
Study Status:	Study complete. Study report submitted.			
Objectives:	Immunogenicity: o To evaluate whether the 9-valent HPV vaccine, Menactra (vaccine against *Neisseria meningitides),* and Adacel (vaccine against diphtheria, tetanus, and Pertussis) induce immune responses in preadolescent and adolescent boys and girls 11 to 15 years of age when given concomitantly that are noninferior to responses induced when given separately. Safety: o To evaluate the tolerability of the concomitant administration of a first dose of the 9-valent HPV L1VLP vaccine with Menactra and Adacel in preadolescent and adolescent boys and girls 11 to 15 years of age.			
Safety related endpoints:	Systemic AEs on Days 1 through 15 following any vaccination visit; injection-site AEs on Days 1 through 5 following any vaccination visit for 9vHPV vaccine, Menactra or Adacel; maximum oral temperature ≥37.8°C (≥100.0°F) on Days 1 through 5 following any vaccination visit; severe injection-site AEs on Days 1 through 5 following any vaccination visit for 9vHPV vaccine and on Days 1 through 5 following any vaccination visit for Menactra or Adacel; number of subjects reporting serious clinical AEs from Days 1 to 15 following any vaccination visit; vaccine-related clinical SAEs at any time.			
Study Population Demographics:		Concomitant vaccinations (%)	Non-concomitant vaccinations (%)	Total (%)
	Race			

	White	48.0	46.8	47.4
	Black	6.1	6.6	6.4
	Asian	1	1.3	1.1
	Other	45.9	45.3	45.2
Study Results:	There were no deaths and no vaccine-related SAEs. The frequency of AEs was generally comparable between the 2 groups. One subject was discontinued in each group due to an AE.			
Conclusion:	No clinically significant safety issues were identified.			

2.3.2 – Safety related data in V503-005

Adverse events are summarized in the table below.

Table 12. Adverse Events documented during V503-005 (Adapted from Adverse Event Summary Table, p. 14)

	9vHPV Vaccine + [Menactra + Adacel Concomitant]		9vHPV Vaccine + [Menactra +Adacel] Non-concomitant		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	613		611		1,224	
with one or more adverse events	553	(90.2)	542	(88.7)	1,095	(89.5)
injection-site	531	(86.6)	509	(83.3)	1,040	(85.0)
non-injection-site	344	(56.1)	339	(55.5)	683	(55.8)
with no adverse event	60	(9.8)	69	(11.3)	129	(10.5)
with vaccine-related† adverse events	538	(87.8)	522	(85.4)	1,060	(86.6)
injection-site	531	(86.6)	509	(83.3)	1,040	(85.0)
non-injection-site	168	(27.4)	168	(27.5)	336	(27.5)
with serious adverse events	5	(0.8)	5	(0.8)	10	(0.8)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	1	(0.2)	1	(0.2)	2	(0.2)
discontinued due to a vaccine-related adverse event	1	(0.2)	1	(0.2)	2	(0.2)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.
Four (4) subjects were randomized but did not receive any vaccination. Two (2) subjects who had been randomized into the Non- concomitant and/or Concomitant Vaccination Groups were classified into a third vaccination group titled Protocol Non- compliant Regimen. Two (2) subjects in the Non-Concomitant Vaccination Group received the Menactra and the Adacel vaccinations in separate limbs at Month 1 visit. Two (2) subjects in the Concomitant Vaccination Group received the Menactra and Adacel vaccinations in separate limbs at the Day 1 visit.

Injection site reactions: Occurrence of injection-site reactions was common in both groups and occurred at roughly equivalent proportions in both arms (86.6% and 83.3% at the 9vHPV injection site in the concomitant and non-concomitant groups, respectively; 74.6 and 70.7 at the Menactra/Adacel injection site in the concomitant and non-concomitant groups, respectively). Observed risk of swelling at the 9vHPV injection site was observed in 14.4% of subjects in the concomitant vaccination group and 9.4 % of subjects in the nonconcomitant group (RD=5.0 (CI=1.4, 8.7)).

Systemic adverse reactions: Systemic adverse events were reported by 43.1% of subjects in the concomitant group and 42.4% of subjects in the nonconcomitant group. The systemic AEs most

commonly reported in the first 15 days following any vaccination (>3% in any group) are summarized below.

Table 13. Commonly reported systemic AEs in V503-003

Adverse Event	**Concomitant Group n (%)**	**Nonconcomitant group n (%)**
Headache	104 (17.0)	82 (13.4)
Oropharyngeal pain	23 (3.8)	16 (2.6)
Vomiting	23 (3.8)	13 (2.1)
Pyrexia	53 (8.6)	56 (9.2)
Nasopharyngitis	25 (4.1)	19 (3.1)

Chills were reported by 8 subjects in the concomitant group (1.3%) and 1 subject (0.2%) in the nonconcomitant group (RD=1.1 (0.2, 2.4)). Risk differences for all other systemic AEs as well as elevated oral temperatures were not statistically significant. Proportion of subjects reporting moderately severe or severe systemic AEs were roughly equivalent between the groups.

Serious adverse events: 10 subjects experienced 11 total SAEs over the course of the study – 6 in the concomitant group and 5 in the non-concomitant group. The most common SAE was appendicitis (3 cases). There was no clustering or pattern of SAEs among the vaccination groups. There was no statistically significant risk difference in observation of SAEs observed between the two groups.

No SAEs were attributed to vaccine administration.

Vaccine-related AE: Vaccine related systemic AEs were reported by 21.0% and 19.3% of subjects in the concomitant and nonconcomitant groups, respectively. The most common (≥2% in either vaccination group) vaccine related systemic AEs were pyrexia (observed in 6.7% of the concomitant group and 6.9% of the nonconcomitant group), headache (observed in 9.6% of the concomitant group and 7.2 % of the nonconcomitant group)), and dizziness (observed in 2% of the concomitant group and 1.6% of the nonconcomitant group).

Deaths and discontinuations: No subjects died during the study period. 2 subjects were discontinued from the study due to AE:

> AN 34232 was an 11 year old male in the concomitant group who experienced severe pyrexia 2 days after his second dose of 9vHPV. The subject also developed moderate headache 2 days after his second dose which resolved spontaneously 3 days later. Pyrexia was attributed to the vaccine, while headache was thought to be unrelated.
>
> AN 34258 was an 11 year old male in the nonconcomitant group who experienced severe pain in the extremity 1 day after receiving the first dose of 9vHPV vaccine. Pain was attributed to the vaccine.

Pregnancy related outcomes: No pregnancies occurred during the study.

New medical history: The proportions of subjects who reported new medical conditions were generally comparable between the concomitant group (28.5%) and the non-concomitant group (27.9%). The most common new medical conditions (>2% in either group) reported following Day 1 were nasopharyngitis (reported by 3.7% and 5.3% in the concomitant and nonconcomitant groups, respectively), upper respiratory tract infection (reported by 2.6% and 2.1% in the concomitant and nonconcomitant groups, respectively), and headache (reported by 2.9% and 2.3% in the concomitant and nonconcomitant groups, respectively). No events considered to be autoimmune conditions by investigators were observed during the study.

2.4 - *Safety data from V503-006*

The design and key results from the V503-006 clinical trial are summarized in the table below.

Table 14. Summary of Clinical trial V503-006

Study Title:	A Phase III Randomized, International, Placebo-Controlled, Double-Blind Clinical Trial to Study the Tolerability and Immunogenicity of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, Given to Females 12-26 Years of Age Who Have Previously Received GARDASIL™			
Study Design:	Randomized, double-blinded, placebo-controlled, international, multi-centered, safety/tolerability and immunogenicity study of the 9vHPV vaccine in females 12 to 26 years of age who received complete GARDASIL vaccination series at least 1 year prior to enrollment. 924 subjects were randomized in a 2:1 ratio to 9vHPV vaccine (618subjects) or saline placebo (306 subjects). Safety was monitored for the duration of the study.			
Study Duration:	25-Feb-2010 to 10-Jun-2011			
Study Status:	Base study complete. Study report submitted. Extension study for vaccination of placebo recipients underway.			
Objectives:	Immunogenicity: o To demonstrate that the 9-valent HPV L1 VLP vaccine is immunogenic with respect to HPV Types 31, 33, 45, 52, and 58 in adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of GARDASIL . Safety: o To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine in adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of GARDASIL .			
Safety related endpoints:	Temperatures (within 5 days following any vaccination); all AEs (Days 1 to 15 following any vaccination; all SAEs that occurred from Day 1 through 30 days following the last vaccination; all SAEs that resulted in death or were determined to be related to the study vaccine that occurred at any time during the study.			
Study Population Demographics:		9vHPV (%)	Placebo (%)	Total (%)
	Age (years)			
	12-15	122 (19.7)	60 (19.6)	182 (19.7)

	16-26	496 (80.3)	296 (80.4)	742 (80.3)
	Race			
	White	78.2%	75.5%	77.3%
	Black	0.5%	1.0%	0.6%
	Asian	6.5%	4.6%	5.8%
	Other	14.9%	19.0	16.2
Study Results:	There were no deaths. 3 SAEs and 1 vaccine-related SAE were reported in each group. Subjects in the 9vHPV group experienced more injection-site AEs than placebo. The frequency of systemic AEs was generally comparable between the 2 groups. Three subjects in the 9vHPV group were discontinued due to non-serious AEs.			
Conclusion:	No clinically significant safety issues were identified.			

2.4.2 – Safety related data in V503-006

Adverse events are summarized in the table below.

Table 15. Adverse Events documented during V503-006 (Adapted from Adverse Event Summary Table, p. 8)

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

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.

Injection site reactions: Occurrence of injection-site reactions was higher in the 9vHPV group (91.1%) than in the placebo group (44.3%). Erythema, pain, swelling, and pruritus all occurred in statistically significant higher proportions of subjects in the 9vHPV group.

Subjects in the 9vHPV group reported more moderate and severe (35.5% and 3.9%, respectively) reactions than subjects in the control group (3.6%and 0.3%). Observation of one or more severe injection-site AEs occurred more frequently in the 9vHPV group (11.2%) than in the control group (1.0%, $p<0.05$).

Systemic adverse reactions: The systemic AEs observed significantly more frequently ($p<0.05$) in the 9vHPV group than in the control group are summarized below.

Table 16. Systemic AEs in V503-006 Observed More Frequently in Investigational Group

Adverse Event	**9vHPV group n (%)**	**Placebo n (%)**	**Difference Estimate (95%CI)**
Abdominal discomfort	8 (1.3)	0 (0)	1.3(0.1, 2.6)
Nausea	52 (8.6)	12 (3.9)	4.6 (1.2, 7.7)
Pyrexia	41 (6.7)	10 (3.3)	3.5 (0.3, 6.2)
Dizziness	30 (4.9)	6 (2.0)	3.0 (0.3, 5.3)

Proportion of subjects reporting moderately severe or severe systemic AEs were roughly equivalent between the groups. Frequency of observation of elevated oral temperatures (>37.8 degrees Celsius) was higher in the 9vHPV group (6.5%) than in the control group (3.0%, $p<0.05$).

Serious adverse events: 6 serious adverse experiences were reported during the study - 3 in the 9vHPV vaccine group (appendicitis, syncope, tonsillitis) and 3 in the placebo group (lumbar vertebral fracture, thoracic vertebral fracture, migraine). Additionally, 1 serious adverse experience of fetal loss (elective abortion) occurred in the placebo group. The AEs of tonsillitis and migraine were thought to be vaccine-related. Clinical data for the subject who experienced tonsillitis is summarized below:

> AN 37801 was an 18 year old female who experienced tonsillitis and earache 1 day following her first dose of 9vHPV. 2 days post-dose, the subject experienced fever and lymphadenopathy. The patient was hospitalized 3 days post-dose and treated with drainage of swollen tonsils, Pamol, Ipren, IV Penicillin and a 10-day course of Metronidazole and Vepicombin. The subject was discharged after two days with a diagnosis of left-sided peritonsillar abscess. The subject recovered completely and completed the remainder of the vaccination series without further AEs, but the investigator attributed tonsillitis to the vaccine.

There was no statistically significant risk difference in observation of SAEs observed between the two groups.

Vaccine-related AE: Vaccine related systemic AEs were reported by 21.0% and 19.3% of subjects in the 9vHPV and placebo groups, respectively. The most common (≥2% in either vaccination group) vaccine related systemic AEs were pyrexia, headache, and dizziness, all of which were reported at similar frequencies in the two groups. .

Deaths and discontinuations: No subjects died during the study period. 3 subjects, all in the 9vHPV group, were discontinued from the study due to non-serious AEs (abdominal pain and diarrhea, tongue swelling, and an injection site reaction).

Pregnancy related outcomes: 4 pregnancies occurred during the study - 2 in each arm. 3 were

ongoing by the time of submission and 1 pregnancy in the placebo group ended in elective abortion.

New medical history: The proportions of subjects who reported new medical conditions were generally comparable between the concomitant group (28.5%) and the non-concomitant group (32.5%). The most common new medical conditions (>2% in either group) reported following Day 1 were nasopharyngitis (reported by 4.9% and 7.5% in the 9vHPV and placebo groups, respectively), and influenza (reported by 3.3% and 2.6% in the 9vHPV and placebo groups, respectively). No events considered to be autoimmune conditions by investigators were observed during the study.

2.5 - *Safety data from V503-007*

The design and key results from the V503-007 clinical trial are summarized in the table below.

Table 17. Summary of Clinical trial V503-007

Study Title:	A Phase III Open-Label Clinical Trial to Study the Immunogenicity and Tolerability of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, Given Concomitantly With Repevax in Preadolescents and Adolescents (11 to 15 Year Olds)			
Study Design:	Open-label, randomized, multicenter, comparative study of 9vHPV vaccine given concomitantly with Repevax (vaccine against diphtheria, tetanus, pertussis and polio) in healthy preadolescents and adolescents. Healthy, preadolescent and adolescent boys and girls were included. Subjects were stratified by gender (1:1 ratio) and randomly assigned to 1 of 2 vaccination groups in a 1:1 ratio. Subjects in vaccination group 1 (262 males, 264 females) received Repevax and first dose of 9vHPV concomitantly on Day 1, and subjects in vaccination group 2 (264 males, 264 females) received the first dose of 9vHPV vaccine on Day 1 and Repevax at Month 1. Safety was monitored for the duration of the study.			
Study Duration:	26-Apr-2010 to 16-Jun-2011			
Study Status:	Study complete. Study report submitted.			
Objectives:	Immunogenicity: o To evaluate whether the 9-valent HPV vaccine and Repevax induce immune responses in preadolescent and adolescent boys and girls 11 to 15 years of age when given concomitantly that are noninferior to responses induced when given separately. Safety: To evaluate the tolerability of the concomitant administration of a first dose of the 9-valent HPV L1VLP vaccine with Repevax in preadolescent and adolescent boys and girls 11 to 15 years of age.			
Safety related endpoints:	Systemic AEs on Days 1 through 15 following any vaccination visit; injection-site AEs on Days 1 through 5 following any vaccination visit for 9vHPV vaccine or Repevax; maximum oral temperature ≥37.8°C (≥100.0°F) on Days 1 through 5 following any vaccination visit; severe injection-site AEs on Days 1 through 5 following any vaccination visit for 9vHPV vaccine and on Days 1 through 5 following any vaccination visit for Repevax; number of subjects reporting serious clinical AEs from Days 1 to 15 following any vaccination visit; vaccine-related clinical SAEs at any time.			
Study Population		Concomitant	Non-concomitant	Total

Demographics:		vaccinations (%)	vaccinations (%)	(%)
	Race			
	White	84.6	85.6	85.1
	Black	0.2	0.4	0.3
	Asian	14.4	13.3	13.9
	Other	0.8	0.8	0.7
Study Results:	There were no deaths and no vaccine-related SAEs. The frequency of AEs was generally comparable between the 2 groups, and there were no discontinuations in either group due to an AE.			
Conclusion:	No clinically significant safety issues were identified.			

2.5.2 – Safety related data in V503-007

Adverse events are summarized in the table below.

Table 18. Adverse Events documented during V503-007 (Adapted from Adverse Event Summary Table, p. 14)

	9vHPV Vaccine + Repevax Concomitant		9vHPV Vaccine + Repevax Non-concomitant		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	525		527		1,052	
with one or more adverse events	513	(97.7)	507	(96.2)	1,020	(97.0)
injection-site	505	(96.2)	496	(94.1)	1,001	(95.2)
non-injection-site	322	(61.3)	314	(59.6)	636	(60.5)
with no adverse event	12	(2.3)	20	(3.8)	32	(3.0)
with vaccine-related† adverse events	509	(97.0)	503	(95.4)	1,012	(96.2)
injection-site	505	(96.2)	496	(94.1)	1,001	(95.2)
non-injection-site	207	(39.4)	196	(37.2)	403	(38.3)
with serious adverse events	9	(1.7)	7	(1.3)	16	(1.5)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.
One (1) subject was randomized but did not receive any vaccination. One (1) subject who had been randomized into the Non- concomitant Vaccination Group was classified into a third vaccination group titled Protocol Non-Compliant Regimen.

Injection site reactions: Occurrence of injection-site reactions was common in both groups and occurred at roughly equivalent proportions in both arms (63.4% and 62.8% at the 9vHPV injection site in the concomitant and non-concomitant groups, respectively; 88.0 and 84.6 at the Repevax injection site in the concomitant and non-concomitant groups, respectively). Injection site swelling was observed at the 9vHPV injection site in 13.0% of subjects in the concomitant vaccination group and 8.2 % of subjects in the nonconcomitant group (RD=4.8 (CI=1.1, 8.6)).

Systemic adverse reactions: Systemic adverse events were reported by 48.6% of subjects in both the concomitant and nonconcomitant group. The systemic AEs most commonly reported in the first 15 days following any vaccination (>3% in any group) are summarized below.

Table 19. Commonly reported systemic AEs in V503-007

Adverse Event	**Concomitant Group n (%)**	**Nonconcomitant group n (%)**
Headache	132 (25.1)	113 (21.4)
Nausea	30 (5.7)	28 (5.3)
Pyrexia	54 (10.3)	50 (9.5)
Abdominal pain upper	13 (2.5)	18 (3.4)
Fatigue	16 (3.0)	19 (3.6)
Nasopharyngitis	9 (1.7)	21 (4.0)
Upper respiratory tract infection	9 (1.7)	18 (3.4)
Oropharyngeal pain	12 (2.3)	20 (3.8)

Risk differences for almost all systemic AEs, as well as elevated oral temperatures, were not statistically significant. The exception was nasopharyngitis, which was reported by more subjects in the nonconcomitant group (RD=-2.3 (-4.5, -0.3)). Proportions of subjects reporting moderately severe or severe systemic AEs were roughly equivalent between the groups.

Serious adverse events: 16 subjects experienced 16 total SAEs over the course of the study – 9 in the concomitant group and 7 in the non-concomitant group. The most common SAEs were appendicitis/appendiceal abscess (4 cases), forearm fracture (2 cases), and pyelonephritis (3 cases). There was no clustering or pattern of SAEs among the vaccination groups. There was no statistically significant risk difference in observation of SAEs observed between the two groups.

No SAEs were attributed to vaccine administration.

Vaccine-related AE: Vaccine related systemic AEs were reported by 29.0% of subjects in both the concomitant and nonconcomitant groups. The most common (≥2% in either vaccination group) vaccine related systemic AEs were pyrexia, headache, nausea , fatigue and abdominal pain upper, all of which were similar in the concomitant and nonconcomitant groups).

Deaths and discontinuations: No subjects died during the study period. No subjects were discontinued from the study due to AE.

Pregnancy related outcomes: No pregnancies occurred during the study.

New medical history: The proportions of subjects who reported new medical conditions were generally comparable between the concomitant group (27.4%) and the non-concomitant group (25.2%). The most common new medical conditions (>2% in either group) reported following Day 1 were nasopharyngitis (reported by 4.8% and 2.8% in the concomitant and

nonconcomitant groups, respectively) and upper respiratory tract infection (reported by 3.6% and 2.5% in the concomitant and nonconcomitant groups, respectively). No events considered to be autoimmune conditions by investigators were observed during the study.

2.6 – *Safety data from V503-009*

The design and key results from the V503-009 clinical trial are summarized in the table below.

Table 20. Summary of Clinical trial V503-009

Study Title:	A Randomized, Double-Blinded, Controlled with GARDASIL® (Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)), Phase III Clinical Trial to Study the Immunogenicity and Tolerability of V503 (9-Valent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescent and Adolescent Girls (9- to 15-year-olds)			
Study Design:	Multicenter immunogenicity and safety/tolerability study with subjects randomized to two groups of 300 girls age 9-15 years to receive 9vHPV vaccine or qHPV vaccine. Immunogenicity of the vaccine was assessed in girls and compared to reference group of young women. Safety was monitored for the duration of the study.			
Study Duration:	23-FEB-2011 to 20-DEC-2011			
Study Status:	Study complete. Study report submitted.			
Objectives:	Immunogenicity: o To demonstrate that administration of the 9vHPV vaccine induces non-inferior Geometric Mean Titres (GMTs) for serum anti-HPV 16 and anti-HPV 18 compared to qHPV vaccine in preadolescent and adolescent girls 9 to 15 years of age. Safety: o To evaluate the tolerability of the 9vHPV vaccine in preadolescent and adolescent girls 9 to 15 years of age.			
Safety related endpoints:	Monitoring of injection site adverse reactions and elevated temperatures Day 1 to Day 5 post-vaccination and systemic adverse events Day 1 to Day 15 post-vaccination, reported on the Vaccination Report Card. In addition, serious adverse events were collected regardless of causality from the time the consent was signed through approximately 4 weeks following the third vaccination.			
Study Population Demographics:		9vHPV (%)	qHPV (%)	Total (%)
	Age (years)			
	9-12	150 (50)	150 (50)	300 (50)
	13-15	150 (50)	150 (50)	300 (50)
	Race			
	White	98.7%	98.0%	98.3%
	Black	0.3%	0.3%	0.3%
	Asian	0%	0.3%	0.2%
	Other	1.0%	1.3	1.2%
Study Results:	Occurrence of AEs was generally comparable among the investigational groups. 3 serious AEs were reported, none were described as vaccine-related. 2 patient withdrawals due to AEs, none attributed to vaccine administration. No deaths occurred during the trial.			
Conclusion:	No clinically significant safety issues were identified.			

2.6.2 – Safety related data in V503-009

Adverse events are summarized in the table below.

Table 21. Adverse Events documented during V503-009 (Adapted from Table 7, p. 8)

	9vHPV Vaccine (N=299) N subj (%)	**qHPV Vaccine (N=300) N subj (%)**
Number (%) of subjects:		
with no adverse event	12 (4.0%)	19 (6.3%)
with one or more adverse event	287 (96.0%)	281 (93.7%)
with one or more vaccine-related adverse event	279 (93.3%)	271 (90.3%)
Injection-site adverse reaction from Days 1 to 5	274 (91.6%)	265 (88.3%)
Solicited injection-site adverse reaction	274 (91.6%)	265 (88.3%)
Injection site erythema	102 (34.1%)	88 (29.3%)
Injection site pain	267 (89.3%)	265 (88.3%)
Injection site swelling	143 (47.8%)	108 (36.0%)
Other injection-site adverse reaction	35 (11.7%)	42 (14.0%)
Systemic adverse event from Days 1 to 15	142 (47.5%)	156 (52.0%)
Vaccine-related systemic adverse event	62 (20.7%)	73 (24.3%)
Serious adverse event at any time	1 (0.3%)	2 (0.7%)
Serious vaccine-related adverse reaction	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)
Withdrawn due to an adverse event at any time	1 (0.3%)	1 (0.3%)
Withdrawn due to a vaccine-related adverse reaction	0 (0%)	0 (0%)
Withdrawn due to a serious adverse event	1 (0.3%)	1 (0.3%)
Withdrawn due to a serious vaccine-related adverse reaction	0 (0%)	0 (0%)

Injection site reactions: Occurrence of injection-site reactions was common in both groups and occurred at roughly equivalent proportions in both arms (91.6% and 88.3% in the 9vHPVand qHPV groups, respectively). No statistically significant differences in overall risk of injection-site AEs, risk of specific AEs related to injection-site reactions, intensity, or overall risk of moderate or severe reactions were observed. The risk difference of injection site swelling between the 9vHPV group (47.8) and qHPV (36.0%) was statistically significant (CI=3.9, 19.6).

Systemic adverse reactions: Systemic adverse events were reported by 47.5% of subjects in the 9vHPV arm and 52.0% of subjects in the qHPV arm. The systemic AEs most commonly reported in the first 15 days following any vaccination (>3% in any group) are summarized below.

Table 22. Commonly reported systemic AEs in V503-009

Adverse Event	9vHPV n (%)	qHPV n (%)
Headache	57 (19.1)	57 (19.0)
Nausea	16 (5.4)	16 (5.3)
Pyrexia	22 (7.4)	17 (5.7)
Abdominal pain upper	11 (3.7)	12 (4.0)
Fatigue	1 (0.3)	10 (3.3)
Nasopharyngitis	5 (1.7)	16 (5.3)
Upper respiratory tract infection	9 (3.0)	11 (3.7)
Oropharyngeal pain	16 (5.4)	17 (5.7)
Cough	9 (3.0)	4 (1.3)

Risk differences for almost all systemic AE were not statistically significant. The exceptions were fatigue and nasopharyngitis, which were reported by more subjects in the control group. Proportions of subjects reporting moderately severe or severe systemic AEs were roughly equivalent between the groups.

Serious adverse events: 3 subjects experienced 4 total SAEs over the course of the study, one of which was in the 9vHPV group and is described below:

> AN 51204 was a 13 year old female from Spain with no significant past medical history. She was hospitalized 5 months after her first dose of 9vHPV following fatigue for four months, with dyspnea for 2 months, tachycardia on slight exertion, appetite decrease with weight loss of 5 kg since the symptoms started, and frequent headache treated with analgesics. The subject was treated with cyclophosphamide and prednisone and discharged after 1 month with the diagnoses of pulmonary capillaritis with positive ANA and multifactorial anemia. The subject was withdrawn from the study due to adverse event, as the drug used to treat pulmonary capillaritis was immunosuppressive. The subject has since fully recovered.

No SAEs were attributed to vaccine administration.

Vaccine-related AE: Vaccine related systemic AEs were reported by 29.0% of subjects in both the concomitant and nonconcomitant groups. The most common (≥2% in either vaccination group) vaccine related systemic AEs were nausea, upper abdominal pain, pyrexia, headache, and oropharyngeal pain. No statistical risk difference in reporting between the investigational group and control group was found for any of these AEs.

Deaths and discontinuations: No subjects died during the study period. Two subjects were discontinued from the study due to AE, including one in the 9vHPV group: AN51204,

discussed above.

Pregnancy related outcomes: No pregnancies occurred during the study.

New medical history: The proportions of subjects who reported new medical conditions were equivalent between the concomitant group (18.7%) and the non-concomitant group (18.7%). The most common new medical condition (>2% in either group) reported following Day 1 was nasopharyngitis (reported by 2.0% and 2.7% in the 9vHPV and qHPV groups, respectively). No events considered to be autoimmune conditions by investigators were observed during the study.

3.0 - REVIEW OF GARDASIL SAFETY INFORMATION

Given that Gardasil is the precursor to Gardasil 9 and served as the primary control vaccine in the clinical trials, review of Gardasil safety information is relevant. At the time of the original licensure of Gardasil, the following safety issues had been identified and included in the label in section 6.1 "Adverse Reactions":

1) Injection-site reactions (pain, swelling, pruritus, erythema, bruising
2) Nausea/vomiting
3) Dizziness
4) Syncope (may be accompanied with tonic-clonic movement or seizure-like activity; also included in Section 5.1 "Warnings and Precautions")
5) Hypersensitivity/Anaphylaxis

Since licensure, Gardasil safety has been reviewed in monthly internal surveillance reports (literature and VAERS reports) as well as the sponsor's annual reports of postmarket surveillance from countries worldwide where it is marketed. Adverse events that have been identified for Gardasil in the postmarketing period and are stated in section 6.2 of the Gardasil label include:

1) Blood and lymphatic system disorders: Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy.
2) Respiratory, thoracic and mediastinal disorders: Pulmonary embolus.
3) Gastrointestinal disorders: Nausea, pancreatitis, vomiting.
4) General disorders and administration site conditions: Asthenia, chills, death, fatigue, malaise.
5) Immune system disorders: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.
6) Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.
7) Nervous system disorders: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope (including syncope associated with tonic-clonic movements and other seizure-like activity) sometimes resulting in falling with injury, transverse myelitis.
8) Infections and infestations: cellulitis.

9) Vascular disorders: Deep venous thrombosis

Given that the components of Gardasil 4 are included in Gardasil 9, the above adverse events will also be included on the label for Gardasil 9. Per guidance for industry published by CBER in January 2006, "decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports or (3) strength of causal relationship to the [product]." Thus, inclusion of an adverse event in this section of the label does not necessarily suggest a causal association with the vaccine. Population-based studies evaluating several of these AEs, including Guillain-Barre syndrome, seizures, syncope, stroke, and venous thromboembolism did not confirm a statistically significant association between the AE and the vaccine [5,6].

Review of the sponsor's most recent Report of Postmarket Surveillance for June 1, 2012 to May 31, 2013 revealed no additional safety signals or concerns.

4.0 - PHARMACOVIGILANCE PLAN

The PVP submitted by the sponsor is summarized in the table below.

Table 23. Pharmacovigilance plan for Gardasil 9

Safety Concern	Planned Action(s)
Important identified risks	
Exposure during pregnancy – Although the product is not indicated for use in pregnant girls and women, the 9vHPV vaccine is indicated for women of child-bearing potential who are at risk for exposure during pregnancy. The sponsor attests that data derived from clinical trials does not reflect a safety risk associated with the product, as rates of spontaneous abortion, late fetal death, and congenital anomalies were comparable to both controls and rates in the general population.	▪ Routine Pharmacovigilance ▪ Pregnancy Registry (US)
Hypersensitivity (Type I) – the sponsor proposes this as a potential safety concern, given that a vaccine component may act as an allergen, causing the immune system to mount an allergic response. The sponsor attests that data derived from the clinical development program does not reflect a safety risk associated with the product. Urticaria was documented at a rate of 0.3% and no cases were documented as "serious." One case of anaphylaxis was documented, which the sponsor indicates is consistent with reporting rates in the literature of 0.2 – 10 cases per million doses of a vaccine.	▪ Routine Pharmacovigilance

Syncope with fall resulting in injury – The sponsor proposes this as a potential safety concern due to possible vasovagal reactions associated with sympathetic activation following injection. The sponsor reports that no falls resulted from 34 reported cases of syncope and thus does not identify "syncope with fall" as a safety risk associated with the product.	▪ Routine Pharmacovigilance
Important potential risks	
Viral type replacement Guillain-Barre Syndrome Product confusion Mixed regimen*	▪ V503-021 Nordic Long-Term Follow-Up Study (10-year extension in subjects from V503-001) ▪ Routine Pharmacovigilance ▪ Routine Pharmacovigilance ▪ Routine Pharmacovigilance
Important missing information	
Long-term effectiveness/ immunogenicity	▪ V503-021 Nordic Long-Term Follow-Up (10-year extension in subjects from V503-001) ▪ V503-002-20 Postdose 3 Follow-Up Study (10-Year Postdose 3 Extension)
Unanticipated safety signals	▪ Routine Pharmacovigilance ▪ Post Authorization Safety Study (PASS) ▪ V503-021 Nordic Long-Term Follow-Up Study (10-year extension in subjects from V503-001) ▪ V503-002-20 Postdose 3 Follow-Up Study (10-Year Postdose 3 Extension)

*Mixed Regimen refers to patients receiving 1 or more doses of HPV4 or other HPV vaccines instead of 3 doses of HPV9 during the 3 dose sequence.

Routine pharmacovigilance is described by the sponsor as standard practices of collection of reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); preparation of reports for regulatory authorities (e.g., individual case safety reports, PSURs, etc.), and maintenance of continuous monitoring of the safety profile of the approved product (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities).

In addition to routine pharmacovigilance, the sponsor plans two post-marketing studies: V503-021 (a 10 year extension to V503-001) and V503-002-20 (a 10 year extension to V503-002):

> **V503-002-20**: study extension to clinical trial V503-002. Study will evaluate longer-term immunogenicity, efficacy, and safety (including previously unanticipated safety signals) of 9vHPV vaccine in subjects who were originally enrolled in Protocol V503-002. The proposed study will extend the study up to Month 126 for preadolescent and adolescent girls and boys between the ages of 9 to 15 years at randomization. All subjects who were enrolled in Protocol V503-002, received 3 doses of the 9-valent HPV L1 VLP vaccine, and consent/assent to participate in Protocol V503-002-20 will be eligible (up to 2552 subjects).

All subjects will be followed up for 10 years post-dose 3. Interim analyses will be conducted at Month 72 and Month 96 to assess the feasibility of continuing through 10 years of follow-up. This study is underway.

V503-021: extension of the Protocol V503-001 base study to take place in the Nordic Region countries of Denmark, Norway and Sweden (due to ready availability of comprehensive clinical data in national health registries). Up to 4453 subjects enrolled and vaccinated from these countries during the original clinical trial will be eligible for this long term follow up (LTFU). Registry-based follow-up for effectiveness and safety data/new medical history will occur at regular intervals during the follow-up period. All safety monitoring will be done via accessing the national health registries for new medical history. Active follow-up for blood collection only will be conducted at Years 5 and 10 of the LTFU study. Effectiveness and safety analyses will occur approximately 2 years following completion of the Protocol V503-001 base study and approximately every 2 years thereafter for 12 years, for a total of 6 analyses. Incidence of viral type replacement will be assessed in enrolled subjects. This study is underway.

Gardasil 9 Pregnancy Registry: This newly established pregnancy registry will assess risks relevant to pregnancy, including pregnancy outcomes of live births, congenital anomalies, spontaneous abortions, and late fetal deaths. The registry is described as an enhanced surveillance program for women exposed to 9vHPV vaccine within 1 month prior to becoming pregnant or anytime during pregnancy. Patient accrual for the pregnancy registry for Gardasil 9 is done on the basis of spontaneous reports received by the sponsor, and eligibility criteria include 1) exposure during pregnancy (receipt of Gardasil 9 at any time from one month prior to last menstrual period (LMP) through to pregnancy outcome, and 2) residency in the US. Both prospective and retrospectively received reports will be included in the registry, with findings from the retrospective reports serving as outcomes of particular interest for evaluation in the prospective reports. Rates of anomalies and other pregnancy outcomes will be compared to baselines established by the Centers for Disease Control Metropolitan Atlanta Congenital Defects Program. Reporting milestones include annual reports for initial 4 years at:

- End date Year 1 + 8 months
- End date Year 2 + 8 months
- End date Year 3 + 8 months
- End date Year 4 + 8 months, and

The final report will be submitted at completion of Final data + 9 months (collection of patient outcome data for all patients enrolled in the registry during initial 5 years of licensure). The registry will open immediately after licensure and close after 5 years.

Post-Authorization Safety Study (PASS): The sponsor included a concept note briefly describing a PASS that will be conducted within a large health care database. This descriptive observational study will not test formal hypotheses/specific safety outcomes but will instead describe the

incidences of medical events occurring in a pre-specified risk period after vaccination and compare them to the incidences of these medical events in a comparison group. The study sample size will be "determined in discussions with HealthAuthorities" and the study duration will depend on vaccine uptake. An independent Safety Review Committee, external to both Merck and the team conducting the study, will review and interpret the study data.

5.0 – **INTEGRATED RISK ASSESSMENT**

Two observations noted in the clinical safety database of potential relevance to safety include an increased risk of injection site reactions and an increased risk of spontaneous abortion in vaccinees who received HPV9 within 30 days before or after conception. In both cases, the increased risk was in comparison to vaccination with qHPV. Additionally, qHPV served as the major comparator (control) during the clinical development of 9vHPV. Use of this comparator allows the clinical safety database to provide evidence regarding rates of AEs after HPV9 vaccination relative to rates observed after qHPV vaccination; it does not provide substantial information on the increase in risk of AEs after HPV9 in comparison to a non-vaccinated population. (Note that there was one study where qHPVwas not the control vaccination: in study V503-006, in which all subjects had previously received qHPVvaccine, the investigational group received additional vaccination with 9vHPV, and the control group received saline. This study was relatively small in size, and the history of qHPV vaccination in all subjects prevents this assessment even in this study.) Thus, the findings of the clinical safety database do not preclude the increased risks associated with the quadrivalent formulation of HPV (above that of a non-vaccinated population) from also being associated with the nanovalent formulation.

5.1 Injection-site Reactions

Injection-site reactions represented the most commonly reported AE in clinical trial subjects; most trial subjects reported local reactions including swelling, pain, and erythema. Local inflammatory reactions attributable to introduction of antigen and/or adjuvant are commonly reported with many vaccines [7]. The clinical trial data suggests that injection-site reactions occurred more commonly and more severely in subjects receiving 9vHPV vaccine than in those receiving qHPV vaccine. The sponsor asserts that the reason for this is the increased antigenic load in the nanovalent formulation, which is a plausible explanation. Given that these reactions were generally non-serious and time-limited, injection-site reactions following vaccination with 9vHPV likely do not represent a significant safety issue.

5.2 Spontaneous Abortion

9vHPV vaccination will not be indicated for use in pregnant women. However, given that females of childbearing age are among the target demographic for the product, there is the potential that female subjects may be pregnant at the time of HPV9 vaccination. Because of this demographic, pregnancy outcomes, including spontaneous abortion, congenital anomalies, ectopic pregnancies, and late fetal death following HPV9 vaccination should be monitored and quantified to the extent possible.. There exists the theoretical risk that a potential association between HPV9 vaccination

and adverse pregnancy outcomes may be related to adjuvant immunostimulation and/or reduced tolerance by the semiallogeneic fetus; however, this supposition is expert conjecture [8] and has not yet been supported by published literature. .

During clinical trials, 1,178 pregnancies and 1,108 pregnancies occurred in the 9vHPV vaccinated subjects and qHPV vaccinated subjects, respectively. Clinical trial data assessed over the entire follow-up period did not reveal an increased risk of adverse pregnancy outcomes in subjects receiving 9vHPV when compared to subjects receiving qHPV. Spontaneous abortions (SA) were documented less frequently in the HPV9 group over the entire study period of follow-up (HPV9 group: 122 [10.4%] SA; HPV4 group: 143 [12.9%] SA).

However, in women who became pregnant within 30 days of receiving HPV9 vaccination, 92 pregnancies were recorded, 89 pregnancies had known pregnancy outcomes, and 17 (19.1%) pregnancies resulted in spontaneous abortion. In comparison, 89 pregnancies occurred during the same timeframe in qHPV recipients; of the 88 pregnancies with known outcomes, 7 (8%) ended in spontaneous abortion (p=0.04). Further statistical analyses by OBE's Division of Biostatistics included assessment of multiple potential confounders, such as age, race, regions, smoking status, previous history of spontaneous abortions, concomitant medications, and history of chlamydia, after which the imbalance between the two groups persisted.

The sponsor confirmed this numerical imbalance in their response to an Information Request (IR) provided May 12, 2014, suggesting that elective abortions in Latin America were misclassified as spontaneous abortions due to social stigmas and the illegality of elective abortions, thus reducing the reliability of this data. Thirty-three % of all pregnant women in the clinical trials were from Latin/South America. Of the total 24 SAs in the clinical trial program that occurred in subjects who received HPV9 within 30 days of conception, 18 (75%) occurred in Latin/South American women. Of these 18 SAs, 12 (66%) occurred in the 9vHPV group compared to 6 (33%) in the qHPV group. This difference was not statistically significant. However, there was a trend towards more frequent SA in subjects receiving 9vHPV vaccination. Further examination of data restricted to the Non-Latin American sites alone reduced the total number of pregnancies to 618 in 9vHPV group and 601 in qHPV group. In these non-Latin American sites, the number of SA events was reduced from a total of 24 (17 in the 9vHPV group and 7 in the qHPV group) to six (five in the 9vHPV group and one in the qHPV group). Thus, despite the reduction in the total number of events, the numerical imbalance persisted.

The sponsor also suggested that the observed imbalance may be attributable to the unexpectedly low rates of spontaneous abortion in the qHPV group due to chance. Finally, the sponsor asserted that imprecision in the assessment of the date of the last menstrual period (LMP) which formed the basis for conception date estimates may have yielded inexact 30 day time windows, potentially calling into question the reliability of this data given the already low number of SA in the qHPV group.

In an additional IR response dated June 13 2014, the sponsor provided results of sensitivity analyses that explored the occurrence of SA relative to proximity to the estimated date of

conception (EDCn) and vaccination date, using data from V503-001. Pertinent information from these analyses follows:

Table 24a. Spontaneous abortions of pregnancies with EDCn within 30 and 60 days of any vaccination, all regions

	9vHPV Vaccine	qHPV Vaccine
Number of spontaneous abortions	121	143
EDCn within 30 days before or after any vaccination	17	7
EDCn within 30 days after any vaccination	13	5
EDCn within 60 days before or after any vaccination	24	16
EDCn within 60 days after any vaccination	20	11

Table 24b. Spontaneous abortions of pregnancies with EDCn within 30 and 60 days of any vaccination, Non Latin America only

	9vHPV Vaccine	qHPV Vaccine
Number of spontaneous abortions	58	71
EDCn within 30 days before or after any vaccination	5	1
EDCn within 30 days after any vaccination	4	0
EDCn within 60 days before or after any vaccination	9	3
EDCn within 60 days after any vaccination	9	1

The numerical imbalance from these analyses demonstrates increased rates of SA in subjects receiving 9vHPV persisting through 60 days; this association also occurs in the data analyses restricted to only Non-Latin-American sites.

The sponsor notes the unexpectedly low rates of SA in the qHPV group, and provided data that asserts that low rates of SA were also seen with qHPV in the Gardasil clinical program. During the Gardasil program (June 2002 through May 2003), in pregnancies from all study sites with EDCn within 30 days of a vaccination visit, SA rates were lower in the qHPV vaccine group than in the placebo group (qHPV vaccine: 20.9%; placebo: 28.3%. In pregnancies from Non-Latin American sites, with EDCn within 30 days of a vaccination visit, SAB rates were also lower in the qHPV vaccine group than in the placebo group (qHPV vaccine: 11.1%; placebo: 21.2%). The sponsor attributes this phenomenon to the effect of random chance on data involving small numbers of observations. Additionally, the sponsor asserted that the observed rates of spontaneous abortion in all groups during both Gardasil and Gardasil 9 clinical development were within background rates documented in the general population, which can be as high as "approximately 33%" [9,10].

The SA rates in the two arms for the entire pregnancy period are similar. However, there is an imbalance between the SA rates in 9vHPV recipients who received vaccination 30 days prior to or following conception, a time period when there is a biologically plausible risk of adverse pregnancy outcomes. This imbalance appears to persist through 60 days around conception and is not adequately explained by known possible confounders. Although it is possible that the imbalance reflects statistical "noise," it could indicate the potential for a serious risk and should be further evaluated in the post-market setting should the product be licensed.

The sponsor asserted that a planned pregnancy registry will provide the data necessary to assess the risk, and on September 15, 2014, submitted a document that included the protocol for the proposed registry. They also provided reasoning as to why a pregnancy registry would be more suited than an observational study to respond to concerns regarding spontaneous abortions. Limitations of observational studies presented in the document are summarized below in italics, with DE reviewer comments immediately following:

1) *"Incomplete information on true number of pregnancies (and thus inability to obtain a reliable denominator for rate estimates): Identification of pregnancies in healthcare databases is challenging, particularly during the first trimester, as many women do not seek health care early in pregnancy when miscarriage rates are highest, and elective abortions may be provided outside their usual health care system."*

   While achieving a reliable estimate of the total number of women who became pregnant (the cohort "denominator") is a frequent challenge involved in obtaining accurate risk assessments , use of a healthcare database allows for comprehensive enrollment of a cohort of both exposed and non-exposed subjects simultaneously, in real-time. This provides for a comparator group that is not subject to time-variable confounders such as the effects of media, high-profile public health events, or other variables that might alter the uptake of the vaccine. Use of the subjects of the qHPV registry as a comparator as proposed by the sponsor (Mid cycle meeting - May 22, 2014) is an inferior strategy, as these subjects were enrolled during a different time period and were thus subject to different influences that could affect not only the outcome of interest but also the probability of inclusion in the registry.

   The document submitted by the sponsor does not provide convincing reasoning as to how a registry would more easily obtain subjects undergoing early spontaneous abortion than an observational study; in fact, it seems possible that a registry would be less likely to include these outcomes, as a woman may experience a spontaneous abortion prior to reporting to the registry. An observational study conducted within a managed care consortium could be designed to include a cohort of patients that had been established in the network for a prespecified period of time prior to enrollment. This criterion would increase the likelihood that the database would include a comprehensive cataloguing of health events, including early spontaneous abortions that may not have prompted an immediate medical visit, but were nevertheless discovered and documented at a subsequent visit within the network database.

2) *"Incomplete data on pregnancies resulting in spontaneous abortions in healthcare databases and extensive misclassification of spontaneous abortions (a large proportion of them are actually elective abortions)"*

   While misclassification is a concern when attempting to discern the outcome of interest, this issue should be resolvable with the use of teratology experts during confirmatory chart review. A less easily resolvable problem would be underreporting, which the

sponsor concedes is an issue with pregnancy registries and spontaneous abortion. Those reporting pregnancy exposures to the registry could differ in many respects from the population that does not voluntarily report and enroll in the registry. A database-focused observational study is presumably more likely than a registry to include pregnancy losses of all kinds, including spontaneous abortions that occur early in pregnancy, and without effects of selective reporting that limit interpretation of registry data.

3) *"Inability to assess the timing of conception with respect to vaccination because of the lack of pregnancy dating information in healthcare databases."*

   Information concerning timing of conception with respect to vaccination will be critical to this risk assessment. However, the sponsor has not indicated why chart review would be insufficient to obtain pregnancy timing data during an observational study. Additionally, the qHPV registry provided conception vs. vaccination timing data for 1,444 pregnancies; of these, 91 (6.3%) had a documented outcome of spontaneous abortion. This low rate is lower than the reported background rates for spontaneous abortions (estimated background rate published in the US National Vital Statistics Report, 2008 is 11.5%), again raising concerns about underreporting within a pregnancy registry.

In summary, registries have several known limitations, including limited knowledge of precise gestational age at time of exposure, selective reporting, underreporting, reporter bias, and inability to calculate reporting rates in vaccinated and unvaccinated individuals. Additionally, the degree to which registry participants actually represent the overall pregnant population is unclear. Despite these limitations, registries remain useful for collection of prospective data particularly regarding congenital anomalies; incidence rates among registered subjects can be compared to historical baselines, as well as to other registries. However, a registry may be insufficient to assess the risk of early spontaneous abortion largely because of the concerns of under-reporting and the lack of a reliable comparator/background rate of this outcome in a similar un-vaccinated population. .

5.2.1 Potential Methods to Assess Risk of Spontaneous Abortions of Pregnancies with EDCn within 30 days of vaccination

A targeted observational study utilizing a computerized database of linked longitudinal medical records from primary care databases would be a strategy preferable to the currently proposed pregnancy registry to evaluate the safety concern of spontaneous abortion. This study design allows inclusion of a cohort of subjects with existing medical records for at least one year prior to LMP, which would enable optimal evaluation of vaccine exposure risks prior to and immediately following conception. Most importantly, this study would provide an unexposed comparator group of enrollees from the same data source which is more likely to be representative of the treated population. This method would provide more complete data from a cohort of individuals allowing

better characterization and quantification of the risk of early SA in HPV9 recipients compared to controls.

Such a study could possibly be conducted in the US using medical record or billing codes to detect the AE in association with vaccination in large healthcare databases. Consultations with the Centers for Disease Control and Prevention (CDC), Vaccine Safety Datalink (VSD) on the capability of HHS partner data sources to evaluate the observed imbalance with spontaneous abortion after 9vHPV vaccination in early pregnancy are in progress.

5.3 General safety concerns of Gardasil

Use of qHPV vaccine as the primary comparator during 9vHPV vaccine development, while appropriate given the similarity of the vaccines, may preclude detection of safety risks that are inherently associated with qHPV. Thus occurrences of AEs labeled in Gardasil information should also be included in the 9vHPV label. These include syncope with fall, hypersensitivity, venous thromboembolism, and autoimmune diseases, all of which were generally comparable between the 9vHPV and qHPV groups, suggesting that these AEs may be observable following vaccination with 9vHPV.

6. RECOMMENDATIONS

A. Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80.

B. Distribution reports should be provided to CBER in accordance with 21 CFR 600.81.

C. No REMS is warranted at this time.

D. An observational postmarketing safety study, possibly conducted in a HHS-associated Federal Partners database using large linked healthcare data and a control cohort, is highly recommended to assess the risk of spontaneous abortion following vaccination, with particular attention to pregnancies that occur within 30 days prior to or following vaccination with 9vHPV.

E. OBE/DE supports the establishment of a post-marketing commitment for the pregnancy registry described by the sponsor.

F. The sponsor should provide a protocol for the proposed PASS study for further evaluation by FDA/CBER.

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