Reference 1464

MRL Report: A safety and immunogenicity study of quadrivalent HPV (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine in preadolescents and adolescents: month 12 safety report (Protocol 018), 15-Sep-2005.

Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine
Protocol 018

A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents

Month 12 Safety Report

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Table Of Contents

List of Tables

List of Abbreviations

AN	Allocation Number
CSR	Clinical Study Report
HPV	Human Papillomavirus
MRL	Merck Research Laboratories
VLP	Virus-Like Particles
VR	Vaccine Related
VRC	Vaccination Report Card

1. Executive Summary

Protocol 018 was a randomized, double-blind (operating under third party and in-house blinding procedures), placebo-controlled, multicenter study to evaluate the safety and immunogenicity of the quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus- Like Particle (VLP) vaccine in preadolescent and adolescent male and female subjects. Merck personnel were unblinded to vaccination allocation at the time of the finalization of the Day 1 to Month 7 data set. Thus, between the date of this unblinding and the date of finalization of the Day 1 to Month 12 data set that this report summarizes, Merck personnel were not blinded to individual vaccination allocation. However, because the study is ongoing, study subjects, study site personnel (with the exception of personnel who administered the vaccine or placebo, but who were not involved in the care of study subjects or data management activity) and laboratory personnel at Merck Research Laboratories (MRL) have remained blinded to vaccination allocation. They will remain blinded through the finalization of all data related to the period up to and including the Month 18 visit in all subjects.

The primary objective of Protocol 018 is to evaluate the safety of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine among 9- to 15-year-old boys and girls. In addition to the standard adverse experience collection tools and standard operating procedures for safety reporting used in all studies, adverse experience collection has been enhanced through active surveillance for common systemic clinical adverse experiences. The study is also unique in that the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is being compared to a non-aluminum-containing placebo (all other studies in the program compared vaccine to aluminum-containing placebo). As part of long-term follow-up for safety, subjects are also evaluated for new medical conditions at 6 and 12 months Postdose 3.

The main findings of the study (covering the period between Day 1 and Month 7 of the study, inclusive) were summarized in the Protocol 018 Clinical Study Report (CSR) [7.2]. This report summarizes data collected during the Month 12 safety assessment. In addition, this report updates safety and medical history data summarized in the main Protocol 018 CSR [7.2]. The signature page of the Principal Authors of this report can be found in [7.3].

There were no deaths, vaccine-related serious clinical adverse experiences, or procedure-related serious adverse experiences reported during the period between the Month 7 visit and the Month 12 safety assessment. One subject became pregnant during this period. Her pregnancy s 47F as of the finalization of this report. Approximately 30% of subjects reported a new medical condition following Month 7. The proportions of subjects reporting such conditions were comparable between the two vaccination groups. In both groups, the most common new condition was an upper respiratory infection (e.g., influenza, pharyngitis, etc.).

Based on the findings of Protocol 018, it is concluded that administration of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9- to 15-year-old boys and girls is generally well-tolerated.

2. Background

The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine clinical program includes efficacy studies in older adolescents and young women 16 to 26 years of age. Since these studies include follow-up visits for up to 3.5 years Postdose 3, they will also be used to evaluate the long-term tolerability of the vaccine.

Protocol 018 [7.1] is one of two Phase III studies of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in a young adolescent population. Protocol 018 was designed with a one year Postdose 3 extension to obtain information regarding the longer-term safety of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in younger adolescents. The data collected in this extension were meant to supplement the long-term safety data collected in older adolescents and adults.

A full description of the study is presented in the main Protocol 018 CSR [7.2]. Briefly, Protocol 018 was designed to enroll ~1650 subjects. Enrollment was stratified by gender (1:1, male:female) and age at enrollment (2:1, 9- to 12-year-old subjects and 13- to 15-year-old subjects). Enrolled subjects were randomized to receive either quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine or non-aluminum-containing placebo in a 2:1 ratio. Randomization was stratified by study site only; not by age or gender. For each subject the planned duration of the study is approximately 1.5 years.

Subjects were vaccinated at Day 1, Month 2 and Month 6. All subjects were observed for at least 30 minutes after each vaccination for any immediate reaction, with particular attention to any evidence of allergic phenomena. Each study participant's parent/legal guardian was given a vaccination report card (VRC) on which to record the subject's oral temperature beginning 4 hours after each injection and at approximately the same time daily for the next 4 days (Days 1 to 5). Any systemic or injection-site adverse experiences were recorded on the VRC starting on the day of vaccination and for 14 days thereafter, for a total of 15 days.

Protocol 018 was divided into 2 segments. The period from enrollment through Month 7 (4 weeks Postdose 3), inclusive, was called the Vaccination Phase. The period starting after the Month 7 visit and continuing until the end of the study was called the Persistence Phase. For the purposes of the tables in this report, the Persistence Phase will be referred to as the "Follow-Up Period".

Data summarizing adverse experiences and interim medical history for the study's Vaccination Period are presented in the main Protocol 018 CSR [7.2].

The study protocol included a safety assessment at Month 12. This visit was conducted in the form of a phone call to the subject's parent/legal guardian to assess for any new or worsening medical conditions, hospitalizations, and receipt of any non-study vaccinations as well as serious adverse experiences that may have occurred. The site also had the opportunity to update information regarding adverse experience or interim medical history occurring during the Day 1 to Month 7 visit. The findings at the Month 12 visit are summarized in this report. Data collected after the Month 12 visit through Month 18 will be summarized in a separate report.

3. Methods

The primary analysis of Protocol 018 was conducted using data collected during the Vaccination Phase. The final screened and audited database for the Vaccination Phase was unblinded to personnel at MRL on 31-Jan-2005. The CSR summarizing the primary results of the study was written and finalized on 19-Aug-2005 [7.2].

Clinical, biostatistics, and data management personnel at Merck were unblinded to individual vaccination assignment following achievement of clean file and unblinding of the database for the Vaccination Phase. However, study personnel, study subjects, and laboratory personnel at MRL remain blinded to individual vaccination assignment and will remain so until the Month 18 visits are complete, and all data in the study are finalized.

The current report includes two types of summaries:

1. Updates on Safety and Interim Medical History Data Presented in the Protocol 018 CSR

Since subjects continued to be followed by study sites, there was an opportunity for site personnel to obtain more information that had not been previously provided by the subject regarding medical events that occurred during the Vaccination Phase of the study (i.e., results presented in the Protocol 018 CSR). Thus, this report contains updates to the data presented for the Vaccination Phase following the closing of the Day 1 to Month 7 analysis database that was used to generate the Protocol 018 CSR [7.2].

2. Interim Medical History Covering the Period Between Month 7 and Month 12

Study site personnel were instructed to call the subject's parent/legal guardian 12 months after the Day 1 visit (± 3 weeks) to assess for any new medical conditions, hospitalizations or non-study vaccines that the subject may have received since the last study visit. The parent/legal guardian was also to be asked whether the subject had any serious adverse experiences since the last study visit. Up to 5 attempts could have been made to contact the subject's parent/legal guardian. If the telephone contact was unsuccessful after 5 attempts but the contact was established at a later time, this information was to be included in the Month 18 medical history.

Data collected during the Month 12 follow-up phone call were recorded on a telephone contact log and later transcribed onto worksheets [7.4; 7.8.1.9]. The data were summarized as new medical history since the Month 7 visit.

In addition, sites were instructed to collect and report the following events occurring after the Month 7 visit:

- any serious adverse experience that was judged by the study investigator to be possibly, probably, or definitely vaccine-related;
- any serious adverse experience that was judged by the study investigator to be possibly, probably, or definitely related to a procedure specified in the protocol; and
- any pregnancy that occurred in the interval between the Month 7 visit and the Month 12 visit.

4. Results

4.1 Subject Disposition

A total of 1775 subjects received at least one dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine or non-aluminum-containing placebo.

The study was divided into two phases: a Vaccination Phase (Day 1 through Month 7) and a Persistence Phase (all visits between Month 7 and Month 18, inclusive of Month 18). For the purposes of the tables in this report the Persistence Phase is also referred to as the "Follow-Up Period". Data collected after Month 12 and through Month 18 will be summarized in a separate report.

A summary of the number of subjects who were randomized, vaccinated, and who are continuing or discontinued from the study, by vaccination group, is provided in Table 4-1.

Overall, 95.0% of subjects randomized in the study (95.3% of subjects in the quadrivalent HPV [Types 6, 11, 16, 18] L1 VLP vaccine group and 94.4% of subjects in the placebo group) entered the Persistence Phase of Protocol 018. Of the subjects who entered the Persistence Phase, 99.7% are continuing in the study. Five (5) subjects discontinued from the study: 3 subjects in the vaccination group and 2 subjects in the placebo group. Of the 3 subjects in the vaccination group who discontinued, 1 subject withdrew consent and 2 subjects were lost to follow-up. In the placebo group, both subjects discontinued from the study due to relocation.

Compared with the Table 6-1 [7.7] in the Protocol 018 CSR there were two changes in subject disposition during the Vaccination Phase. In particular, the disposition of one subject s 47F in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group during the Vaccination Phase was changed from "Continuing" to "Discontinued without

long-term follow-up due to being lost-to-follow-up". Another subject s 47F in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group was considered "Discontinued without long-term follow-up due to moving" during the Vaccination Phase. However, the subject returned and was re-admitted to the study. The subject skipped the Month 7 visit and entered the long-term follow-up period; thus, for the purposes of classification, this subject is considered as "Continuing" because s 47F met neither the criteria for "Completed" nor "Discontinued".

Table 4-1

Subject Disposition by Vaccination Group

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine		Non-Alum Placebo		Total	
	n	(%)	n	(%)	n	(%)
SCREENING FAILURES					20	
RANDOMIZED	1184		597		1781	
VACCINATED AT:						
Dose 1	1179	(99.6)	596	(99.8)	1775	(99.7)
Dose 2	1149	(97.0)	573	(96.0)	1722	(96.7)
Dose 3	1123	(94.8)	562	(94.1)	1685	(94.6)
VACCINATION PERIOD (Day 1 Through Month 7)						
ENTERED	1179		596		1775	
COMPLETED[†]	1120	(95.0)	560	(94.0)	1680	(94.6)
CONTINUING[‡]	1	(0.1)	0	(0.0)	1	(0.1)
DISCONTINUED	58	(4.9)	36	(6.0)	94	(5.3)
WITH LONG-TERM FOLLOW-UP[§]	7	(0.6)	4	(0.7)	11	(0.6)
Clinical Adverse Experience	2	(0.2)	0	(0.0)	2	(0.1)
Other reasons	5	(0.4)	4	(0.7)	9	(0.5)
WITHOUT LONG-TERM FOLLOW-UP[‖]	51	(4.3)	32	(5.4)	83	(4.7)
Clinical Adverse Experience	1	(0.1)	0	(0.0)	1	(0.1)
Lost to follow-up	18	(1.5)	7	(1.2)	25	(1.4)
Moved	3	(0.3)	1	(0.2)	4	(0.2)
Other reasons	1	(0.1)	2	(0.3)	3	(0.2)
Parent withdrew consent	9	(0.8)	8	(1.3)	17	(1.0)
Withdrew consent	19	(1.6)	14	(2.3)	33	(1.9)

Table 4-1 (Cont.)

Subject Disposition by Vaccination Group

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine		Non-Alum Placebo		Total	
	n	(%)	n	(%)	n	(%)
FOLLOW-UP PERIOD (After Month 7)						
ENTERED	1128		564		1692	
CONTINUING	1125	(99.7)	562	(99.6)	1687	(99.7)
DISCONTINUED	3	(0.3)	2	(0.4)	5	(0.3)
Lost to follow-up	2	(0.2)	0	(0.0)	2	(0.1)
Moved	0	(0.0)	2	(0.4)	2	(0.1)
Withdrew consent	1	(0.1)	0	(0.0)	1	(0.1)

[1] Subjects completed 3 doses of vaccinations and entered the long-term follow-up period.
[2] Subject [redacted] was considered as "Continuing" since [redacted] skipped the Month 7 visit but continued into the long-term follow-up period. [redacted] met neither the criteria for "Completed" nor "Discontinued".
[3] Subjects received fewer than 3 doses of vaccinations and entered the long-term follow-up period.
[4] Subjects discontinued on or before Month 7 and did not enter the long-term follow-up period.
Status percentages are calculated based on the number of subjects who entered the respective time period.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.4]

4.2 Concomitant Vaccinations and Concomitant Medications

Table 4-2 in this report summarizes the number and percentage of subjects (incidence >0% in one or more vaccination groups) who received specific concomitant vaccination from Day 1 through Month 12 of the study. During the 12 month study period, 16.1% of subjects received one or more concomitant vaccinations. The most common categories of concomitant vaccines administered to study subjects were influenza vaccine, measles/mumps/rubella vaccine, and tetanus toxoid vaccine.

Study sites were asked to minimize non-study vaccination during the Vaccination Phase of the study. In addition, administration of non-study vaccine during the 15 day post-vaccination period was considered to be a protocol violation. Thus, sites often delayed non-study vaccination until after the completion of the Month 7 study visit. Thus, in comparing Table 4-2 with Table 11-8 [7.7] in the main Protocol 018 CSR, it appears that approximately 10% of study subjects were given at least one non-study vaccine between the Month 7 and Month 12 visits.

Table 4-3 in this report summarizes the number and percentage of subjects (incidence >0% in one or more vaccination groups) who received specific aluminum-containing concomitant vaccinations during the period between Day 1 and Month 12. Table 11-9 [7.7] in the Protocol 018 CSR summarizes concomitant vaccinations containing aluminum adjuvant administered at any time during the Vaccination Phase of the study (Day 1 to Month 7). The proportion of subjects who received aluminum-containing vaccines increased from 2.6% during the Vaccination Phase to 5.5% over the Day 1 to Month 12 period.

Table 4-2

Number (%) of Subjects With Specific Concomitant Vaccination (Incidence >0% in One or More Vaccination Groups)
(Day 1 Through Month 12) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Subjects in analysis population	1179		596	
Subjects with one or more concomitant vaccinations	178	(15.1)	107	(18.0)
Subjects with no concomitant vaccinations	1001	(84.9)	489	(82.0)
Concomitant vaccinations				
BCG vaccine	16	(1.4)	4	(0.7)
diphtheria toxoid	3	(0.3)	1	(0.2)
diphtheria toxoid (+) pertussis vaccine (unspecified) (+) tetanus toxoid	2	(0.2)	1	(0.2)
diphtheria toxoid (+) pertussis whole cell vaccine (+) tetanus toxoid	0	(0.0)	2	(0.3)
diphtheria toxoid (+) poliovirus vaccine inactivated (Vero) (+) tetanus toxoid	3	(0.3)	2	(0.3)
diphtheria toxoid (+) tetanus toxoid	17	(1.4)	11	(1.8)
hepatitis A virus vaccine (unspecified)	4	(0.3)	0	(0.0)
hepatitis A virus vaccine (unspecified) (+) hepatitis B virus vaccine (unspecified)	0	(0.0)	1	(0.2)
hepatitis A virus vaccine inactivated	5	(0.4)	3	(0.5)
hepatitis A virus vaccine inactivated (+) hepatitis B virus vaccine rHBsAg (yeast)	2	(0.2)	1	(0.2)
hepatitis B virus vaccine (unspecified)	4	(0.3)	5	(0.8)
hepatitis B virus vaccine rHBsAg (yeast)	7	(0.6)	6	(1.0)
influenza virus 3v reassortant vaccine live intranasal (cold adapted Ann Arbor master strain)	6	(0.5)	6	(1.0)
influenza virus sAg 3v vaccine inactivated	2	(0.2)	2	(0.3)
influenza virus split virion 3v vaccine inactivated	21	(1.8)	15	(2.5)
influenza virus vaccine (unspecified)	19	(1.6)	14	(2.3)
influenza virus whole virion 3v vaccine inactivated	1	(0.1)	0	(0.0)
measles virus vaccine live (Enders-Edmonston) (+) mumps virus vaccine live (Jeryl Lynn) (+) rubella virus vaccine live (HPV-77)	11	(0.9)	5	(0.8)

Table 4-2 (Cont.)

Number (%) of Subjects With Specific Concomitant Vaccination (Incidence >0% in One or More Vaccination Groups (Day 1 Through Month 12) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
measles virus vaccine live (Enders-Edmonston) (+) mumps virus vaccine live (Jeryl Lynn) (+) rubella virus vaccine live (Wistar RA 27/3) (+) varicella virus vaccine live (Oka/Merck original process)	14	(1.2)	9	(1.5)
measles virus vaccine live (Schwartz) (+) mumps virus vaccine live (RIT 4385) (+) rubella virus vaccine live (Wistar RA 27/3)	2	(0.2)	0	(0.0)
measles virus vaccine live (unspecified)	12	(1.0)	10	(1.7)
measles virus vaccine live (unspecified) (+) mumps virus vaccine live (unspecified) (+) rubella virus vaccine live (unspecified)	5	(0.4)	1	(0.2)
measles virus vaccine live (unspecified) (+) rubella virus vaccine live (unspecified)	1	(0.1)	2	(0.3)
meningococcal C conj vaccine (tet toxoid)	1	(0.1)	0	(0.0)
meningococcal C polysaccharide vaccine	1	(0.1)	1	(0.2)
meningococcal vaccine (unspecified)	2	(0.2)	0	(0.0)
pneumococcal 23v polysaccharide vaccine	1	(0.1)	0	(0.0)
poliovirus vaccine inactivated (unspecified)	2	(0.2)	5	(0.8)
poliovirus vaccine live oral	1	(0.1)	2	(0.3)
rabies virus vaccine (Vero)	0	(0.0)	1	(0.2)
rabies virus vaccine (chick embryo)	0	(0.0)	2	(0.3)
tetanus toxoid	23	(2.0)	17	(2.9)
tick-borne encephalitis virus vaccine	1	(0.1)	0	(0.0)
typhoid vaccine inactivated	1	(0.1)	0	(0.0)

Table 4-2 (Cont.)

Number (%) of Subjects With Specific Concomitant Vaccination (Incidence >0% in One or More Vaccination Groups)
(Day 1 Through Month 12) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
varicella virus vaccine live (Oka/Merck)	1	(0.1)	0	(0.0)
varicella virus vaccine live (Oka/RIT)	0	(0.0)	2	(0.3)
yellow fever virus vaccine	8	(0.7)	2	(0.3)

Percentages are calculated as the number of subjects with the specific concomitant vaccination divided by the number of subjects in the analysis population for the vaccination group.
Although a subject may have had two or more concomitant vaccinations, the subject is counted only once for a given concomitant vaccination.
N = Number of subjects allocated to each vaccination group.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.2]

Table 4-3

Number (%) of Subjects With Specific Aluminum-Containing Concomitant Vaccinations (Incidence >0% in One or More Vaccination Groups)
(Day 1 through Month 12) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Subjects in analysis population	1179		596	
Subjects with one or more aluminum-containing concomitant vaccinations	59	(5.0)	39	(6.5)
Subjects with no aluminum containing concomitant vaccinations	1120	(95.0)	557	(93.5)
Concomitant vaccinations				
diphtheria toxoid	3	(0.3)	1	(0.2)
diphtheria toxoid (+) pertussis vaccine (unspecified) (+) tetanus toxoid	2	(0.2)	1	(0.2)
diphtheria toxoid (+) poliovirus vaccine inactivated (Vero) (+) tetanus toxoid	3	(0.3)	2	(0.3)
diphtheria toxoid (+) tetanus toxoid	17	(1.4)	11	(1.8)
hepatitis A virus vaccine (unspecified)	4	(0.3)	0	(0.0)
hepatitis A virus vaccine (unspecified) (+) hepatitis B virus vaccine (unspecified)	0	(0.0)	1	(0.2)
hepatitis A virus vaccine inactivated	5	(0.4)	3	(0.5)
hepatitis A virus vaccine inactivated (+) hepatitis B virus vaccine rHBsAg (yeast)	2	(0.2)	1	(0.2)
hepatitis B virus vaccine (unspecified)	4	(0.3)	5	(0.8)
tetanus toxoid	23	(2.0)	17	(2.9)
tick-borne encephalitis virus vaccine	1	(0.1)	0	(0.0)

Percentages are calculated as the number of subjects with the specific concomitant vaccination divided by the number of subjects in the analysis population for the vaccination group.
Although a subject may have had two or more concomitant vaccinations, the subject is counted only once for a given concomitant vaccination.
n = Number of subjects with the indicated concomitant vaccination.
N = Number of subjects randomized in each vaccination group.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.2]

4.3 Medical Conditions

Table 4-4 summarizes the number and percentage of subjects, by vaccination group and system organ class, with specific pre-existing (prior to Day 1) medical conditions (incidence ≥1% in one or more vaccination groups).

Compared to Table 6-12 [7.7] in the Protocol 018 CSR, the following changes occurred with regard to medical history prior to Day 1:

- One (1) subject in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group who was previously reported to have had no prior medical conditions was now reported to have had a prior medical condition;
- One (1) case each of Meniere's Disease, dizziness, depression, major depression, and asthma were added to the pre-study medical history in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group; and
- One (1) case each of allergic conjunctivitis and skin papilloma were added to the pre-study medical history in the placebo group.

Table 4-5 summarizes the number and percentage of subjects, by vaccination group and system organ class, with new medical conditions (incidence ≥1% in one or more vaccination groups) reported during the vaccination period (Day 1 though Month 7).

Compared to Table 8-25 [7.7] in the Protocol 018 CSR, the following changes occurred with regard to new medical conditions reported between the Day 1 and Month 7 visits:

- One report of dysmenorrhea was added to the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group; and
- One report of asthma in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group was moved from the Day 1 to Month 7 period to prior Medical History (see above).

Table 4-6 summarizes the number and percentage of subjects, by vaccination group and system organ class, with new medical conditions (incidence ≥1% in one or more vaccination groups) reported during the follow-up period (Month 7 through Month 12). Overall, 29.6% of subjects (29.0% in the quadrivalent HPV [Types 6, 11, 16, 18] L1 VLP vaccine group and 31.0% in the placebo group) reported a new medical condition after the Month 7 period. The most common conditions reported were upper respiratory infections (e.g., influenza, pharyngitis, etc.).

At one study site (Site 044), the Month 12 visits were conducted by the unblinded study coordinator. Because the protocol states that the unblinded study site personnel were to have no contact with study subjects or have been involved with subject management, a separate analysis of new medical conditions was conducted excluding subjects at that site (Table 4-7). Excluding data from subjects enrolled at this site does not change the overall findings with regard to new medical history.

Table 4-8 summarizes the number and percentage of subjects, by vaccination group and system organ class, with new medical conditions (incidence >0% in one or more vaccination groups) reported during the follow-up period (Month 7 through Month 12) excluding subjects who received aluminum-containing concomitant vaccines at any time during the study. Overall, 28.5% of these subjects reported a new medical condition after Month 7. Slightly fewer subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group reported such conditions than subjects in the placebo group. The most common new medical condition reported was upper respiratory infection (e.g., influenza, pharyngitis, etc.).

Table 4-9 summarizes the number and percentage of subjects, by vaccination group and system organ class, with new medical conditions (incidence >0% in one or more vaccination groups) reported during the follow-up phase (Month 7 through Month 12) in subjects who received aluminum-containing concomitant vaccines at any time during the study. Overall, 48.5% of these subjects reported a new medical condition after Month 7. More subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group reported such conditions than subjects in the placebo group. The most common new medical condition reported was influenza.

Table 4-4

Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) in All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Subjects in analysis population	1179		596	
Subjects with one or more medical conditions	806	(68.4)	416	(69.8)
Subjects with no medical conditions	373	(31.6)	180	(30.2)
Blood And Lymphatic System Disorders	**12**	**(1.0)**	**6**	**(1.0)**
Congenital, Familial And Genetic Disorders	**22**	**(1.9)**	**17**	**(2.9)**
Ear And Labyrinth Disorders	**33**	**(2.8)**	**19**	**(3.2)**
Ear Pain	10	(0.8)	8	(1.3)
Eye Disorders	**60**	**(5.1)**	**33**	**(5.5)**
Astigmatism	9	(0.8)	6	(1.0)
Conjunctivitis	21	(1.8)	11	(1.8)
Myopia	21	(1.8)	13	(2.2)
Gastrointestinal Disorders	**91**	**(7.7)**	**49**	**(8.2)**
Abdominal Pain	18	(1.5)	11	(1.8)

Table 4-4 (Cont.)

Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Constipation	17	(1.4)	8	(1.3)
Gastrooesophageal Reflux Disease	10	(0.8)	6	(1.0)
General Disorders And Administration Site Conditions	**29**	**(2.5)**	**13**	**(2.2)**
Immune System Disorders	**233**	**(19.8)**	**108**	**(18.1)**
Drug Hypersensitivity	58	(4.9)	36	(6.0)
Hypersensitivity	32	(2.7)	17	(2.9)
Seasonal Allergy	141	(12.0)	56	(9.4)
Infections And Infestations	**429**	**(36.4)**	**234**	**(39.3)**
Bronchitis	21	(1.8)	14	(2.3)
Cellulitis	3	(0.3)	8	(1.3)
Impetigo	12	(1.0)	5	(0.8)
Influenza	27	(2.3)	12	(2.0)
Nasopharyngitis	13	(1.1)	8	(1.3)

Table 4-4 (Cont.)

Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Otitis Externa	12	(1.0)	9	(1.5)
Otitis Media	61	(5.2)	41	(6.9)
Otitis Media Chronic	7	(0.6)	9	(1.5)
Pharyngitis	78	(6.6)	45	(7.6)
Pharyngitis Streptococcal	44	(3.7)	28	(4.7)
Pneumonia	21	(1.8)	9	(1.5)
Rhinitis	12	(1.0)	10	(1.7)
Sinusitis	53	(4.5)	20	(3.4)
Tonsillitis	13	(1.1)	13	(2.2)
Upper Respiratory Tract Infection	82	(7.0)	48	(8.1)
Urinary Tract Infection	14	(1.2)	6	(1.0)
Varicella	28	(2.4)	17	(2.9)
Viral Infection	24	(2.0)	19	(3.2)
Viral Pharyngitis	14	(1.2)	8	(1.3)
Injury, Poisoning And Procedural Complications	**128**	**(10.9)**	**61**	**(10.2)**
Contusion	15	(1.3)	10	(1.7)
Joint Injury	12	(1.0)	3	(0.5)

Table 4-4 (Cont.)

Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Joint Sprain	15	(1.3)	9	(1.5)
Limb Injury	11	(0.9)	8	(1.3)
Skin Laceration	7	(0.6)	6	(1.0)
Investigations	**24**	**(2.0)**	**11**	**(1.8)**
Metabolism And Nutrition Disorders	**36**	**(3.1)**	**20**	**(3.4)**
Obesity	18	(1.5)	13	(2.2)
Musculoskeletal And Connective Tissue Disorders	**103**	**(8.7)**	**54**	**(9.1)**
Arthralgia	20	(1.7)	14	(2.3)
Back Pain	19	(1.6)	7	(1.2)
Scoliosis	12	(1.0)	6	(1.0)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**42**	**(3.6)**	**25**	**(4.2)**

Table 4-4 (Cont.)

Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Skin Papilloma	37	(3.1)	23	(3.9)
Nervous System Disorders	**140**	**(11.9)**	**83**	**(13.9)**
Headache	99	(8.4)	56	(9.4)
Migraine	25	(2.1)	17	(2.9)
Psychiatric Disorders	**104**	**(8.8)**	**43**	**(7.2)**
Abnormal Behaviour	13	(1.1)	0	(0.0)
Attention Deficit/Hyperactivity Disorder	78	(6.6)	35	(5.9)
Depression	12	(1.0)	3	(0.5)
Renal And Urinary Disorders	**26**	**(2.2)**	**9**	**(1.5)**
Reproductive System And Breast Disorders	**73**	**(6.2)**	**36**	**(6.0)**
Dysmenorrhoea	51	(4.3)	22	(3.7)

Table 4-4 (Cont.)

Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Respiratory, Thoracic And Mediastinal Disorders	**253**	**(21.5)**	**148**	**(24.8)**
Asthma	115	(9.8)	69	(11.6)
Asthma Exercise Induced	6	(0.5)	6	(1.0)
Bronchospasm	18	(1.5)	13	(2.2)
Cough	28	(2.4)	14	(2.3)
Epistaxis	8	(0.7)	6	(1.0)
Pharyngolaryngeal Pain	10	(0.8)	11	(1.8)
Rhinitis Allergic	77	(6.5)	41	(6.9)
Skin And Subcutaneous Tissue Disorders	**173**	**(14.7)**	**81**	**(13.6)**
Acne	58	(4.9)	27	(4.5)
Dermatitis Atopic	12	(1.0)	9	(1.5)
Dermatitis Contact	15	(1.3)	6	(1.0)
Eczema	34	(2.9)	22	(3.7)

Table 4-4 (Cont.)

Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Surgical And Medical Procedures	**95**	**(8.1)**	**55**	**(9.2)**
Adenoidectomy	18	(1.5)	6	(1.0)
Ear Tube Insertion	19	(1.6)	10	(1.7)
Tonsillectomy	18	(1.5)	15	(2.5)

Although a subject may have had two or more medical conditions, the subject is counted only once within a category. The same subject may appear in different categories.
Terms for medical conditions are from MedDRA Version 7.1.
n = Number of subjects with the indicated characteristic.
N = Number of allocated subjects in each vaccination group.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.5]

Table 4-5

Number (%) of Subjects With New Medical Conditions
(Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Vaccination Period, Day 1 Through Month 7)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1179)		Non-Alum Placebo (N= 594)	
	n	(%)	n	(%)
Subjects in analysis population	1179		594	
Subjects with one or more new medical conditions	520	(44.1)	280	(47.1)
Subjects with no new medical conditions	659	(55.9)	314	(52.9)
Ear And Labyrinth Disorders	**13**	**(1.1)**	**10**	**(1.7)**
Eye Disorders	**23**	**(2.0)**	**7**	**(1.2)**
Gastrointestinal Disorders	**43**	**(3.6)**	**30**	**(5.1)**
Abdominal Pain	8	(0.7)	8	(1.3)
General Disorders And Administration Site Conditions	**17**	**(1.4)**	**5**	**(0.8)**
Immune System Disorders	**21**	**(1.8)**	**9**	**(1.5)**
Seasonal Allergy	12	(1.0)	5	(0.8)
Infections And Infestations	**265**	**(22.5)**	**150**	**(25.3)**
Bacterial Infection	7	(0.6)	6	(1.0)
Gastroenteritis Viral	7	(0.6)	7	(1.2)
Influenza	20	(1.7)	13	(2.2)

Table 4-5 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Vaccination Period, Day 1 Through Month 7)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1179)		Non-Alum Placebo (N= 594)	
	n	(%)	n	(%)
Nasopharyngitis	26	(2.2)	21	(3.5)
Otitis Media	10	(0.8)	12	(2.0)
Pharyngitis	30	(2.5)	13	(2.2)
Pharyngitis Streptococcal	19	(1.6)	11	(1.9)
Sinusitis	12	(1.0)	9	(1.5)
Tinea Pedis	15	(1.3)	7	(1.2)
Tonsillitis	12	(1.0)	10	(1.7)
Upper Respiratory Tract Infection	41	(3.5)	15	(2.5)
Viral Infection	9	(0.8)	6	(1.0)
Injury, Poisoning And Procedural Complications	**90**	**(7.6)**	**45**	**(7.6)**
Musculoskeletal And Connective Tissue Disorders	**53**	**(4.5)**	**27**	**(4.5)**
Arthralgia	15	(1.3)	7	(1.2)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	**11**	**(0.9)**	**7**	**(1.2)**
Nervous System Disorders	**66**	**(5.6)**	**36**	**(6.1)**
Headache	58	(4.9)	30	(5.1)
Psychiatric Disorders	**16**	**(1.4)**	**10**	**(1.7)**

Table 4-5 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Vaccination Period, Day 1 Through Month 7)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1179)		Non-Alum Placebo (N= 594)	
	n	(%)	n	(%)
Reproductive System And Breast Disorders	**24**	**(2.0)**	**7**	**(1.2)**
Respiratory, Thoracic And Mediastinal Disorders	**54**	**(4.6)**	**32**	**(5.4)**
Cough	12	(1.0)	10	(1.7)
Pharyngolaryngeal Pain	16	(1.4)	7	(1.2)
Skin And Subcutaneous Tissue Disorders	**46**	**(3.9)**	**28**	**(4.7)**
Acne	11	(0.9)	8	(1.3)
Surgical And Medical Procedures	**36**	**(3.1)**	**17**	**(2.9)**

Percentages are calculated based on the number of subjects in analysis population.
Although a subject may have had two or more new medical conditions, the subject is counted only once within a category. The same subject may appear in different categories.
Terms for medical conditions are from MedDRA Version 7.1.
n = Number of subjects with the indicated characteristic.
N = Number of allocated subjects in each vaccination group who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.5]

Table 4-6

Number (%) of Subjects With New Medical Conditions
(Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Follow-up Period, Month 7 through Month 12)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1128)		Non-Alum Placebo (N= 562)	
	n	(%)	n	(%)
Subjects in analysis population	1128		562	
Subjects with one or more new medical conditions	327	(29.0)	174	(31.0)
Subjects with no new medical conditions	801	(71.0)	388	(69.0)
Ear And Labyrinth Disorders	**8**	**(0.7)**	**7**	**(1.2)**
Gastrointestinal Disorders	**31**	**(2.7)**	**18**	**(3.2)**
Infections And Infestations	**192**	**(17.0)**	**96**	**(17.1)**
Influenza	32	(2.8)	18	(3.2)
Nasopharyngitis	20	(1.8)	8	(1.4)
Otitis Media	11	(1.0)	6	(1.1)
Pharyngitis	30	(2.7)	9	(1.6)
Pharyngotonsillitis	11	(1.0)	5	(0.9)
Sinusitis	8	(0.7)	6	(1.1)
Tonsillitis	6	(0.5)	7	(1.2)
Upper Respiratory Tract Infection	19	(1.7)	11	(2.0)
Injury, Poisoning And Procedural Complications	**51**	**(4.5)**	**23**	**(4.1)**

Table 4-6 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Follow-up Period, Month 7 through Month 12)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1128)		Non-Alum Placebo (N= 562)	
	n	(%)	n	(%)
Musculoskeletal And Connective Tissue Disorders	**25**	**(2.2)**	**14**	**(2.5)**
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	**7**	**(0.6)**	**6**	**(1.1)**
Psychiatric Disorders	**7**	**(0.6)**	**6**	**(1.1)**
Reproductive System And Breast Disorders	**12**	**(1.1)**	**5**	**(0.9)**
Respiratory, Thoracic And Mediastinal Disorders	**22**	**(2.0)**	**19**	**(3.4)**
Pharyngolaryngeal Pain	4	(0.4)	6	(1.1)
Skin And Subcutaneous Tissue Disorders	**27**	**(2.4)**	**19**	**(3.4)**
Surgical And Medical Procedures	**10**	**(0.9)**	**7**	**(1.2)**

Percentages are calculated based on the number of subjects in analysis population.
Although a subject may have had two or more new medical conditions, the subject is counted only once within a category. The same subject may appear in different categories.
Terms for medical conditions are from MedDRA Version 7.1.
n = Number of subjects with the indicated characteristic.
N = Number of subjects allocated to each vaccination group who entered the long-term follow-up period and who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP- Virus-like particles.

Data Source: [7.8.1.5]

Table 4-7

Number (%) of Subjects With New Medical Conditions
(Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Follow-up Period, Month 7 through Month 12) Excluding Study Site 044

	Quadrivalent HPV (Types 6,11,16,18) L1 VP Vaccine (N= 1109)		Non-Alum Placebo (N= 552)	
	n	(%)	n	(%)
Subjects in analysis population	1109		552	
Subjects with one or more new medical conditions	321	(28.9)	172	(31.2)
Subjects with no new medical conditions	788	(71.1)	380	(68.8)
Ear And Labyrinth Disorders	**8**	**(0.7)**	**7**	**(1.3)**
Gastrointestinal Disorders	**31**	**(2.8)**	**18**	**(3.3)**
Infections And Infestations	**190**	**(17.1)**	**95**	**(17.2)**
Influenza	32	(2.9)	18	(3.3)
Nasopharyngitis	20	(1.8)	8	(1.4)
Otitis Media	11	(1.0)	6	(1.1)
Pharyngitis	30	(2.7)	9	(1.6)
Pharyngotonsillitis	11	(1.0)	5	(0.9)
Sinusitis	8	(0.7)	6	(1.1)
Tonsillitis	6	(0.5)	7	(1.3)
Upper Respiratory Tract Infection	19	(1.7)	11	(2.0)
Injury, Poisoning And Procedural Complications	**49**	**(4.4)**	**23**	**(4.2)**

Table 4-7 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Follow-up Period, Month 7 through Month 12) Excluding Study Site 044

	Quadrivalent HPV (Types 6,11,16,18) L1 VP Vaccine (N= 1109)		Non-Alum Placebo (N= 552)	
	n	(%)	n	(%)
Musculoskeletal And Connective Tissue Disorders	**25**	**(2.3)**	**14**	**(2.5)**
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	**7**	**(0.6)**	**6**	**(1.1)**
Psychiatric Disorders	**6**	**(0.5)**	**6**	**(1.1)**
Reproductive System And Breast Disorders	**12**	**(1.1)**	**5**	**(0.9)**
Respiratory, Thoracic And Mediastinal Disorders	**21**	**(1.9)**	**18**	**(3.3)**
Skin And Subcutaneous Tissue Disorders	**25**	**(2.3)**	**19**	**(3.4)**
Surgical And Medical Procedures	**8**	**(0.7)**	**7**	**(1.3)**

Percentages are calculated based on the number of subjects in analysis population.
Although a subject may have had two or more new medical conditions, the subject is counted only once within a category. The same subject may appear in different categories.
Terms for medical conditions are from MedDRA Version 7.1.
n = Number of subjects with the indicated characteristic.
N = Number of allocated subjects in each vaccination group who entered the long-term follow-up period excluding subjects at site 044.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.5]

Table 4-8

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Subjects in analysis population	1070		523	
Subjects with one or more new medical conditions	295	(27.6)	159	(30.4)
Subjects with no new medical conditions	775	(72.4)	364	(69.6)
Congenital, Familial And Genetic Disorders	**3**	**(0.3)**	**0**	**(0.0)**
Dermoid Cyst	1	(0.1)	0	(0.0)
Pigmented Naevus	2	(0.2)	0	(0.0)
Ear And Labyrinth Disorders	**7**	**(0.7)**	**6**	**(1.1)**
Cerumen Impaction	2	(0.2)	0	(0.0)
Ear Pain	3	(0.3)	3	(0.6)
Hypoacusis	0	(0.0)	1	(0.2)
Middle Ear Effusion	1	(0.1)	0	(0.0)
Otorrhoea	0	(0.0)	1	(0.2)
Tinnitus	1	(0.1)	0	(0.0)
Vertigo	0	(0.0)	1	(0.2)
Endocrine Disorders	**2**	**(0.2)**	**0**	**(0.0)**
Autoimmune Thyroiditis	1	(0.1)	0	(0.0)
Hypothyroidism	1	(0.1)	0	(0.0)
Precocious Puberty	1	(0.1)	0	(0.0)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Eye Disorders	**9**	**(0.8)**	**2**	**(0.4)**
Chalazion	3	(0.3)	2	(0.4)
Conjunctivitis	4	(0.4)	0	(0.0)
Conjunctivitis Allergic	2	(0.2)	0	(0.0)
Gastrointestinal Disorders	**29**	**(2.7)**	**18**	**(3.4)**
Abdominal Pain	7	(0.7)	4	(0.8)
Abdominal Pain Lower	1	(0.1)	0	(0.0)
Abdominal Pain Upper	2	(0.2)	0	(0.0)
Abdominal Tenderness	0	(0.0)	1	(0.2)
Colitis	0	(0.0)	2	(0.4)
Constipation	0	(0.0)	1	(0.2)
Diarrhoea	1	(0.1)	2	(0.4)
Dyspepsia	3	(0.3)	1	(0.2)
Enteritis	1	(0.1)	2	(0.4)
Food Poisoning	4	(0.4)	1	(0.2)
Gastritis	4	(0.4)	2	(0.4)
Gastrooesophageal Reflux Disease	0	(0.0)	1	(0.2)
Gingivitis	2	(0.2)	0	(0.0)
Haematochezia	0	(0.0)	1	(0.2)
Mouth Ulceration	1	(0.1)	0	(0.0)
Nausea	2	(0.2)	1	(0.2)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Stomatitis	0	(0.0)	1	(0.2)
Tooth Fracture	0	(0.0)	1	(0.2)
Toothache	0	(0.0)	1	(0.2)
Vomiting	5	(0.5)	1	(0.2)
General Disorders And Administration Site Conditions	**5**	**(0.5)**	**2**	**(0.4)**
Chest Pain	1	(0.1)	0	(0.0)
Influenza Like Illness	2	(0.2)	0	(0.0)
Malaise	1	(0.1)	0	(0.0)
Pyrexia	2	(0.2)	2	(0.4)
Immune System Disorders	**3**	**(0.3)**	**2**	**(0.4)**
Allergic Oedema	1	(0.1)	0	(0.0)
Drug Hypersensitivity	2	(0.2)	0	(0.0)
Seasonal Allergy	0	(0.0)	2	(0.4)
Infections And Infestations	**169**	**(15.8)**	**87**	**(16.6)**
Acute Sinusitis	0	(0.0)	1	(0.2)
Acute Tonsillitis	1	(0.1)	2	(0.4)
Body Tinea	1	(0.1)	0	(0.0)
Breast Infection	1	(0.1)	0	(0.0)
Bronchitis	5	(0.5)	3	(0.6)
Bronchitis Bacterial	1	(0.1)	0	(0.0)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Croup Infectious	0	(0.0)	1	(0.2)
Cystitis	2	(0.2)	2	(0.4)
Dengue Fever	1	(0.1)	1	(0.2)
Dental Caries	1	(0.1)	0	(0.0)
Ear Infection	1	(0.1)	1	(0.2)
Fungal Skin Infection	1	(0.1)	1	(0.2)
Gastroenteritis	1	(0.1)	3	(0.6)
Gastroenteritis Viral	6	(0.6)	3	(0.6)
Hand-Foot-And-Mouth Disease	1	(0.1)	0	(0.0)
Herpes Simplex	1	(0.1)	0	(0.0)
Herpes Simplex Ophthalmic	0	(0.0)	1	(0.2)
Herpes Zoster	1	(0.1)	0	(0.0)
Herpetic Stomatitis	0	(0.0)	1	(0.2)
Hordeolum	2	(0.2)	0	(0.0)
Impetigo	6	(0.6)	3	(0.6)
Infected Insect Bite	1	(0.1)	0	(0.0)
Infectious Mononucleosis	1	(0.1)	0	(0.0)
Influenza	27	(2.5)	12	(2.3)
Laryngopharyngitis	0	(0.0)	1	(0.2)
Lice Infestation	0	(0.0)	1	(0.2)
Lobar Pneumonia	1	(0.1)	0	(0.0)
Localised Infection	1	(0.1)	0	(0.0)
Lower Respiratory Tract Infection	0	(0.0)	1	(0.2)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Myringitis Bullous	1	(0.1)	0	(0.0)
Nail Infection	1	(0.1)	0	(0.0)
Nasopharyngitis	18	(1.7)	7	(1.3)
Otitis Externa	4	(0.4)	2	(0.4)
Otitis Media	9	(0.8)	6	(1.1)
Otitis Media Acute	0	(0.0)	1	(0.2)
Parasitic Infection Intestinal	5	(0.5)	2	(0.4)
Paronychia	1	(0.1)	0	(0.0)
Pharyngitis	28	(2.6)	9	(1.7)
Pharyngitis Streptococcal	7	(0.7)	3	(0.6)
Pharyngotonsillitis	10	(0.9)	4	(0.8)
Pneumonia	3	(0.3)	2	(0.4)
Pneumonia Mycoplasmal	1	(0.1)	0	(0.0)
Pneumonia Primary Atypical	0	(0.0)	1	(0.2)
Pneumonia Viral	0	(0.0)	1	(0.2)
Respiratory Tract Infection	0	(0.0)	1	(0.2)
Respiratory Tract Infection Viral	0	(0.0)	1	(0.2)
Rhinitis	0	(0.0)	2	(0.4)
Sinusitis	8	(0.7)	6	(1.1)
Staphylococcal Infection	1	(0.1)	0	(0.0)
Tinea Pedis	0	(0.0)	1	(0.2)
Tonsillitis	2	(0.2)	6	(1.1)
Tooth Abscess	0	(0.0)	1	(0.2)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Upper Respiratory Tract Infection	16	(1.5)	11	(2.1)
Urinary Tract Infection	3	(0.3)	3	(0.6)
Vaginal Candidiasis	1	(0.1)	0	(0.0)
Vaginal Mycosis	1	(0.1)	0	(0.0)
Viral Infection	0	(0.0)	1	(0.2)
Viral Pharyngitis	4	(0.4)	4	(0.8)
Viral Upper Respiratory Tract Infection	8	(0.7)	2	(0.4)
Injury, Poisoning And Procedural Complications	**43**	**(4.0)**	**21**	**(4.0)**
Animal Bite	2	(0.2)	0	(0.0)
Ankle Fracture	1	(0.1)	1	(0.2)
Arthropod Bite	2	(0.2)	0	(0.0)
Back Injury	3	(0.3)	1	(0.2)
Cartilage Injury	0	(0.0)	1	(0.2)
Chemical Eye Injury	1	(0.1)	0	(0.0)
Chest Injury	1	(0.1)	0	(0.0)
Clavicle Fracture	0	(0.0)	2	(0.4)
Concussion	1	(0.1)	0	(0.0)
Contusion	2	(0.2)	3	(0.6)
Femoral Neck Fracture	1	(0.1)	0	(0.0)
Foot Fracture	1	(0.1)	0	(0.0)
Head Injury	0	(0.0)	1	(0.2)
Joint Injury	4	(0.4)	1	(0.2)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Joint Sprain	8	(0.7)	3	(0.6)
Laceration	1	(0.1)	0	(0.0)
Ligament Sprain	0	(0.0)	1	(0.2)
Limb Injury	4	(0.4)	2	(0.4)
Mouth Injury	1	(0.1)	0	(0.0)
Muscle Strain	5	(0.5)	1	(0.2)
Nail Avulsion	1	(0.1)	0	(0.0)
Open Fracture	1	(0.1)	0	(0.0)
Open Wound	1	(0.1)	0	(0.0)
Pelvic Organ Injury	1	(0.1)	0	(0.0)
Radius Fracture	1	(0.1)	1	(0.2)
Rib Fracture	1	(0.1)	0	(0.0)
Road Traffic Accident	1	(0.1)	1	(0.2)
Skin Injury	1	(0.1)	0	(0.0)
Skin Laceration	0	(0.0)	1	(0.2)
Soft Tissue Injury	1	(0.1)	2	(0.4)
Splinter	1	(0.1)	0	(0.0)
Upper Limb Fracture	2	(0.2)	0	(0.0)
Investigations	**3**	**(0.3)**	**2**	**(0.4)**
Biopsy Brain	0	(0.0)	1	(0.2)
Body Height Below Normal	0	(0.0)	1	(0.2)
Colonoscopy	1	(0.1)	0	(0.0)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Endoscopy Gastrointestinal	1	(0.1)	0	(0.0)
Nuclear Magnetic Resonance Imaging	1	(0.1)	0	(0.0)
Weight Decreased	1	(0.1)	0	(0.0)
Metabolism And Nutrition Disorders	**2**	**(0.2)**	**3**	**(0.6)**
Anorexia	0	(0.0)	1	(0.2)
Dehydration	1	(0.1)	0	(0.0)
Metabolic Syndrome	0	(0.0)	1	(0.2)
Overweight	0	(0.0)	1	(0.2)
Weight Gain Poor	1	(0.1)	0	(0.0)
Musculoskeletal And Connective Tissue Disorders	**23**	**(2.1)**	**11**	**(2.1)**
Arthralgia	6	(0.6)	4	(0.8)
Back Pain	3	(0.3)	3	(0.6)
Bone Cyst	1	(0.1)	0	(0.0)
Chest Wall Pain	3	(0.3)	0	(0.0)
Costochondritis	1	(0.1)	1	(0.2)
Flank Pain	1	(0.1)	0	(0.0)
Jaw Disorder	1	(0.1)	0	(0.0)
Joint Stiffness	1	(0.1)	0	(0.0)
Joint Swelling	0	(0.0)	1	(0.2)
Juvenile Arthritis	1	(0.1)	0	(0.0)
Muscle Spasms	2	(0.2)	0	(0.0)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Neck Pain	1	(0.1)	0	(0.0)
Pain In Extremity	4	(0.4)	1	(0.2)
Patellofemoral Pain Syndrome	1	(0.1)	0	(0.0)
Plantar Fasciitis	0	(0.0)	1	(0.2)
Rotator Cuff Syndrome	0	(0.0)	1	(0.2)
Scoliosis	1	(0.1)	0	(0.0)
Temporomandibular Joint Syndrome	1	(0.1)	0	(0.0)
Tendonitis	1	(0.1)	0	(0.0)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	**7**	**(0.7)**	**6**	**(1.1)**
Epithelioma	1	(0.1)	0	(0.0)
Medulloblastoma	0	(0.0)	1	(0.2)
Skin Papilloma	6	(0.6)	5	(1.0)
Nervous System Disorders	**8**	**(0.7)**	**3**	**(0.6)**
Headache	6	(0.6)	2	(0.4)
Migraine	2	(0.2)	1	(0.2)
Psychiatric Disorders	**7**	**(0.7)**	**5**	**(1.0)**
Abnormal Behaviour	1	(0.1)	0	(0.0)
Affective Disorder	2	(0.2)	1	(0.2)
Attention Deficit/hyperactivity Disorder	1	(0.1)	1	(0.2)
Depression	1	(0.1)	1	(0.2)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Depression Suicidal	1	(0.1)	0	(0.0)
Insomnia	1	(0.1)	0	(0.0)
Personality Disorder	0	(0.0)	1	(0.2)
Sleep Disorder	0	(0.0)	1	(0.2)
Social Phobia	0	(0.0)	1	(0.2)
Stress Symptoms	1	(0.1)	0	(0.0)
Renal And Urinary Disorders	**5**	**(0.5)**	**3**	**(0.6)**
Dysuria	2	(0.2)	0	(0.0)
Enuresis	1	(0.1)	0	(0.0)
Haematuria	0	(0.0)	1	(0.2)
Nephrolithiasis	2	(0.2)	0	(0.0)
Urethral Pain	0	(0.0)	1	(0.2)
Urinary Incontinence	0	(0.0)	1	(0.2)
Reproductive System And Breast Disorders	**11**	**(1.0)**	**5**	**(1.0)**
Amenorrhoea	2	(0.2)	0	(0.0)
Breast Pain	1	(0.1)	0	(0.0)
Dysmenorrhoea	4	(0.4)	2	(0.4)
Epididymitis	0	(0.0)	1	(0.2)
Fibrocystic Breast Disease	1	(0.1)	0	(0.0)
Menorrhagia	1	(0.1)	0	(0.0)
Menstruation Irregular	1	(0.1)	1	(0.2)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Pelvic Pain	0	(0.0)	1	(0.2)
Polycystic Ovaries	1	(0.1)	0	(0.0)
Vaginal Discharge	1	(0.1)	0	(0.0)
Respiratory, Thoracic And Mediastinal Disorders	**18**	**(1.7)**	**17**	**(3.3)**
Allergic Sinusitis	1	(0.1)	0	(0.0)
Asthma	3	(0.3)	2	(0.4)
Asthma Exercise Induced	0	(0.0)	1	(0.2)
Bronchospasm	3	(0.3)	1	(0.2)
Cough	3	(0.3)	4	(0.8)
Dyspnoea	1	(0.1)	0	(0.0)
Dyspnoea Exertional	1	(0.1)	0	(0.0)
Epistaxis	0	(0.0)	1	(0.2)
Nasal Turbinate Hypertrophy	0	(0.0)	1	(0.2)
Pharyngolaryngeal Pain	3	(0.3)	5	(1.0)
Pleuritic Pain	0	(0.0)	1	(0.2)
Rhinitis Allergic	3	(0.3)	1	(0.2)
Skin And Subcutaneous Tissue Disorders	**26**	**(2.4)**	**17**	**(3.3)**
Acanthosis Nigricans	1	(0.1)	0	(0.0)
Acne	6	(0.6)	2	(0.4)
Dermal Cyst	1	(0.1)	1	(0.2)
Dermatitis	2	(0.2)	1	(0.2)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Dermatitis Allergic	1	(0.1)	0	(0.0)
Dermatitis Contact	5	(0.5)	4	(0.8)
Dermatosis	1	(0.1)	1	(0.2)
Dry Skin	1	(0.1)	0	(0.0)
Eczema	4	(0.4)	3	(0.6)
Hyperkeratosis	0	(0.0)	1	(0.2)
Pityriasis Rosea	1	(0.1)	0	(0.0)
Rash	1	(0.1)	3	(0.6)
Rash Erythematous	0	(0.0)	1	(0.2)
Swelling Face	0	(0.0)	1	(0.2)
Urticaria	2	(0.2)	1	(0.2)
Surgical And Medical Procedures	**9**	**(0.8)**	**7**	**(1.3)**
Adenoidectomy	0	(0.0)	1	(0.2)
Cautery To Nose	1	(0.1)	0	(0.0)
Contraception	0	(0.0)	2	(0.4)
Cryotherapy	1	(0.1)	0	(0.0)
Endodontic Procedure	0	(0.0)	1	(0.2)
Limb Operation	1	(0.1)	0	(0.0)
Mouth Cyst Excision	0	(0.0)	1	(0.2)
Oral Contraception	2	(0.2)	0	(0.0)
Post Coital Contraception	1	(0.1)	0	(0.0)
Suture Insertion	2	(0.2)	0	(0.0)

Table 4-8 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1070)		Non-Alum Placebo (N= 523)	
	n	(%)	n	(%)
Toe Operation	0	(0.0)	1	(0.2)
Turbinectomy	0	(0.0)	1	(0.2)
Wart Excision	1	(0.1)	1	(0.2)
Vascular Disorders	**1**	**(0.1)**	**3**	**(0.6)**
Haematoma	0	(0.0)	1	(0.2)
Hypertension	1	(0.1)	0	(0.0)
Petechiae	0	(0.0)	1	(0.2)
Raynaud's Phenomenon	0	(0.0)	1	(0.2)

Percentages are calculated based on the number of subjects in analysis population.
Although a subject may have had two or more new medical condition, the subject is counted only once within a category. The same subject may appear in different categories.
Terms for medical conditions are from MedDRA Version 7.1.
n = Number of subjects with the indicated medical condition.
N = Number of subjects in each vaccination group excluding those subjects who received an aluminum-containing concomitant vaccination.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.5; 7.8.1.2]

Table 4-9

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 58)		Non-Alum Placebo (N= 39)	
	n	(%)	n	(%)
Subjects in analysis population	58		39	
Subjects with one or more new medical conditions	32	(55.2)	15	(38.5)
Subjects with no new medical conditions	26	(44.8)	24	(61.5)
Congenital, Familial And Genetic Disorders	**0**	**(0.0)**	**1**	**(2.6)**
Epidermal Naevus	0	(0.0)	1	(2.6)
Ear And Labyrinth Disorders	**1**	**(1.7)**	**1**	**(2.6)**
Cerumen Impaction	0	(0.0)	1	(2.6)
Ear Pain	1	(1.7)	0	(0.0)
Endocrine Disorders	**0**	**(0.0)**	**1**	**(2.6)**
Anovulatory Cycle	0	(0.0)	1	(2.6)
Gastrointestinal Disorders	**2**	**(3.4)**	**0**	**(0.0)**
Abdominal Pain	1	(1.7)	0	(0.0)
Dyspepsia	1	(1.7)	0	(0.0)
General Disorders And Administration Site Conditions	**1**	**(1.7)**	**0**	**(0.0)**
Pyrexia	1	(1.7)	0	(0.0)

Table 4-9 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 58)		Non-Alum Placebo (N= 39)	
	n	(%)	n	(%)
Infections And Infestations	**23**	**(39.7)**	**9**	**(23.1)**
Acute Sinusitis	0	(0.0)	1	(2.6)
Body Tinea	1	(1.7)	0	(0.0)
Bronchitis	1	(1.7)	0	(0.0)
Gastroenteritis	1	(1.7)	0	(0.0)
Gastroenteritis Viral	1	(1.7)	0	(0.0)
Influenza	5	(8.6)	6	(15.4)
Nasopharyngitis	2	(3.4)	1	(2.6)
Otitis Media	2	(3.4)	0	(0.0)
Otitis Media Acute	1	(1.7)	0	(0.0)
Parasitic Infection Intestinal	1	(1.7)	0	(0.0)
Pharyngitis	2	(3.4)	0	(0.0)
Pharyngitis Streptococcal	1	(1.7)	0	(0.0)
Pharyngotonsillitis	1	(1.7)	1	(2.6)
Tonsillitis	4	(6.9)	1	(2.6)
Upper Respiratory Tract Infection	3	(5.2)	0	(0.0)
Urinary Tract Infection	0	(0.0)	1	(2.6)
Viral Pharyngitis	1	(1.7)	0	(0.0)
Viral Upper Respiratory Tract Infection	1	(1.7)	0	(0.0)
Injury, Poisoning And Procedural Complications	**8**	**(13.8)**	**2**	**(5.1)**
Excoriation	1	(1.7)	0	(0.0)
Facial Bones Fracture	1	(1.7)	0	(0.0)

Table 4-9 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 58)		Non-Alum Placebo (N= 39)	
	n	(%)	n	(%)
Foot Fracture	1	(1.7)	0	(0.0)
Joint Sprain	2	(3.4)	1	(2.6)
Limb Injury	2	(3.4)	0	(0.0)
Skin Laceration	0	(0.0)	1	(2.6)
Soft Tissue Injury	1	(1.7)	0	(0.0)
Wound	1	(1.7)	0	(0.0)
Musculoskeletal And Connective Tissue Disorders	**2**	**(3.4)**	**3**	**(7.7)**
Arthralgia	1	(1.7)	0	(0.0)
Costochondritis	0	(0.0)	1	(2.6)
Muscle Spasms	1	(1.7)	0	(0.0)
Patellofemoral Pain Syndrome	0	(0.0)	1	(2.6)
Plantar Fasciitis	0	(0.0)	1	(2.6)
Psychiatric Disorders	**0**	**(0.0)**	**1**	**(2.6)**
Abnormal Behaviour	0	(0.0)	1	(2.6)
Reproductive System And Breast Disorders	**1**	**(1.7)**	**0**	**(0.0)**
Oligomenorrhoea	1	(1.7)	0	(0.0)
Respiratory, Thoracic And Mediastinal Disorders	**4**	**(6.9)**	**2**	**(5.1)**
Asthma	1	(1.7)	0	(0.0)
Asthma Exercise Induced	1	(1.7)	0	(0.0)

Table 4-9 (Cont.)

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Follow-Up Period, Month 7 through Month 12) Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 58)		Non-Alum Placebo (N= 39)	
	n	(%)	n	(%)
Dyspnoea	1	(1.7)	0	(0.0)
Pharyngolaryngeal Pain	1	(1.7)	1	(2.6)
Rhinitis Allergic	1	(1.7)	1	(2.6)
Skin And Subcutaneous Tissue Disorders	**1**	**(1.7)**	**2**	**(5.1)**
Dermal Cyst	1	(1.7)	0	(0.0)
Dermatitis	0	(0.0)	1	(2.6)
Drug Eruption	0	(0.0)	1	(2.6)
Surgical And Medical Procedures	**1**	**(1.7)**	**0**	**(0.0)**
Wart Excision	1	(1.7)	0	(0.0)
Vascular Disorders	**1**	**(1.7)**	**0**	**(0.0)**
Hypertension	1	(1.7)	0	(0.0)

Percentages are calculated based on the number of subjects in analysis population.
Although a subject may have had two or more new medical conditions, the subject is counted only once within a category. The same subject may appear in different categories.
Terms for medical conditions are from MedDRA Version 7.1.
n = Number of subjects with the indicated characteristic.
N = Number of subjects in each vaccination group who received an aluminum-containing concomitant vaccination.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.5; 7.8.1.2]

4.4 Safety Evaluation

4.4.1 Clinical Adverse Experiences

Table 4-10 displays, by vaccination group, the clinical adverse experience summary Day 1 to Day 15 after any vaccination. There were no changes in the clinical adverse experience summary in Table 4-10 compared with Table 8-1 [7.7] in the Protocol 018 CSR.

Table 4-10

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)	
	n	(%)	n	(%)
Subjects in analysis population	1179		594	
Subjects without follow-up	14		10	
Subjects with follow-up	1165		584	
Number (%) of subjects:				
with no adverse experience	202	(17.3)	192	(32.9)
with one or more adverse experiences	963	(82.7)	392	(67.1)
injection-site adverse experiences	877	(75.3)	292	(50.0)
systemic adverse experiences	541	(46.4)	260	(44.5)
with vaccine-related† adverse experiences	913	(78.4)	339	(58.0)
injection-site adverse experiences	877	(75.3)	292	(50.0)
systemic adverse experiences	274	(23.5)	134	(22.9)
with serious adverse experiences	5	(0.4)	0	(0.0)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)

Table 4-10 (Cont.)

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)	
	n	(%)	n	(%)
discontinued[‡] due to an adverse experience	3	(0.3)	0	(0.0)
discontinued due to a vaccine-related adverse Experience	2	(0.2)	0	(0.0)
discontinued due to a serious adverse Experience	1	(0.1)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
[†] Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
[‡] Discontinued = Subject discontinued from therapy.
n = Number of subjects with the indicated characteristic.
N = Number of subjects randomized in the vaccination group who received only the clinical material in the given column. .
HPV = Human papillomavirus; VLP = Virus-like-particles.

Data Source: [7.8.1.13]

4.4.1.1 Injection-Site Adverse Experiences

Table 4-11 summarizes, by vaccination group, the number and percentage of subjects with injection-site adverse experiences (incidence ≥1% in one or more vaccination groups) reported Day 1 to 5 following any vaccination visit. The findings are identical to those reported in Table 8-4 [7.7] of the Protocol 018 CSR.

Table 4-12 lists injection-site adverse experiences with onsets at least 6 days following any vaccination visit. The injection-site adverse experiences reported are identical with those reported in the main Protocol 018 CSR.

Table 4-11

Number (%) of Subjects With Injection-Site Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups)
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	1179				594			
Subjects without follow-up	14				10			
Subjects with follow-up	1165				584			
Number(%) of subjects with one or more injection-site adverse experiences	877	(75.3)			289	(49.5)		
Injection Site Erythema	237	(20.3)	237	(20.3)	77	(13.2)	77	(13.2)
Injection Site Haemorrhage	27	(2.3)	27	(2.3)	15	(2.6)	15	(2.6)
Injection Site Pain	853	(73.2)	853	(73.2)	265	(45.4)	265	(45.4)
Injection Site Paraesthesia	17	(1.5)	17	(1.5)	10	(1.7)	10	(1.7)
Injection Site Pruritus	13	(1.1)	13	(1.1)	5	(0.9)	5	(0.9)
Injection Site Reaction	13	(1.1)	13	(1.1)	4	(0.7)	4	(0.7)
Injection Site Swelling	241	(20.7)	241	(20.7)	45	(7.7)	45	(7.7)

Percentages are calculated based on the number of subjects with follow-up.
Although a subject may have had two or more adverse experiences, the subject is counted only once in the overall total.
Adverse experience terms are from MedDRA Version 7.1.
VR = Vaccine related. Entries in this column refer to the number (%) of subjects with injection-site adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to the vaccine.
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.13]

Table 4-12

Listing of Subjects With Nonserious Injection-Site Adverse Experience
(Day 6 and Beyond Following Any Vaccination Visit Through Month 12)

Study Number	AN	Gender	Race	Age at First Vaccination	Relative Day from Start of Trial	Dose Number (Vaccine Given)	Relative Day of Onset Postdose	Adverse Experience	Duration of Adverse Experience	Intensity /Size †	Serious	Vaccine Relationship	Action Taken	Outcome
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine														
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	9	1 (HPV rL1 6 11 16 18 VLP vaccine)	9	Injection site pain	1 hr	mild	N	prob not	none	recovered
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	51	2 (HPV rL1 6 11 16 18 VLP vaccine)	6	Injection site swelling	2 day	mild	N	def	none	recovered
	[redacted]	[redacted]	[redacted]	[redacted] yr	11	1 (HPV rL1 6 11 16 18 VLP vaccine)	11	Injection site pain	12 hr	mild	N	def	none	recovered
	[redacted]	[redacted]	[redacted]	[redacted] yr	6	1 (HPV rL1 6 11 16 18 VLP vaccine)	6	Injection site pain	12 hr	mod	N	prob	none	recovered
Non-Alum Placebo														
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	62	2 (non-alum placebo)	6	Injection site pain	5 day	mild	N	poss	none	recovered
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	13	1 (non-alum placebo)	13	Injection site reaction	3 day	mod	N	prob	none	recovered
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	7	1 (non-alum placebo)	7	Injection site erythema	3 day	mild	N	prob	none	recovered
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	8	1 (non-alum placebo)	8	Injection site pain	3 day	mild	N	poss	none	recovered

† Injection-site swelling and injection-site erythema are graded according to size.
Adverse experience terms are from MedDRA Version 7.1.
AN = Allocation number; Hispa = Hispanic.
def = Definitely; poss = Possibly; prob = Probably; prob not = Probably not; mod = Moderate.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.13]

4.4.1.2 Systemic Clinical Adverse Experiences

Table 4-13 summarizes the number and percentage of subjects who reported a systemic clinical adverse experience (incidence ≥1% in one or more vaccination groups) Days 1 to 15 following any vaccination visit by system organ class and vaccination group. The number of subjects who reported systemic adverse experiences overall and within each system organ class were generally well-balanced between the two vaccination groups.

Compared with the data reported in Table 8-11 [7.7] in the Protocol 018 CSR, the following data were updated based on additional information received from the subject's parent/legal guardian:

- A case of eye infection was reclassified as blepharitis in a subject in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group.
- A case of myalgia as an adverse experience was removed from the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group.

Table 4-14 lists nonserious adverse experiences with an onset on Day 16 or later following any vaccination. A single subject reported such a nonserious adverse experience.

Table 4-13

Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1179				594			
Subjects without follow-up	14				10			
Subjects with follow-up	1165				584			
Number (%) of Subjects with one or more systemic adverse experiences	541	(46.4)			260	(44.5)		
Number (%) of Subjects with no systemic adverse experience	624	(53.6)			324	(55.5)		
Ear And Labyrinth Disorders	**19**	**(1.6)**	**8**	**(0.7)**	**7**	**(1.2)**	**3**	**(0.5)**
Gastrointestinal Disorders	**150**	**(12.9)**	**51**	**(4.4)**	**91**	**(15.6)**	**30**	**(5.1)**
Abdominal pain	19	(1.6)	7	(0.6)	12	(2.1)	7	(1.2)
Abdominal pain upper	38	(3.3)	12	(1.0)	17	(2.9)	3	(0.5)
Diarrhoea	43	(3.7)	11	(0.9)	21	(3.6)	3	(0.5)
Nausea	38	(3.3)	18	(1.5)	22	(3.8)	13	(2.2)
Vomiting	26	(2.2)	10	(0.9)	18	(3.1)	6	(1.0)

Table 4-13 (Cont.)

Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
General Disorders And Administration Site Conditions	**149**	**(12.8)**	**102**	**(8.8)**	**60**	**(10.3)**	**42**	**(7.2)**
Fatigue	18	(1.5)	11	(0.9)	7	(1.2)	4	(0.7)
Pyrexia	100	(8.6)	74	(6.4)	45	(7.7)	32	(5.5)
Infections And Infestations	**116**	**(10.0)**	**15**	**(1.3)**	**71**	**(12.2)**	**7**	**(1.2)**
Influenza	10	(0.9)	5	(0.4)	12	(2.1)	3	(0.5)
Nasopharyngitis	34	(2.9)	5	(0.4)	22	(3.8)	1	(0.2)
Upper respiratory tract infection	8	(0.7)	1	(0.1)	9	(1.5)		
Injury, Poisoning And Procedural Complications	**31**	**(2.7)**			**15**	**(2.6)**		
Musculoskeletal And Connective Tissue Disorders	**80**	**(6.9)**	**35**	**(3.0)**	**36**	**(6.2)**	**15**	**(2.6)**
Arthralgia	21	(1.8)	10	(0.9)	9	(1.5)	5	(0.9)

Table 4-13 (Cont.)

Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Myalgia	30	(2.6)	18	(1.5)	10	(1.7)	6	(1.0)
Pain in extremity	19	(1.6)	10	(0.9)	14	(2.4)	7	(1.2)
Nervous System Disorders	**241**	**(20.7)**	**146**	**(12.5)**	**120**	**(20.5)**	**83**	**(14.2)**
Dizziness	25	(2.1)	19	(1.6)	9	(1.5)	7	(1.2)
Headache	221	(19.0)	133	(11.4)	110	(18.8)	76	(13.0)
Reproductive System And Breast Disorders	**14**	**(1.2)**			**8**	**(1.4)**		
Dysmenorrhoea	9	(0.8)			7	(1.2)		
Respiratory, Thoracic And Mediastinal Disorders	**85**	**(7.3)**	**10**	**(0.9)**	**51**	**(8.7)**	**7**	**(1.2)**

Table 4-13 (Cont.)

Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Cough	14	(1.2)	3	(0.3)	14	(2.4)	3	(0.5)
Nasal congestion	12	(1.0)			9	(1.5)	1	(0.2)
Pharyngolaryngeal pain	52	(4.5)	6	(0.5)	24	(4.1)	2	(0.3)
Rhinorrhoea	6	(0.5)	1	(0.1)	8	(1.4)	2	(0.3)
Skin And Subcutaneous Tissue Disorders	**25**	**(2.1)**	**6**	**(0.5)**	**20**	**(3.4)**	**4**	**(0.7)**
Rash	7	(0.6)	3	(0.3)	8	(1.4)	1	(0.2)

Percentages are calculated based on the number of subjects with follow-up.
Although a subject may have had two or more systemic adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.
Adverse experience terms are from MedDRA Version 7.1.
n = Number of subjects with the indicated adverse experience.
N = Number of subjects who received only the clinical material in the given column. .
VR = Vaccine related. Entries in this column refer to the number (%) of subjects with systemic adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to the vaccine.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.13]

Table 4-14

Listing of Subjects With Nonserious Systemic Clinical Adverse Experiences
(Day 16 and Beyond Following Any Vaccination Visit Through Month 12)

Study Number	AN	Gender	Race	Age at First Vaccination	Relative Day from Start of Trial	Dose Number (Vaccine Given)	Relative Day of Onset Postdose	Adverse Experience	Duration of Adverse Experience	Intensity /Size [1]	Serious	Vaccine Relationship	Action Taken	Outcome
Non-Alum Placebo														
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	167	2 (non-alum placebo)	106	Nasopharyngitis	11 day	mild	N	def not	none	recovered

[1] Injection-site swelling and injection-site erythema are graded according to size.
Adverse experience terms are from MedDRA Version 7.1.
AN = Allocation number; def not = Definitely not

Data Source: [7.8.1.13]

4.4.1.3 Temperatures

Table 4-15 displays the number and percentage of subjects with elevated temperatures Days 1 to 5 following any vaccination visit by vaccination group. Table 4-16 displays a summary of the distribution of methods for maximum computed temperatures by vaccination group.

Compared with the data presented in the Protocol 018 CSR, data regarding temperatures in 7 subjects (2 subjects Postvaccination 1 and 5 subjects Postvaccination 2) have been added.

The information from these subjects was obtained regarding post-vaccination temperatures recorded on the VRC from subjects who discontinued from the study after any vaccination visit. In these cases, the information was obtained by the VRC being mailed to the study site or the subjects' parent/legal guardian providing the information by phone call to the study site. Updated tables from the Protocol 018 CSR have been provided containing the additional information collected from these subjects. None of the additional temperatures collected was considered to be an adverse experience.

Table 4-15

Number (%) of Subjects With Elevated Temperatures by Vaccination Group
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)	
	n	(%)	n	(%)
Subjects in analysis population	1179		594	
Subjects without follow-up	20		15	
Subjects with follow-up	1159		579	
Maximum Temperature (oral or oral equivalent):				
< 37.8 °C (<100 °F) or normal	1076	(92.8)	541	(93.4)
≥ 37.8 °C (≥100 °F) and < 38.9 °C (< 102 °F)	67	(5.8)	33	(5.7)
≥ 38.9 °C (≥102 °F) and < 39.9 °C (< 103.8 °F)	13	(1.1)	5	(0.9)
≥ 39.9 °C (≥103.8 °F) and < 40.9 °C (< 105.6 °F)	2	(0.2)	0	(0.0)
≥ 40.9 °C (≥105.6 °F)	1	(0.1)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
Multiple occurrences of maximum temperature are counted only once per vaccination or per any vaccination.
All non-oral temperatures have been converted to oral equivalent by adding 1°F to axillary temperatures or subtracting 1°F from rectal temperatures.
n = Number of subject with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.11]

Table 4-16

Distribution of Methods for Maximum Computed Temperatures by Vaccination Group
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Temperatures		ELV		All Temperatures		ELV	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1179				594			
Subjects without follow-up	20				15			
Subjects with follow-up	1159				579			
Temperature Method:								
Axillary	0	(0.0)			1	(0.2)	1	(0.2)
Oral	1152	(99.4)	83	(7.2)	572	(98.8)	37	(6.4)
Rectal	1	(0.1)			0	(0.0)		
Qualitative	6	(0.5)			6	(1.0)		

Temperature methods summarized are those associated with the maximum temperature for the follow-up period.
Multiple occurrences of maximum temperature are counted only once per vaccination or per any vaccination.
Percentages are calculated based on the number of subjects with follow-up.
'Missing/Underivable' refers to methods that are either missing or unable to be converted into rectal, oral or axillary equivalency.
'ELV' refers to the number (%) of subjects with elevated temperatures ≥37.8 and < 38.9 deg Celsius Oral.
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.11]

Table 4-17

Number (%) of Subjects With Elevated Temperatures by Gender Within Each Vaccination Group
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine				Non-Alum Placebo			
	Boys 9 to 15 Years of Age (N=564)		Girls 9 to 15 Years of Age (N=615)		Boys 9 to 15 Years of Age (N=274)		Girls 9 to 15 Years of Age (N=320)	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	564		615		274		320	
Subjects without follow-up	12		8		5		10	
Subjects with follow-up	552		607		269		310	
Maximum Temperature (oral or oral equivalent):								
< 37.8 °C (<100 °F) or normal	511	(92.6)	565	(93.1)	254	(94.4)	287	(92.6)
≥ 37.8 °C (≥ 100 °F) and < 38.9 °C (< 102 °F)	34	(6.2)	33	(5.4)	13	(4.8)	20	(6.5)
≥ 38.9 °C (≥ 102 °F) and < 39.9 °C (< 103.8 °F)	6	(1.1)	7	(1.2)	2	(0.7)	3	(1.0)
≥ 39.9 °C (≥ 103.8 °F) and < 40.9 °C (< 105.6 °F)	0	(0.0)	2	(0.3)	0	(0.0)	0	(0.0)
≥ 40.9 °C (≥ 105.6 °F)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
Multiple occurrences of maximum temperature are counted only once per vaccination or per any vaccination.
All non-oral temperatures have been converted to oral equivalent by adding 1°F to axillary temperatures or subtracting 1°F from rectal temperatures.
n = Number of subjects with the indicated characteristic.
N = Number of subjects within each gender category who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.11]

Table 4-18

Number (%) of Subjects With Elevated Temperatures by Age Group Within Each Vaccination Group
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine				Non-Alum Placebo			
	Subjects 9 to 12 Years of Age (N=692)		Subjects 13 to 15 Years of Age (N=487)		Subjects 9 to 12 Years of Age (N=370)		Subjects 13 to 15 Years of Age (N=224)	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	692		487		370		224	
Subjects without follow-up	12		8		9		6	
Subjects with follow-up	680		479		361		218	
Maximum Temperature (oral or oral equivalent):								
< 37.8 °C (< 100 °F) or normal	637	(93.7)	439	(91.6)	336	(93.1)	205	(94.0)
≥ 37.8 °C (≥ 100 °F) and < 38.9 °C (< 102 °F)	34	(5.0)	33	(6.9)	20	(5.5)	13	(6.0)
≥ 38.9 °C (≥ 102 °F) and < 39.9 °C (< 103.8 °F)	8	(1.2)	5	(1.0)	5	(1.4)	0	(0.0)
≥ 39.9 °C (≥ 103.8 °F) and < 40.9 °C (< 105.6 °F)	0	(0.0)	2	(0.4)	0	(0.0)	0	(0.0)
≥ 40.9 °C (≥ 105.6 °F)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
Multiple occurrences of maximum temperature are counted only once per vaccination or per any vaccination.
All non-oral temperatures have been converted to oral equivalent by adding 1°F to axillary temperatures or subtracting 1°F from rectal temperatures.
n = Number of subjects with the indicated characteristic.
N = Number of subjects within each age category who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.11]

Table 4-19

Number (%) of Subjects With Elevated Temperatures by Vaccination Visit
(Days 1 to 5 Postvaccination 1)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)	
	n	(%)	n	(%)
Subjects in analysis population	1179		594	
Subjects without follow-up	24		20	
Subjects with follow-up	1155		574	
Maximum Temperature (oral or oral equivalent):				
< 37.8 °C (<100 °F) or normal	1124	(97.3)	557	(97.0)
≥ 37.8 °C (≥ 100 °F) and < 38.9 °C (<102 °F)	27	(2.3)	17	(3.0)
≥ 38.9 °C (≥ 102 °F) and < 39.9 °C (<103.8 °F)	3	(0.3)	0	(0.0)
≥ 39.9 °C (≥ 103.8 °F) and < 40.9 °C (<105.6 °F)	0	(0.0)	0	(0.0)
≥ 40.9 °C (≥ 105.6 °F)	1	(0.1)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
Multiple occurrences of maximum temperature are counted only once per vaccination or per any vaccination.
All non-oral temperatures have been converted to oral equivalent by adding 1°F to axillary temperatures or subtracting 1°F from rectal temperatures.
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.11]

Table 4-20

Number (%) of Subjects With Elevated Temperatures by Vaccination Visit
(Days 1 to 5 Postvaccination 2)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1149)		Non-Alum Placebo (N=571)	
	n	(%)	n	(%)
Subjects in analysis population	1149		571	
Subjects without follow-up	25		15	
Subjects with follow-up	1124		556	
Maximum Temperature (oral or oral equivalent):				
< 37.8 °C (<100 °F) or normal	1095	(97.4)	542	(97.5)
≥37.8 °C (≥100 °F) and < 38.9 °C (<102 °F)	24	(2.1)	9	(1.6)
≥ 38.9 °C (≥102 °F) and < 39.9 °C (<103.8 °F)	4	(0.4)	5	(0.9)
≥ 39.9 °C (≥103.8 °F) and < 40.9 °C (<105.6 °F)	1	(0.1)	0	(0.0)
≥ 40.9 °C (≥105.6 °F)	0	(0.0)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
Multiple occurrences of maximum temperature are counted only once per vaccination or per any vaccination.
All non-oral temperatures have been converted to oral equivalent by adding 1°F to axillary temperatures or subtracting 1°F from rectal temperatures.
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column and who received at least two injections.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.11]

Table 4-21

Number (%) of Subjects With Elevated Temperatures by Vaccination Group
(Days 1 to 5 Following Any Vaccination Visit) Excluding Subjects Who Received Any Aluminum-Containing Concomitant Vaccinations at Any Time During the Study)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1154)		Non-Alum Placebo (N=579)	
	n	(%)	n	(%)
Subjects in analysis population	1149		578	
Subjects without follow-up	20		15	
Subjects with follow-up	1129		563	
Maximum Temperature (oral or oral equivalent):				
< 37.8 °C (< 100 °F) or normal	1047	(92.7)	526	(93.4)
≥ 37.8 °C (≥ 100 °F) and < 38.9 °C (< 102 °F)	66	(5.8)	32	(5.7)
≥ 38.9 °C (≥ 102 °F) and < 39.9 °C (< 103.8 °F)	13	(1.2)	5	(0.9)
≥ 39.9 °C (≥ 103.8 °F) and < 40.9 °C (< 105.6 °F)	2	(0.2)	0	(0.0)
≥ 40.9 °C (≥ 105.6 °F)	1	(0.1)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
Multiple occurrences of maximum temperature are counted only once per vaccination or per any vaccination.
All non-oral temperatures have been converted to oral equivalent by adding 1°F to axillary temperatures or subtracting 1°F from rectal temperatures.
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column and did not receive any aluminum-containing concomitant vaccinations.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [7.8.1.11]

4.4.2 Pregnancies

Although pregnancy was not considered to be an adverse experience, it was the responsibility of the investigators to report to the Sponsor any pregnancy in a subject which occurred during the study. All subjects who became pregnant were followed to the completion/termination of the pregnancy according to the Pregnancy Reporting and Follow-Up Guidelines – Phase III addendum [7.5].

One (1) subject became pregnant after the Month 7 visit. [redacted], a [redacted]-year-old female, reported to the study site on [redacted] 2005 that she was pregnant. The pregnancy was confirmed at the study site by a serum pregnancy test performed on [redacted] 2005. The subject's last vaccination occurred on [redacted] 2004 and she completed the Month 7 visit on [redacted] 2004. The pregnancy [redacted] on [redacted] 2005.

4.4.3 Serious Clinical Adverse Experiences

Table 4-17 lists the subjects with serious clinical adverse experiences reported from Day 1 through Month 12. None of these serious clinical adverse experiences was judged by the investigator to be vaccine related. No vaccine-related or procedure-related serious clinical adverse experiences were reported in the period between Month 7 to Month 12. A change in the onset date for the serious adverse experience of appendicitis reported by subject [redacted] initiated a change in the information in Table 4-17 as compared to Table 8-21 in the Protocol 018 CSR. The serious adverse experience was originally reported with onset date being the day of diagnosis but the onset date was later changed to the date at which the symptoms of the adverse experience were first present [7.6].

Table 4-18 lists the subjects who discontinued the study due to a clinical adverse experience. No subjects discontinued the study due to an adverse experience in the period between Month 7 and Month 12.

Table 4-22

Listing of Subjects With Serious Clinical Adverse Experiences
(Day 1 Through Month 12)

Study Number	AN	Gender	Race	Age at First Vaccination	Relative Day from Start of Trial	Dose Number	Relative Day of Onset Postdose	Adverse Experience	Duration of Adverse Experience	Intensity /Size †	Vaccine Relationship	Action Taken	Outcome
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine													
S 47F	[redacted]	[redacted]	[redacted]	[redacted] yr	6	1	6	Renal failure acute	16 day	mod	prob not	no further test vaccines	recovered
S 47F	[redacted]	[redacted]	[redacted]	[redacted] yr	70	2	2	Appendicitis	5 day	severe	prob not	none	recovered
S 47F	[redacted]	[redacted]	[redacted]	[redacted] yr	42	2	2	Localised infection	3 hr	mild	def not	none	recovered
					42	2	2	Pain in extremity	3 hr	mild	def not	none	recovered
S 47F	[redacted]	[redacted]	[redacted]	[redacted] yr	90	2	11	Anaemia	6 day	severe	def not	none	recovered
					90	2	11	Dysfunctional uterine bleeding	6 day	severe	def not	none	recovered
S 47F	[redacted]	[redacted]	[redacted]	[redacted] yr	2	1	2	Diabetes mellitus insulin-dependent	4 day	mild	def not	none	recovered

† Injection-site swelling and injection-site erythema are graded according to size.
Adverse experience terms are from MedDRA Version 7.1.
AN = Allocation number; Hispa = Hispanic.
def not = Definitely not; prob not = Probably not; mod = Moderate.

Data Source: [7.8.1.13]

Table 4-23

Listing of Subjects Discontinued Due to Clinical Adverse Experiences
(Day 1 Through Month 12)

Study Number	AN	Gender	Race	Age at First Vaccination	Relative Day from Start of Trial	Dose Number	Relative Day of Onset Postdose	Adverse Experience	Duration of Adverse Experience	Intensity /Size †	Serious	Vaccine Relationship	Outcome
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine													
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	6	1	6	Renal failure acute	16 day	mod	Y	prob not	recovered
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	1	1	1	Injection site pain	6 hr	mod	N	poss	recovered
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	71	2	1	Injection site swelling	5 day	4	N	def	recovered

† Injection-site swelling and injection-site erythema are graded according to size.
Adverse experience terms are from MedDRA Version 7.1.
AN = Allocation number; Hispa = Hispanic.
def = Definitely; poss = Possibly; prob not = Probably not; mod = Moderate.

Data Source: [7.8.1.11; 7.8.1.4]

5. Discussion

The objective of this report was to supplement information on general safety outcomes following administration of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9- to 15-year-old subjects presented in the Protocol 018 CSR by evaluating new medical history in the 6 months following completion of the vaccination regimen.

As described in the Protocol 018 CSR [7.2], administration of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine was generally well tolerated in 9- to 15-year-old subjects. Updated information regarding Day 1 to Month 7 events that was obtained during the Month 12 contact with subjects and their guardians did not change the overall conclusions of the CSR. No new clinical adverse experiences were reported. One report of new onset dysmenorrhea was added to the summaries of new medical conditions reported between Day 1 and Month 7.

There were no deaths, vaccine-related serious clinical adverse experiences, or procedure-related serious adverse experiences reported following the Month 7 visit. One subject became pregnant during this period. Her pregnancy s 47F as of the finalization of this report.

Approximately 30% of subjects reported a new medical condition following Month 7. The proportions of subjects reporting such conditions were comparable between the two vaccination groups. In both groups, the most common new condition was influenza.

Through Month 12, 5.5% of the study subjects (58 in the vaccine group and 39 in the placebo group) received aluminum vaccinations other than study vaccine. Within this subpopulation, subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reported a somewhat higher incidence of new medical conditions compared with placebo-recipients. There appeared to be more respiratory infections (e.g., upper respiratory infection, tonsillitis) and injuries (e.g., joint sprains) among vaccine recipients compared with placebo recipients. These differences were likely a play of chance associated with small sample sizes.

6. Conclusions

Administration of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9- to 15-year-old boys and girls is generally well-tolerated.

7. List of Appendices

7.1 Protocol Amendment 018-04

7.2 Protocol 018 Synopsis

7.3 Principal Authors' Signatures Page

7.4 Worksheets V501-018 Month 12

7.5 Pregnancy Reporting Guidelines – Phase III Addendum

7.6 Medium WAES Report – Subject s 47F

7.7 Memorandum-Reference Tables from V501 Protocol 018 CSR (V501_P018V1) for Month 12 Safety Report

7.8 Data

7.8.1 Individual Patient Data – SAS Transport Files

7.8.1.1 Prior and Concomitant Therapy

7.8.1.2 Prior and Concomitant Vaccination

7.8.1.3 Patient Demographics

7.8.1.4 Patient Disposition

7.8.1.5 Medical History

7.8.1.6 Maternal Information

7.8.1.7 Pregnancy History

7.8.1.8 Serum Pregnancy

7.8.1.9 Subject Telephone Contact

7.8.1.10 Serology

7.8.1.11 Temperatures

7.8.1.12 Vaccinations

7.8.1.13 Adverse Experiences

Product: V501
Protocol/Amendment No.: 018-04

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THIS PROTOCOL REPLACES PROTOCOL NUMBER 018-00 AND 018-02 AND SHOULD BE SIGNED BY ALL INVESTIGATORS SIGNING THE ORIGINAL PROTOCOL NUMBER 018-00 AND AMENDMENT 018-02.

SPONSOR:

Merck & Co., Inc. (hereafter referred to as the **SPONSOR**)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ, 08889-0100, U.S.A.

TITLE:

A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents

INVESTIGATOR:

PRIMARY:

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

Product: V501
Protocol/Amendment No.: 018-04

SUMMARY OF CHANGES:

The following revisions appear in the attached Complete Protocol Amendment (018-04):

Protocol Section	Revision
Table of Contents 1. Clinical Sections E. Study Design, 3. Study Procedures j. Laboratory Measurements	• Changed the letter j to i.
Protocol Synopsis Objectives Hypotheses Vaccination Dosage/Dosage Form, Route, and Dose Regimen Paragraph 1, Line 5 Study Procedures Data Analysis	• Secondary immunogenicity objective was revised. • Secondary immunogenicity hypothesis was revised. • Added language concerning subjects that receive placebo. • Deleted "each visit." • Added Day 1, Month 2, and Month 6 visits. • Added "a volume of 3.0 mL of serum is needed for this assay." • Added "at or below -20°C" concerning storage of serum samples at the investigative site. • Changed "negative" to "lower" concerning cutoff values. • Added language regarding vaccine availability for subjects that receive placebo. • Amended details of secondary immunogenicity analysis and associated power. • Deleted VRC-prompted AEs.
Study Flow Chart Appendix 2	• The Study Procedures by Visit containing study procedures and worksheet identifications has been removed from the main body of the protocol and placed into Appendix 2. • The Study Flow Chart has been removed from Appendix 2 and inserted into the main body of the protocol. • Visits at month 6 through 18 have been renumbered.
Sponsor Contact Information-U.S. Site(s)	• Deleted [redacted] Fax No.: [redacted] • Added Fax No.: [redacted] under [redacted], M.D., Ph.D. • Deleted contact information for [redacted]. • Added contact information for [redacted]. • Added Sumneytown Pike to Clinical Packaging Technician address.

Product: V501
Protocol/Amendment No.: 018-04

1. Clinical Sections **Immunogenicity** **Luminex Assay for Serum Antibody Response to HPV**	• **Deleted first paragraph containing original language detailing HPV 6, 11, 16, and 18 cLIA.** • **Added most up-to-date verbiage regarding anti-HPV 6, 11, 16, and 18 cLIA.**
A. Background and Rationale **Table 1.**	• **Deleted Days 0 to 14 Following Any Vaccination and added Day 1 through 15 Post-vaccination.**
A. Background and Rationale **c. Determination of the Target Immune Response**	• **Deleted this section.**
A. Background and Rationale **d. Immunogenicity of the Quadrivalent HPV vaccine**	• **Changed d. to c.** • **Added Figure 1.**
A. Background and Rationale **3. Rationale for the Current Study**	• **Changed 9 to 10 in reference to the ages of subjects in Protocol 016.** • **Changed the word "promoted" to "prompted"**
B. Objectives **Secondary**	• **Immunogenicity objective changed to comparison between genders.**
C. Hypotheses **Secondary**	• **Immunogenicity hypothesis changed to comparison between genders.**

Product: V501
Protocol/Amendment No.: 018-04

E. Study Design **2. Treatment** **c. Prior and Concomitant Medication(s)/Treatment(s)** **3. Study Procedures** **b. Subject Discontinuation/ Withdrawal** **g. Vaccine/Placebo Administration** **1) Preparation and Administration of the Vaccine by Unblinded Personnel** **h. Clinical Follow-Up**	• **Added rationale for capturing nonstudy vaccines throughout the course of the study.** • **Added sentence concerning subjects that discontinue from test therapy but continue in the study.** • **Deleted sentence, "vaccine may be removed from the refrigerator and allowed to sit at room temperature for no longer than 15 minutes prior to administration."** • **Concerning upper cutoff for cLIA, changed "will develop" to "developed."** • **Removed verbiage concerning negative, positive and indeterminate results.** • **Moved last paragraph to section I.F. Efficacy/Pharmacokinetic/Imunogenicity, Etc., Measurements**
F. Efficacy/Pharmacokinetic/Imunogenicity, Etc., Measurements	• **Changed title of section.** • **Removed sentence comparing upper cutoff to 200 mMU/mL limit.** • **Inserted the higher cutoff values.** • **Added paragraph from section I.E. 3.h. Clinical Follow-up.**
G. Safety Measurements **1. Evaluating and Recording Adverse Experiences**	• **Added definition of overdose.** • **Changed title of section 3. from "Reporting of Pregnancy to SPONSOR" to "Unblinding of Serious Adverse Experiences."**
I. Data Analysis **2. Hypotheses** **3. Variables and Time Points** **5. Statistical Methods** **7. Sample Size and Power Calculation**	• **Immunogenicity hypothesis changed to noninferiority comparison of GMTs between genders.** • **Changed main immunogenicity endpoint from proportion ≥200 mMU/mL to GMT.** • **Details of secondary immunogenicity analysis revised.** • **Power statement for secondary immunogenicity analysis revised.**
List of References	• **Added Reference No. 15.** • **Added Reference No. 16.**

Product: V501
Protocol/Amendment No.: 018-04

HPV Adolescent/Preadolescent Safety Study

TABLE OF CONTENTS

Product: V501
Protocol/Amendment No.: 018-04

HPV Adolescent/Preadolescent Safety Study

TABLE OF CONTENTS (CONT.)

Product: V501
Protocol/Amendment No.: 018-04

HPV Adolescent/Preadolescent Safety Study

TABLE OF CONTENTS (CONT.)

Product: V501
Protocol/Amendment No.: 018-04

HPV Adolescent/Preadolescent Safety Study

TABLE OF CONTENTS (CONT.)

PROTOCOL SYNOPSIS

PRODUCT: V501

PROTOCOL TITLE: A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents

PROTOCOL/AMENDMENT NO.: 018-04 / Multicenter

U.S. IND NO.: 9,030 CLINICAL PHASE: III

OBJECTIVES:

Primary: To demonstrate that a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents.

Secondary: (1) **To demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls**; and (2) To describe the persistence of immune response to the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, when given in a 3-dose regimen.

HYPOTHESES:

Primary: The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents.

Secondary: **The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine induces noninferior immune responses with respect to each of the vaccine components individually at Week 4 Postdose 3 in preadolescent and adolescent boys who are seronegative to the relevant HPV types on Day 1, relative to preadolescent and adolescent girls who are seronegative to the relevant HPV type on Day 1. (Each vaccine HPV type will be analyzed separately. The statistical criterion for noninferiority requires that the lower bounds of the 95% confidence intervals for the fold difference in GMTs (boys/girls) exclude a decrease of 2-fold or more.)**

STUDY DESIGN AND DURATION: This is a randomized, double-blind (with third party blinding and in-house blinding procedures), placebo-controlled, multicenter safety and immunogenicity study in preadolescents and adolescents aged 9 to 15 years. Enrollment will be stratified by age at enrollment and gender. The age range will be divided into 2 strata: 9 to 12 year olds and 13 to 15 year olds. The ratio of children enrolled into the 2 age strata will be ~2:1 (respectively). The ratio of boys to girls enrolled will be ~1:1. Approximately 1650 subjects will be randomized in a 2:1 ratio to receive either quadrivalent HPV vaccine or non-aluminum-containing-placebo. For each subject enrolled, the duration of the study will be ~1.5 years WITH A POSSIBLE EXTENSION FOR subjects in Spain that volunteer to receive VAQTA™† (hepatitis A vaccine, purified inactivated).

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† VAQTA is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

Vaccination

Subjects will receive vaccine or placebo at Day 1, Month 2, and Month 6 visits. VAQTA™ will be offered to all subjects in Spain at the Month 18 visit after all study procedures for that visit have been completed. An additional Month 24 visit will consist of a booster dose of VAQTA™. Subject participation is voluntary.

After the study is completed, subjects who received placebo will be offered vaccination with the marketed HPV vaccine, if and when the vaccine becomes commercially available for the indication to be used in the subjects' population in the country where the subject was enrolled.

Evaluation

A complete medical history and physical examination will be conducted at the Day 1 visit. A pregnancy test will be performed on female subjects prior to each injection. Any female subject with a positive pregnancy test at Day 1 will not be vaccinated and will not be allowed to participate in the study. Any female with a positive pregnancy test after Day 1 will not receive further vaccinations. However, she will be eligible to participate in the study and complete the remaining study visits and procedures as per protocol. All subjects will be followed up for Adverse Experience (AE) events. All adverse experiences will be collected on the subject's Vaccination Report Card (VRC) daily for 15 days after each vaccination. At Month 2, Month 6, Month 7, Month 12 and Month 18, subjects will be evaluated for any new medical condition or health concerns. Serum samples will be collected from all subjects on Day 1, Month 7 and Month 18 for anti-HPV testing.

All subjects receiving optional VAQTA™ will be followed for Serious Adverse Experience (SAE) events for 14 days following each vaccination.

SUBJECT SAMPLE: Approximately 1650 adolescents and preadolescents will be enrolled into 2 age strata (at the time of enrollment): 9 to 12 year olds and 13 to 15 year olds, in a ratio of ~2:1 (respectively). Enrollment will also be stratified by gender, in a ratio of ~1:1. At the time of enrollment, subjects must meet all inclusion criteria and must not meet any exclusion criteria. The study will not have a screening phase. All subjects enrolled will receive full-dose vaccine or placebo and will be included in the safety data analysis. The serology test results obtained at the Day 1 visit will be used to determine each subject's HPV exposure status at enrollment. Only subjects who demonstrate negative type-specific HPV serology test results at the Day 1 visit will be included in the immunogenicity analysis of the same HPV type.

DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN: Subjects will be randomized 2:1 to receive quadrivalent HPV vaccine (1100 subjects) or non-aluminum-containing-placebo (550 subjects) at the Day 1, Month 2, and Month 6 visits. The vaccine contains HPV L1 VLPs (HPV 6–20 µg, HPV 11–40 µg, HPV 16–40 µg, and HPV 18–20 µg), as well as 225 µg of aluminum adjuvant per dose. The placebo contains all excipients except HPV L1 VLPs and aluminum adjuvant. Each subject will receive one injection at **Day 1, Month 2, and Month 6 visits**. Vaccine or placebo will be given as a 0.5-mL intramuscular injection.

Because the vaccine and placebo can be visibly distinguished, the vaccine/placebo in this study must be prepared by an unblinded third party who is otherwise not involved in the conduct of the study.

All subjects in Spain will be offered VAQTA™ at the Month 18 visit after all study procedures for that visit have been completed. An additional Month 24 study visit will consist only of the administration of the booster dose of VAQTA™ and follow-up for Serious Adverse Experience (SAE) events. Participation will be voluntary. At the Month 18 visit, subjects will receive a single 0.5-mL dose of VAQTA™ that contains ~25U of hepatitis A virus antigen and ~225 µg of aluminum. A single 0.5-mL booster dose of VAQTA™ is to be administered at an additional Month 24 visit. VAQTA™ is for intramuscular injection; the deltoid muscle is the preferred site for intramuscular injection.

STUDY PROCEDURES: At the Day 1 visit, prior to obtaining informed consent, an informational brochure will be given to all subjects and their parent(s) or legal guardian(s). The purpose of this brochure is to provide the subject and guardian with information regarding HPV infection and the current study, and to screen for study eligibility without requiring the subject to reveal the reason for exclusion in those subjects that do not want to participate or do not meet inclusion criteria. If the subject and the parent/legal guardian agree to participate, written consent will be obtained from the subject's parent/legal guardian, and assent will be obtained from the subject, prior to the subject being entered into the study. If the subject meets inclusion/exclusion criteria, he/she will be randomized and assigned an allocation number.

A pregnancy test will be performed at the site prior to each injection for all female subjects at the Day 1 visit, Month 2 visit, and the Month 6 visit. Pregnancy test results must be available prior to any vaccination. Any subject found to be pregnant at the Day 1 visit will not be randomized and will not participate in the study. If a subject is found to be pregnant after the first vaccination, no further vaccinations will be given. However, the subject will be eligible to remain in the study and complete all subsequent study visits and other study procedures as scheduled. After randomization, all pregnancies (including discontinued subjects) will be followed to the completion/termination of the pregnancy. In addition, if the pregnancy continues to term, the outcome (health of the infant) must be reported to SPONSOR. (See Appendix 1, "Pregnancy Reporting and Follow-Up HPV Vaccine Clinical Program.")

A medical history will be obtained, and a physical exam will be conducted at the Day 1 visit for all subjects. A complete adverse experience assessment will be performed at the Month 2, Month 6, and Month 7 visits, and all subjects will be observed for at least 30 minutes after each vaccination for any immediate reaction.

Ten milliliters (10 mL) of blood samples for HPV 6, 11, 16, and 18 antibody assays will be obtained at Day 1 and Months 7 and 18 from all study subjects. **A volume of 3.0 mL serum is needed for this assay.** An additional 1.5 mL of serum, at the same time points as above, is to be stored at or below -20°C at the investigative site as retention serum samples. The SPONSOR will notify the site when the retention samples can be sent to the SPONSOR. Serology samples will be used to measure HPV type-specific serum responses following vaccination or natural exposure with vaccine HPV types.

A physical exam and final assessment will be performed at the Month 18 visit. The "Study Procedures by Visit" flow chart summarizes study procedures and specimen collection at each scheduled visit in the order in which the specimens should be obtained. (See Appendix 2, "Study Procedures by Visit.")

Serum samples will be tested for antibodies against the 4 HPV types contained in the vaccine. If a test result is above the lower cutoff in an adolescent subject at Day 1 (prevaccination), that

result will be communicated to the primary investigator who enrolled that subject. The investigator will then communicate that result to the subject and the subject's parent/guardian, together with appropriate counseling regarding what the result may mean in terms of current or previous HPV infection and how such infection may have occurred, as well as what follow-up may be necessary.

At any time during the study, a test for syphilis, hepatitis B serology, hepatitis C serology, and/or HIV test may be obtained if risk factors warrant such testing. Subjects who test positive for syphilis, HIV, hepatitis B (e.g., hepatitis B surface antigen [HBsAg]), or hepatitis C (e.g., hepatitis C antibody [HCAb]) once enrolled into the study may remain in the study and should be referred for appropriate counseling and treatment. Subjects with a positive HIV test will not be included in the immunogenicity analysis.

Ongoing education is to be provided to the subjects, which may include written materials (e.g., IRB/ERC-approved pamphlets from the clinical site), to increase the subject's knowledge base regarding HPV and other health-related issues.

All subjects in Spain that receive VAQTA™ (Months 18 and 24) will be observed for at least 30 minutes after each vaccination for any immediate reaction, with particular attention to allergic phenomena. All subjects receiving VAQTA™ will be followed for Serious Adverse Experience (SAE) events for 14 days following each vaccination.

At completion of the study, subjects' addresses and telephone numbers will be obtained by the study site investigator. After the study is completed, subjects who received placebo will be offered vaccination with the marketed HPV vaccine, if and when the vaccine becomes commercially available for the indication to be used in the subjects' population in the country where the subject was enrolled.

SAFETY MEASUREMENTS: Complete adverse experience (AE) assessments will be performed. All subjects will be observed for at least 30 minutes after each vaccination for any immediate reactions, with particular attention to any evidence of allergic phenomena. Temperatures will be recorded for 5 days following each injection (beginning 4 hours after the injection and **at approximately the same time** daily for the next 4 days). All AEs will be collected on the subject's Vaccination Report Card (VRC) daily for 15 days after each vaccination. At the Month 2, 6, and 7 visits, the VRC will be reviewed and subjects will be evaluated for any health concerns or serious adverse experiences (SAEs). At Month 12, subjects and their parents will receive a telephone call to review any new medical conditions or events that meet the protocol's definition of an SAE. At the Month 18 visit, a physical exam and final assessment will be performed on all study subjects. Safety measurements will include all clinical adverse experiences reported Days 1 to 15 following each vaccination and elevated temperatures (≥100°F, oral equivalent) for Days 1 to 5 following each vaccination injection (beginning 4 hours after the injection and **at approximately the same time** daily for the next 4 days). Safety evaluation is focused on VRC-prompted injection-site adverse experiences (swelling/redness and pain/tenderness/soreness), VRC-prompted systemic adverse experiences, severe adverse experiences, and fevers. A pregnancy test will be performed on female participants prior to each injection and pregnant subjects will not be vaccinated. All pregnancies (including discontinued subjects) are to be reported to the SPONSOR and will be followed to the completion or termination of the pregnancy. In addition, if pregnancy continues to term, the outcome (health of the infant) must be reported to the SPONSOR (See "Pregnancy Reporting and Follow-Up, HPV Vaccine Clinical Program," Appendix 1.)

All subjects in Spain that receive VAQTA™ will be observed for at least 30 minutes after each vaccination for any immediate reactions, with particular attention to any evidence of allergic phenomena. All subjects receiving VAQTA™ will be followed for Serious Adverse Experience (SAE) events for 14 days following each vaccination. All SAE events will be collected on the appropriate SAE worksheet. At 14 days following the optional VAQTA™ (Months 18 and 24) vaccinations, the subject's parent/guardian will receive a telephone call from the investigative site to determine if any SAEs occurred during the follow-up period.

IMMUNOGENICITY MEASUREMENTS: Serum samples will be collected on Day 1 and at the Month 7 and Month 18 visits, for measurement of anti-HPV 6, 11, 16, and 18 levels. Only those subjects who demonstrate negative type-specific anti-HPV serology test results at Day 1 visit will be included in the main immunogenicity analysis for a given HPV type.

DATA ANALYSIS: Incidences of all adverse events reported Days 1 to 15 and elevated temperatures (≥100°F, oral equivalent) reported Days 1 to 5 following each injection and any injection will be summarized by treatment group for each vaccination and across vaccinations. The 2 treatment groups will be compared with respect to the incidences of VRC-prompted AEs, SAEs and other AEs which occur in ≥1% of subjects in either treatment group. Comparisons will be made using risk differences and associated 95% confidence intervals; in addition, p-values will be provided for SAEs and VRC-prompted AEs (vaccine-related adverse experiences, injection-site adverse experiences (swelling/redness or pain/tenderness/soreness), systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), and fever). All subjects who received at least 1 injection and have follow-up data will be included in the primary safety analysis. The primary safety analysis will be performed on the pooled age and gender strata. In addition, adverse experiences will be summarized separately for boys and girls, but no formal comparisons will be performed. Site specific summaries of the incidences of SAEs will be provided by treatment group (Quadrivalent HPV Vaccine or Placebo) at the 14-day post Month 18 and 14-day post Month 24 time points for those subjects in Spain where VAQTA™ is administered at Month 18 and Month 24.

The primary hypothesis in this study relates to the tolerability of the quadrivalent HPV vaccine. If no vaccine-related SAEs are observed among 1100 vaccinated subjects, this study will provide 95% confidence (one-sided) that the true incidence is no greater than 0.27% and 80% confidence (one-sided) that the true incidence is no greater than 0.15%.

For the secondary analysis of immunogenicity, the null hypothesis for each HPV type is that the fold difference in GMTs between genders (boys/girls) is ≤0.5, and it will be tested against the alternative hypothesis that the fold difference in GMTs between genders (boys/girls) for the respective type is >0.5. A one-sided test at an α=0.025 significance level will be used to test the hypothesis for each HPV type. The statistical analysis will be based on the two-sided 95% confidence interval for the fold difference. For each HPV type, a lower bound on the confidence interval >0.5 will lead to a conclusion that the GMT for boys is noninferior to the GMT for girls with respect to that type. The vaccine must meet the noninferiority criterion for all 4 vaccine HPV types for success to be declared. In addition, reverse cumulative distribution functions (RCDFs) for Month 7 serum samples will be provided for each treatment group. The secondary immunogenicity analysis will be performed on a per-protocol basis. Per-protocol subjects are those who complete the vaccination regimen within acceptable day ranges, have at least 1 valid serology result after the third injection (within an acceptable day range), and adhere to protocol guidelines for vaccine administration. To be included in the immunogenicity summaries and analyses for HPV types 6 and 11, subjects must

be seronegative for both HPV types at the Day 1 visit; to be included in the immunogenicity summaries and analyses for HPV types 16 or 18, subjects must be seronegative for the respective type at the Day 1 visit. Supportive summaries and analyses including all subjects with valid serology will also be provided. **The immunogenicity analyses will be performed on the combined age strata; immune responses will also be summarized separately by age stratum, but no formal comparisons will be performed.**

Assuming a standard deviation for the log titer for each of the HPV types in the vaccine of 1.2 (based on previous studies), baseline seropositivity rates of 8, 9, and 9% for Types 6 and 11, Type 16 and Type 18, respectively, and assuming that 15% of subjects will be lost to follow-up by Month 7 (resulting in 847 evaluable subjects for Types 6 and 11 and 836 evaluable subjects for Types 16 and 18), this study has >99% power to declare noninferiority of the immune response in boys relative to girls.

ANY SERIOUS ADVERSE EXPERIENCE, INCLUDING DEATH DUE TO ANY CAUSE, WHICH OCCURS TO ANY SUBJECT FROM THE TIME THE CONSENT IS SIGNED THROUGH 14 DAYS FOLLOWING THE FIRST VACCINATION(S) AND FROM THE TIME OF ANY SUBSEQUENT VACCINATION(S) THROUGH 14 DAYS THEREAFTER, WHETHER OR NOT RELATED TO THE INVESTIGATIONAL PRODUCT, MUST BE REPORTED WITHIN 24 HOURS TO ONE OF THE INDIVIDUAL(S) LISTED ON THE SPONSOR CONTACT INFORMATION PAGE.

ADDITIONALLY, ANY SERIOUS ADVERSE EXPERIENCE BROUGHT TO THE ATTENTION OF AN INVESTIGATOR WHO IS A QUALIFIED PHYSICIAN AT ANY TIME OUTSIDE OF THE TIME PERIOD SPECIFIED IN THE PREVIOUS PARAGRAPH ALSO MUST BE REPORTED IMMEDIATELY TO ONE OF THE INDIVIDUALS LISTED ON THE SPONSOR CONTACT INFORMATION PAGE IF THE EVENT IS EITHER:

1. *A DEATH WHICH RESULTED IN THE SUBJECT DISCONTINUING THE STUDY*

OR

2. *A SERIOUS ADVERSE EXPERIENCE THAT IS CONSIDERED BY AN INVESTIGATOR WHO IS A QUALIFIED PHYSICIAN TO BE POSSIBLY, PROBABLY, OR DEFINITELY VACCINE RELATED.*

ALL SUBJECTS WITH SERIOUS ADVERSE EXPERIENCES MUST BE FOLLOWED UP FOR OUTCOME.

STUDY FLOW CHART

Event/Test	Consent	Visit and Treatment Months					
	Visit 1 (Day 1)	Visit 2 (Month 2)	Visit 3 (Month 6)	Visit 4 (Month 7)	Visit 5 (Month 12) Phone call	Visit 6 (Month 18)	Visit 7 (Month 24)
Information brochure/prescreening	+						
Obtain informed consent/assent	+						
Medical history/physical exam	+					+	
Specimen collection/laboratory measurements (in serial order):							
Pregnancy test†	+	+	+			+	+
Serum for antibody measurements‡							
HPV Serology (Types 6, 11, 16, 18)	+			+		+	
Retention serum, stored frozen at site	+			+		+	
Vaccination§	+	+	+				
Clinical follow-up for safety‖	+	+	+	+	+	+	
Optional VAQTA™ Vaccination¶						+	+
Clinical follow-up for SAEs only (VAQTA™ recipients)#						+	+

Note: Any test may be repeated if medically indicated.

† By a serum or urine test performed the day of vaccination. The urine pregnancy test must be sensitive to 25 IU HCG and be negative for vaccination. This test will be performed on the girls prior to any vaccinations.

‡ Serum for antibody measurements must be collected before vaccination. Assay testing to be performed at Merck Research Laboratories.

§ Temperature will be measured prior to each injection.

‖ Participants are observed at the study site for 30 minutes after each vaccination for immediate untoward effects. The participant's parent/guardian will record on a Vaccination Report Card (VRC) the participant's oral temperature beginning 4 hours after each injection and at approximately the same time daily for the next 4 days. Any injection-site or systemic complaint, which may occur on Day 1 or during the 14 calendar days after each injection, will also be recorded on the VRC. At Months 2, 6 and 7, the study personnel together with the participant's parent/guardian will review the VRC. At Months 2, 6, 7, 12 and 18, the subjects' parent/guardian will be solicited for any serious AEs that the subject may have encountered.

¶ **Optional VAQTA™ (Months 18 and 24) vaccinations will be offered to all subjects in Spain.**

Subjects in Spain that receive optional VAQTA™ (Months 18 and 24) vaccinations will be observed at the study site for 30 minutes after each vaccination for immediate untoward effects. At 14 days following the optional VAQTA™ (Months 18 and 24) vaccinations, the subject's parent/guardian will receive a telephone call from the investigative site to determine if the subject had an SAE.

SPONSOR CONTACT INFORMATION—U.S. SITE(S)

REPORTING OF SERIOUS ADVERSE EXPERIENCES

ANY SERIOUS‡ ADVERSE EXPERIENCE, INCLUDING DEATH DUE TO ANY CAUSE, WHICH OCCURS TO ANY SUBJECT FROM THE TIME THE CONSENT IS SIGNED THROUGH 14 DAYS FOLLOWING THE FIRST VACCINATION(S) AND FROM THE TIME OF ANY SUBSEQUENT VACCINATION(S) THROUGH 14 DAYS THEREAFTER, WHETHER OR NOT RELATED TO THE INVESTIGATIONAL PRODUCT, MUST BE REPORTED WITHIN 24 HOURS TO ONE OF THE INDIVIDUAL(S) LISTED ON THE SPONSOR CONTACT INFORMATION PAGE.

ADDITIONALLY, ANY SERIOUS ADVERSE EXPERIENCE BROUGHT TO THE ATTENTION OF AN INVESTIGATOR WHO IS A QUALIFIED PHYSICIAN AT ANY TIME OUTSIDE OF THE TIME PERIOD SPECIFIED IN THE PREVIOUS PARAGRAPH ALSO MUST BE REPORTED IMMEDIATELY TO ONE OF THE INDIVIDUALS LISTED ON THE SPONSOR CONTACT INFORMATION PAGE IF THE EVENT IS EITHER:

1. *A DEATH WHICH RESULTED IN THE SUBJECT DISCONTINUING THE STUDY*

OR

2. *A SERIOUS ADVERSE EXPERIENCE THAT IS CONSIDERED BY THE INVESTIGATOR TO BE POSSIBLY, PROBABLY, OR DEFINITELY VACCINE RELATED.*

ALL SUBJECTS WITH SERIOUS ADVERSE EXPERIENCES MUST BE FOLLOWED UP FOR OUTCOME.

[redacted], M.D., Ph.D.	Eliav Barr, M.D.
Associate Director, Clinical Research	Senior Director
Merck Research Laboratories, UN- C141	Merck Research Laboratories, UN- C141
Sumneytown Pike	Sumneytown Pike
West Point, PA 19486-0004	West Point, PA 19486-0004
Telephone – Office: [redacted]	Telephone – Office: [redacted]
FAX No.: [redacted]	FAX No.: [redacted]
24 Hour Contact: [redacted]	
or	or
[redacted]	Fran Alvarez, R.N.
Associate Medical Program Clinical Specialist	Senior Medical Program Clinical Specialist
Merck Research Laboratories, UN- C141	Merck Research Laboratories, UN- C141
Sumneytown Pike	Sumneytown Pike
West Point, PA 19486-0004	West Point, PA 19486-0004
Telephone – Office: [redacted]	Telephone – Office: [redacted]
FAX No.: [redacted]	FAX No.: [redacted]
24 Hour Contact: [redacted]	

‡ See Protocol Section I.G., Safety Measurements, for definitions of serious adverse experiences.

SPONSOR CONTACT INFORMATION—U.S. SITE(S) (CONT.)

RETURN ALL CLINICAL SUPPLIES WITH INVENTORY DOCUMENTATION TO:
See Protocol Section II.A., Labeling, Packaging, Storage, and Return of Clinical Supplies.

Clinical Packaging Technician
WP 17
Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486, U.S.A.

SHIP BIOLOGICAL SPECIMENS TO:
See Protocol Section II.B., Biological Specimens.

§ 47F
MRL/Clinical Sample Processing and Management Dock
466 Devon Park Drive
Wayne, PA 19087
U.S.A.
Telephone – Office: § 47F
FAX No.: § 47F

THE INVESTIGATOR WILL FORWARD THE ORIGINAL SIGNED SIGNATURE FORM(S) AND LABEL PAGES/DISCLOSURE ENVELOPES TO:
See Protocol Section II.C., Clinical and Laboratory Data Collection.

Research Information Mail Desk, UN-101
§ 47F g, M.D., Ph.D.
Merck Research Laboratories, UN-C141
Sumneytown Pike
West Point, PA 19486-0004
Telephone: § 47F

SPONSOR CONTACT INFORMATION—NON-U.S. SITE(S)

REPORTING OF SERIOUS ADVERSE EXPERIENCES

ANY SERIOUS‡ ADVERSE EXPERIENCE, INCLUDING DEATH DUE TO ANY CAUSE, WHICH OCCURS TO ANY SUBJECT FROM THE TIME THE CONSENT IS SIGNED THROUGH 14 DAYS FOLLOWING THE FIRST VACCINATION(S) AND FROM THE TIME OF ANY SUBSEQUENT VACCINATION(S) THROUGH 14 DAYS THEREAFTER, WHETHER OR NOT RELATED TO THE INVESTIGATIONAL PRODUCT, MUST BE REPORTED WITHIN 24 HOURS TO ONE OF THE INDIVIDUAL(S) LISTED ON THE SPONSOR CONTACT INFORMATION PAGE.

ADDITIONALLY, ANY SERIOUS ADVERSE EXPERIENCE BROUGHT TO THE ATTENTION OF THE INVESTIGATOR WHO IS A QUALIFIED PHYSICIAN AT ANY TIME OUTSIDE OF THE TIME PERIOD SPECIFIED IN THE PREVIOUS PARAGRAPH ALSO MUST BE REPORTED IMMEDIATELY TO ONE OF THE INDIVIDUALS LISTED ON THE SPONSOR CONTACT INFORMATION PAGE IF THE EVENT IS EITHER:

1. *A DEATH WHICH RESULTED IN THE SUBJECT DISCONTINUING THE STUDY*

OR

2. *A SERIOUS ADVERSE EXPERIENCE THAT IS CONSIDERED BY THE INVESTIGATOR TO BE POSSIBLY, PROBABLY, OR DEFINITELY VACCINE RELATED.*

ALL SUBJECTS WITH SERIOUS ADVERSE EXPERIENCES MUST BE FOLLOWED UP FOR OUTCOME.

‡ See Protocol Section I.G., Safety Measurements, for definitions of serious adverse experiences.

SPONSOR CONTACT INFORMATION—NON-U.S. SITE(S) (CONT.)

RETURN ALL CLINICAL SUPPLIES WITH INVENTORY DOCUMENTATION TO:
See Protocol Section II.A., Labeling, Packaging, Storage, and Return of Clinical Supplies.

Clinical Packaging Technician
WP 17
Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486, U.S.A.

SHIP BIOLOGICAL SPECIMENS TO:
See Protocol Section II.B., Biological Specimens.

§ 47F
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THE INVESTIGATOR WILL FORWARD THE ORIGINAL SIGNED SIGNATURE FORM(S) AND LABEL PAGES/DISCLOSURE ENVELOPES TO:
See Protocol Section II.C., Clinical and Laboratory Data Collection.

Research Information Mail Desk, UN-101
§ 47F, M.D., Ph.D.
Merck Research Laboratories, UN-C141
Sumneytown Pike
West Point, PA 19486-0004
Telephone: § 47F

HPV Adolescent/Preadolescent Safety Study

I. CLINICAL SECTIONS

A. BACKGROUND AND RATIONALE

1. Epidemiology

Over 50% of sexually active adults will become infected with human papillomavirus (HPV) during their lifetime [1]. HPV infection can result in 2 related anogenital diseases: dysplasia that may result in cancer, and genital warts. These diseases are associated with substantial morbidity and mortality [1]. Every year, 471,000 cases of cervical cancer are diagnosed worldwide [2]. The 5-year survival rate for this disease is ~70% [3]. In the developed world, routine Pap screening has reduced the incidence of cervical cancer by 75% [4]. However, sporadic Pap screening in the developing world and among the disadvantaged in the United States has failed to reduce the incidence of cervical cancer [2; 3; 5; 6]. The incidence of HPV-related anal cancer has doubled in the last 25 years [7]. Screening programs to detect early disease are not available. Genital warts cause significant morbidity [8 to 10]. The HPV types associated with genital warts also cause recurrent respiratory papillomatosis, a devastating pediatric disease that occurs by transmission of HPV from an infected mother to her child [11].

Over 90 HPV types have been identified [12]. HPV 16 and 18 cause ~70% of high-grade cervical dysplasia (cervical intraepithelial neoplasia 2/3 or CIN 2/3) cases and cervical and anal cancers, whereas HPV 6 and 11 cause >90% of genital warts [1]. HPV 6, 11, 16, or 18 are present in ~50% of low-grade cervical dysplasia (CIN 1) cases [1]. Therefore, a prophylactic vaccine that reduces infection with these 4 HPV types will greatly reduce the burden of HPV disease in men and women.

2. Merck's Ongoing HPV Vaccine Clinical Program

More than 4300 women have been enrolled in 6 HPV vaccine clinical studies. More than 2700 received ≥1 dose of an HPV vaccine. In all studies, vaccines were administered at Day 1, Month 2, and Month 6 visits.

a. Demographic and Behavioral Characteristics of the Study Population

Most of Merck's HPV vaccine studies have enrolled young women with ≤5 lifetime male sexual partners to reduce the enrollment of those who had already acquired a vaccine-type HPV infection. However, some study subjects were seropositive for ≥1 vaccine-type HPV or had PCR evidence of infection with ≥1 vaccine-type HPV at enrollment. For analysis of immunogenicity to each vaccine type, only subjects who were PCR-negative and seronegative to the vaccine HPV type being analyzed were included (for example, for analysis of HPV 16 vaccine immunogenicity, only baseline HPV 16 negative subjects were included). All enrolled subjects have been included in analyses of vaccine safety.

b. Tolerability of HPV Vaccines (Preliminary Data)

Monovalent HPV Vaccines

In monovalent HPV vaccine studies that are not in-house blinded, the incidences of systemic and injection site adverse experiences (AEs) were comparable between vaccinees (n=643) and placebo recipients (n=120). There have been no serious AEs (SAEs) attributed to the vaccines to date.

Protocol 005 is a prospective, double-blind, placebo-controlled efficacy study of HPV 16 VLP vaccine. Pooled AE data from Protocol 005 (N=2392) are available. In the study, 0.3% of the cohort experienced an SAE (none vaccine related); 0.3% discontinued due to a nonserious AE (mostly due to a vaccine/placebo-related AE).

Quadrivalent HPV Vaccine

An interim analysis of Protocol 007 was conducted to select the formulation of HPV vaccine for use in this study. Based on safety and immunogenicity data, the formulation chosen includes 20, 40, 40, and 20 µg of HPV 6, 11, 16, and 18 L1 VLPs, respectively, along with 225 µg of Merck Aluminum Adjuvant. Table 1 presents the overall AE rates for this formulation and for alum (225 µg/dose) placebo. In the study, 286 subjects received ≥1 dose of quadrivalent HPV vaccine 20/40/40/20 µg formulation, and 145 subjects received alum (225 µg/dose) placebo. There was a slight increase in injection site AE rates in vaccine-recipients compared with placebo-recipients. The incidence of systemic AEs were comparable among treatment groups. The most common local adverse experience was pain/tenderness at the injection site. The most common systemic adverse experience was headache.

Table 1

Clinical Adverse Experience Summary
(Day 1 Through 15 Post-Vaccination)
(Incidence ≥2% Per Treatment Arm to Preserve Blinding)

	20/40/40/20 (N=286)		Placebo 225 (N=145)	
	n	(%)	N	(%)
Number of subjects	286		145	
Subjects without follow-up	4		1	
Subjects with follow-up	282		144	
Number (%) of subjects				
With no adverse experience	31	(11.0)	22	(15.3)
With one or more adverse experience	251	(89.0)	122	(84.7)
Injection-site adverse experiences	232	(82.3)	103	(71.5)
Systemic adverse experiences	183	(64.9)	92	(63.9)
With vaccine-related adverse experiences[†]	242	(85.8)	110	(76.4)
Injection-site adverse experiences	232	(82.3)	103	(71.5)
Systemic adverse experiences	97	(34.4)	48	(33.3)

Percentages are calculated based on the number of subjects with follow-up after each visit.
[†] Determined by the investigator to be possibly, probably, or definitely related to vaccine.

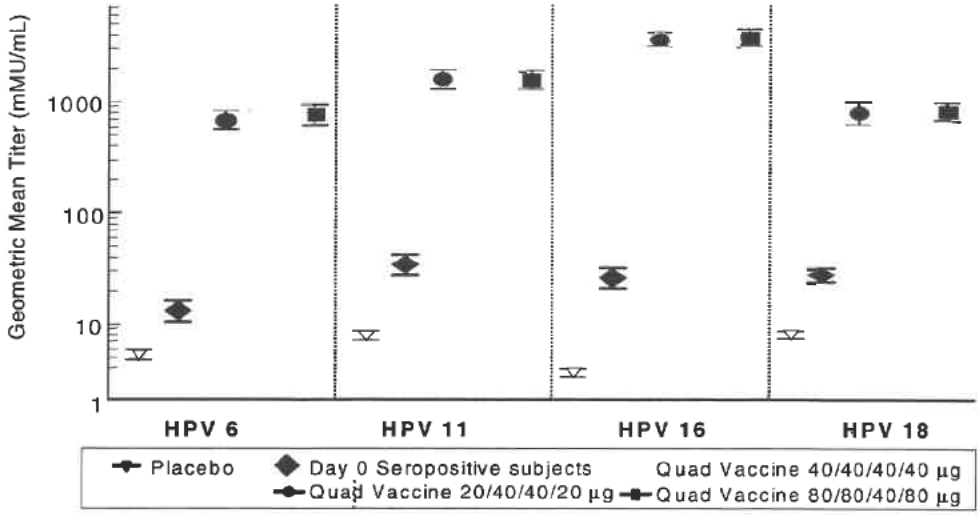
Further information can be obtained in the "Quadrivalent HPV Vaccine Confidential Investigator Brochure."

c. Immunogenicity of the Quadrivalent HPV Vaccine

The interim analysis of Protocol 007 showed that all formulations of quadrivalent HPV vaccine induced high-titer anti-HPV 6, 11, 16, and 18 cRIA geometric mean titers (GMTs) Postdose 3. A dose-response relationship for anti-HPV responses was not seen. Protocol 007 enrolled some subjects who were seropositive for HPV 6, 11, 16, and/or 18 at baseline. These subjects had been infected with HPV prior to enrollment and had mounted an anti-HPV response to this infection. Such subjects provide a reference against which to examine vaccine-induced anti-HPV responses. All vaccine formulations achieved anti-HPV 6, 11, 16, 18 GMTs that were substantially higher than those associated with an ongoing or previous infection with vaccine-HPV types (**see Figure 1**).

Figure 1

Protocol 007 Phase IIb Quadrivalent HPV Vaccine Dose-Ranging Study Postdose 3 Anti-HPV cRIA GMTs With 95% Confidence Intervals in Subjects Who Were Seronegative and PCR Negative for the Relevant HPV Type at Baseline Compared With Seronegative Placebo Recipients and With Day 1 Anti-HPV GMTs in Subjects Who Were Seropositive at Baseline (Interim Analysis—Preliminary Data)



3. Rationale for the Current Study

Anogenital HPV is a sexually transmitted disease. The incidence of HPV infection peaks soon after the onset of sexual activity [13]. Therefore, an effective program to prevent HPV infection and disease through prophylactic immunization would ideally target individuals immediately prior to coitarche. In the United States, ~49% and 48% of high school male and female students, respectively, have had sexual intercourse. By age 15, 38% of students will have experienced coitarche [14]. These data suggest that preadolescents and adolescents represent an attractive target age group to implement HPV vaccination programs. Merck's HPV vaccine program has demonstrated that the

quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is highly immunogenic and generally well tolerated in young adult women (age ≥16 years). A separate program, consisting of 2 studies, will: (1) bridge the efficacy of the HPV vaccine (demonstrated in 16 to 23 year olds) to adolescents; and (2) evaluate vaccine tolerability in preadolescents and adolescents. Protocol 016 is an ongoing study to address safety and immunogenicity of the quadrivalent vaccine in younger aged subjects. In Protocol 016, 500 boys aged **10** to 15 years and 500 girls aged **10** to 15 years will receive the full dose quadrivalent HPV vaccine. Protocol 018 will further expand the exposure and immunogenicity database in preadolescents and adolescents. In addition, this study will provide important tolerability information, including: (a) comparison to a non-aluminum-containing placebo; (b) safety follow-up for 12 months post-vaccination, and (c) active surveillance for common systemic AEs. The protocol is focused on a detailed tolerability analysis**.** The prespecified adverse experiences are VRC-**prompted** injection-site adverse experiences, VRC-**prompted** systemic adverse experience, severe adverse experience, and fever.

Comparisons of immune responses to vaccine-HPV type L1 VLPs will be made only in subjects who are naïve for the particular vaccine-HPV type. To ensure that subjects are HPV-naïve, the protocol will enroll only subjects who are virgins at Day 1 and who do not plan to become sexually active over the 18 months of the study (cervical and external genital HPV testing will not be feasible due to the age of the subjects). The main immunogenicity cohort will consist only of subjects who are HPV-naïve for the HPV types of interest at baseline. For HPV 6 and 11 L1 VLPs, the evaluable cohort will include subjects who are seronegative for both HPV 6 and 11 at baseline (Day 1). For HPV 16, the evaluable cohort will include subjects who are seronegative for HPV 16 at baseline (Day 1). For HPV 18, the evaluable cohort will include subjects who are seronegative for HPV 18 at baseline (Day 1). All subjects will be included in the evaluation of vaccine tolerability.

Rationale for the Amendment

To address the concern of Spain's Ethics Review Committee regarding the use of a placebo arm in this age group, all subjects in Spain, both vaccine and placebo recipients, will be eligible to receive optional VAQTA™[1] vaccinations. The purpose of this supplement is to enhance the benefits to study participants in Spain.

[1] VAQTA is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

B. OBJECTIVES

Primary Safety Objectives

To demonstrate that a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents.

Secondary

1. **To demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls.**

2. To describe the persistence of immune response to the quadrivalent HPV (Types 6, 11, 16, 18) LI VLP vaccine, when given in a 3-dose regimen.

C. HYPOTHESES

Primary Safety Hypotheses

The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents.

Secondary Hypotheses

The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine induces noninferior immune responses with respect to each of the vaccine components individually at Week 4 Postdose 3 in preadolescent and adolescent boys who are seronegative to the relevant HPV type at Day 1, relative to preadolescent and adolescent girls who are seronegative to the relevant HPV type at Day 1.

(The statistical criterion for noninferiority requires that the lower bounds of the 95% confidence intervals for the fold difference in GMTs (boys/girls) exclude a decrease of 2-fold or more. Each vaccine HPV type will be analyzed separately.)

D. SUBJECT DEFINITION

1. Inclusion Criteria

a. Healthy preadolescents or adolescents between the ages 9 years and 0 days and 15 years and 364 days.

b. Must not yet have had coitarche and does not plan on becoming sexually active through the course of the study.

c. Must agree to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes.

d. No temperature ≥100°F or ≥37.8°C (oral) within 24 hours prior to the first injection.

e. Not pregnant now (as determined by a serum pregnancy test or urine pregnancy test sensitive to 25 IU HCG) or is a male.

2. Exclusion Criteria

a. Individuals concurrently enrolled in clinical studies of investigational agents or studies involving collection of cervical specimens.

b. History of known prior vaccination with a HPV vaccine.

c. Receipt of inactivated vaccines within 14 days prior to enrollment or receipt of live virus vaccines within 21 days prior to enrollment.

d. History of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention.

e. Individuals allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).

f. Individuals who have received any immune globulin preparation (including RhoGAM™ [Ortho-Clinical Diagnostics, Inc.]) or blood-derived products within the 6 months prior to the first injection, or plan to receive any through the completion of the study.

g. Individuals with a history of splenectomy, known immune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis), or receiving immunosuppressives (e.g., substances or treatments known to diminish immune response such as radiation therapy, administration of antimetabolites, antilymphocytic sera, systemic corticosteroids). Individuals who have received periodic treatments with immunosuppressives, defined as at least 3 courses of systemic corticosteroids each lasting at least 1 week in duration for the year prior to enrollment, will be excluded. Subjects using topical steroids (i.e., inhaled or nasal) will be eligible for vaccination.

h. Individuals with known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

i. Any condition which in the opinion of the investigator might interfere with the evaluation of the study objectives.

j. Any plan to permanently relocate from the area prior to the completion of the study or to leave for an extended period of time when study visits would need to be scheduled.

k. Individuals who are immunocompromised or have been diagnosed as having HIV infection.

l. History of recent or ongoing alcohol or other drug abuse.

   Alcohol abusers are defined as those who drink despite recurrent social, interpersonal, and legal problems as a result of alcohol use.

m. Inability to give consent/assent.

E. STUDY DESIGN

1. Summary of Study Design

This is a randomized, double-blind (with third party blinding for vaccination and in-house blinding procedures), placebo-controlled, multicenter safety and immunogenicity study in preadolescents and adolescents aged 9 to 15 years at the time of enrollment (age X is defined as the time period from X^{th} birthday to the last day before $(X+1)^{th}$ birthday). Enrollment will be stratified by age and gender. The age range will be divided into 2 strata ages: 9 to 12 years and 13 to 15 years at enrollment. The ratio of children enrolled into the 2 age strata will be ~2:1 (respectively). The ratio of boys to girls enrolled will be ~1:1. Approximately 1650 subjects will be randomized in a 2:1 ratio to receive either quadrivalent HPV vaccine or non-aluminum-containing-placebo. For each subject enrolled, the duration of the study will be ~1.5 years with a possible extension for subjects in Spain that volunteer to receive VAQTA™.

Study vaccine or placebo will be administered at the Day 1, Month 2, and Month 6 visits. All subjects will be followed for Adverse Experiences (AEs). A pregnancy test will be performed before each injection on all female subjects. Any female subject with a positive pregnancy test at Day 1 will not be vaccinated and will not be allowed to participate in the study. Female subjects with a positive pregnancy test after Day 1 will not be vaccinated; however they will be eligible to continue to participate in the study.

A medical history and physical examination will be conducted at Day 1 for all subjects. Vital signs will be taken prior to each vaccination. Serum samples will be obtained at Day 1, Month 7 and 18 from all subjects for anti-HPV 6, 11, 16 and 18 testing. A medical history and physical exam will be performed at the Month 18 visit. The "Study Procedures by Visit" flow chart summarizes study procedures and specimen collection at each scheduled visit in the order in which the specimens should be obtained. (See Appendix 2, "Study Procedures by Visit.")

VAQTA™ will be provided to all subjects at the Month 18 study visit after all study procedures for that visit have been completed and at an additional Month 24 study visit which will consist only of the administration of the booster dose of VAQTA™ and follow-up for Serious Adverse Experience (SAE) events. All subjects in Spain are eligible to receive VAQTA™. Subject participation is voluntary. All subjects receiving optional VAQTA™ will be followed for Serious Adverse Experience (SAE) events for 14 days following each vaccination.

2. Treatment

a. Treatment Plan

Participants will receive a total of 3 intramuscular injections of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine at Day 1, Month 2 (±3 weeks), and Month 6 (±4 weeks). Approximately 1100 subjects will be randomized to receive the full-dose formulation (HPV 6—20 µg, HPV 11—40 µg, HPV 16—40 µg and HPV 18—20 µg). Each subject will receive one injection at each vaccination visit (Day 1, Month 2, and Month 6). The vaccine formulation contains 225 µg of aluminum adjuvant per dose. Vaccine will be given as a 0.5-mL intramuscular injection, preferably in the nondominant arm. The deltoid muscle is the preferred site for intramuscular injection in adolescents and preadolescents. Data suggest that injections given in the buttocks frequently are given in fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate than was expected. Therefore, the vaccine is not to be administered into the buttocks. A needle that is long enough to ensure intramuscular deposition of vaccine should be used for both injections. Vaccine should be administered using a 1.0-mL

syringe with the following needle length and gauge specifications: 1 to 1.5 inches, 22 to 23 gauge, for males ≤120 kg; 1 inch, 22 to 23 gauge, for females <70 kg; 1.5 inches, 22 to 23 gauge, for females 70 to 100 kg; and 2 inches, 22 to 23 gauge, for males >120 kg and females >100 kg. If the injection is given in the thigh, a 1½-inch needle, 22 to 23 gauge, should be used.

Distribution of clinical supplies will be managed through the Interactive Voice Response System (IVRS). At Day 1 visit, study personnel will access the IVRS after a subject has met inclusion/exclusion criteria and has signed the consent/assent form. The IVRS will assign the subject an allocation number and then subsequently assign a unique vial identification number for the vial of clinical material the subject should receive at that visit. IVRS will assign the proper clinical material based on the subject's treatment allocation. The study personnel will access IVRS at each subsequent visit when administration of vaccine is to occur for assignment of a unique vial identification number for the clinical material to be administered to the subject.

Used vials may be discarded per site's handling of hazardous waste after documentation of vaccine administration/accountability guidelines have been met. The unused vials should be returned to the SPONSOR by the SPONSOR representative or subsidiary representative at the completion of the study. All vaccine should be appropriately accounted for on the vaccine accountability log sheet contained within the Administrative Binder.

b. Clinical Material

1) Quadrivalent HPV L1 VLP Vaccine

The vaccine is provided by the SPONSOR in single-dose vials containing a target volume of 0.75 mL. The vaccine will be administered as a 0.5-mL dose. Each 0.5-mL dose contains 225 µg of aluminum as amorphous aluminum hydroxyphosphate sulfate (Merck-alum). The vaccine must be stored between 2 to 8°C (36 to 47°F) range. **Freezing destroys the vaccine.** If vaccine freezes or is subjected to freezing temperatures, it should not be used. Refrigerator temperature logs should be maintained at each vaccine storage site and storage temperatures should be monitored daily. Should the refrigerator go out of the 2 to 8°C (36 to 47°F) range, IVRS technical support and the SPONSOR should be notified immediately, and vaccine must not be administered until notification from the SPONSOR.

2) **Placebo**

To provide an appropriate control for the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine, the placebo used in this study will contain the exact ingredients as in the vaccine except HPV L1 VLPs and aluminum adjuvant. Placebo will be provided by the SPONSOR in single-dose vials containing a target volume of 0.75 mL. The placebo dose will be administered as a 0.5-mL dose. Storage conditions should be identical to those for the vaccine. Should the refrigerator go out of the 2 to 8°C (36 to 47°F) range, IVRS technical support and the SPONSOR should be notified immediately. **Subjects who received placebo will be offered vaccination with the marketed HPV vaccine, if and when the vaccine becomes commercially available for the indication to be used in the subjects' population in the country where the subject was enrolled.**

3) **Labeling of Material for Injection**

The HPV quadrivalent vaccine/placebo used for the study is supplied in a vial. A double-panel, blinded label will be affixed to each vial.

Each vial of vaccine will bear a unique component identification number. **This number is not the subject's allocation number**.

The clinical supplies will be managed by an Interactive Voice Response System (IVRS). The IVRS will assign an allocation number and appropriate component identification number for the vaccination. Upon subsequent visits, the site coordinator will enter the IVRS (using a password) and provide the subject's allocation number and visit number. The IVRS then assigns the appropriate component identification numbers to be used for subject vaccination. The IVRS verbally confirms each transaction and faxes a confirmation sheet, detailing the IVRS transaction, to the investigator site. This documentation is to be retained in the subject's files.

All clinical material (i.e., vaccine) must be accounted for by appropriately documenting the administration (or wasting) of each vial. Upon receipt at the site, any empty or partially empty vials must be disposed of according to standard methods for handling medical hazardous waste, AFTER the SPONSOR representative is able to account for all of the vials originally shipped to the site. IVRS is to be notified immediately of the condition of damaged vials at the time of shipment receipt at the site.

4) Subject Blinding

This is a double-blind (operating under in-house blinding procedures) study in which the parent/guardian of the subject, the subject enrolled, the investigator(s) (except for the unblinded study personnel responsible for preparation and administration of vaccine/placebo), and SPONSOR personnel will be blinded to the vaccine(s) received until all subjects have completed the study, the data have been screened for completeness and accuracy, and protocol violators have been identified. The roles and responsibilities of the blinded and unblinded personnel are defined in I.E.3.g.1) and 2).

5) Subject Unblinding

The subject's treatment groups should only be unblinded in the case of a medical emergency. Every effort should be made to contact the SPONSOR. If the SPONSOR cannot be reached prior to unblinding, the subject's treatment group can be unblinded by calling the IVRS technical support and entering the unblinding password in the "unblinding" option. This menu option is available to the investigator only. Any unblinding that occurs at the site must be documented. A blinded confirmation fax will be sent to the SPONSOR if a subject is unblinded through the IVRS. This documentation is to be retained in the subject's files. Additional information for the unblinding of serious adverse experiences (SAEs) can be found in Section I.G.3.

6) VAQTA™ [Hepatitis A Vaccine, Purified Inactivated], Merck & Co., Inc.

The pediatric/adolescent formulation 0.5-mL single dose vial of VAQTA™ Hepatitis A Vaccine, Purified Inactivated contains ~25U of hepatitis A virus antigen adsorbed onto ~225 µg of aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 35 µg of sodium borate as a pH stabilizer, in 0.9% sodium chloride. VAQTA™ is for intramuscular injection; the deltoid muscle is the preferred site for intramuscular injection.

VAQTA™ must be stored between 2 to 8°C (36 to 46°F) range. Freezing destroys potency. VAQTA™ will be funded and distributed by the SPONSOR.

c. **Prior and Concomitant Medication(s)/Treatment(s)**

The placebo used in this study does not contain aluminum that may be present in nonstudy vaccines as Alum adjuvant. Therefore, it is recommended that the administration of nonstudy vaccines be deferred until the end of the study. If this is not feasible, the information of vaccination with nonstudy vaccines should be recorded on previous and/or concomitant nonstudy vaccination worksheets for every subject enrolled in the study and a summary of nonstudy vaccines should be generated.

To reduce their potential interference with the evaluation of the immunologic response and reactogenicity of the study vaccine, nonstudy inactivated vaccines must not be received within the 14 days before or 14 days after any dose of study vaccine. Nonstudy live virus vaccines must not be received within the 21 days prior to or 14 days after any dose of study vaccine. Immune globulin (including Rho-GAM™) or blood-derived products must not be administered within 6 months prior to vaccination, and should not be administered at any time during the study. Any such treatment should be discussed with the clinical monitor. If the subject receives any oral or parenteral corticosteroids, then the interval between the end of the course of corticosteroid and vaccination must be at least 2 weeks.

Subjects may receive allergen desensitization therapy and tuberculin testing while participating in this study.

d. **Diet/Activity/Other**

No special restrictions will apply except for those noted under the inclusion/exclusion criteria.

3. **Study Procedures (See Appendix 2, Study Procedures by Visit)**

a. **Informational Brochure and Prescreening**

At the Day 1 visit, prior to obtaining informed consent, an informational brochure will be given to all subjects and their parent or legal guardian. The purpose of the brochure is to provide the subject and parent with information regarding HPV infection as well as a brief description of the vaccine and the study. It will outline the duration of the study and the number of study visits as well as study procedures, such as the number of vaccine injections and the number of venipunctures required. In addition, the brochure will contain a section that will query whether the subject is interested in participating in the study. Considerations for participation contained in this section will include the willingness to undergo the study procedures described in the brochure, as

well as an outline of conditions that exclude participation, including history of sexual debut or plan of becoming sexually active during the study period. The purpose of this section of the brochure is to screen for eligible subjects in this age group. The subject will not be required to specify a justification for nonparticipation, if that is his or her choice. For example, a portion of them may have had sexual debut and may not want this information disclosed to their parents. If both the subject and the parent agree to participate, written consent will be obtained.

b. Consent

Written consent must be obtained from each subject's legal guardian and written assent must be obtained from each subject, prior to the subject being entered into the study. If the subject meets inclusion/exclusion criteria, he/she will be randomized and assigned an allocation number prior to vaccine administration. A copy of the signed consent and assent forms will be given to each subject for his/her records. Verification of the subject's identity and age is to be determined prior to obtaining written consent.

Nonrandomized Subjects

If a legal guardian has signed an informed consent form and a subject has signed an assent form but is not randomized, the investigator must submit a STATUS case report form to the SPONSOR for the subject. This form reports basic demographics and the reason(s) for exclusion. The investigator shall also submit an AE form if applicable. Unless otherwise directed, no other data need be submitted for these subjects.

Subject Discontinuation/Withdrawal

Subjects may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject has been discontinued/withdrawn due to an adverse experience (telephone or FAX). When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. **When a subject discontinues from test therapy but is continuing in the study, a status form must be completed along with all of the worksheets for that visit except the RXV worksheet.** Any adverse experiences which are present at the time of discontinuation/withdrawal should be documented according to the safety requirements outlined in Sections I.G.2.a. and b.

A single subject cannot be assigned more than one allocation number.

c. Medical History/Examinations, Scheduled Procedures

A medical history and physical examination will be conducted at Day 1 on all subjects. The Physical exam will include temperature, height, weight, sitting blood pressure, sitting pulse rate, and respiration rate.

Ten milliliters (10 mL) of blood samples will be collected from all subjects at Day 1, Month 7 and Month 18 visits for HPV 6, 11, 16, and 18 antibody assays. **A volume of 3.0 mL of serum is needed for this assay.** An additional 1.5 mL of serum, at the same time points as above, is to be stored at the investigative site. This retention serum should be stored in a labeled vial provided by the SPONSOR in a freezer at -20ºC or below until shipped frozen on dry ice to the address of the SPONSOR upon request only. The SPONSOR will notify the site when the retention samples can be sent to the SPONSOR.

All study examinations and specimen collection will take place prior to vaccination on Day 1, Month 2 and Month 6 visits. Temperature measurement and a serum or urine pregnancy test (females only) will be done prior to each injection. If the subject has had a temperature of ≥100˚F or ≥37.8˚C (oral) within 24 hours prior to an injection, the injection will be postponed. A pregnancy test (sensitive to 25 IU β-hCG) will be performed at the investigative site prior to each injection on all female subjects on Day 1, Months 2, and Month 6 visits. Pregnancy test results must be available before vaccination. Any subject with a positive pregnancy test must not be vaccinated. Any subject found to be pregnant at the Day 1 visit will not be randomized and will not participate in the study. If a subject is found to be pregnant after the first vaccination, no further vaccinations will be given. However, the subject will be eligible to remain in the study and complete all subsequent study visits and other study procedures as scheduled. After randomization, all pregnancies through Month 7 (including discontinued subjects) will be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant) must be reported to SPONSOR. (See Appendix 1, "Pregnancy Reporting and Follow-Up HPV Vaccine Clinical Program.")

Serum samples will be tested by serology assay for antibodies against the 4 HPV types contained in the vaccine. If a serology result of a subject's specimen is above the lower cutoff in a subject at Day 1 (prevaccination), that result will be communicated to the primary investigator who enrolled that subject. The investigator will then communicate that result to the subject and the subject's parent/guardian, together with appropriate counseling regarding what the result may mean in terms of current or previous HPV infection and how such infection may have occurred, as well as what follow-up may be necessary.

A physical exam and final assessment will be performed at the Month 18 visit. The exam will include temperature, weight, sitting blood pressure, sitting pulse rate, and respirations.

d. Study Visit Requirements

Subjects and study personnel should adhere to the following procedures: if necessary, any scheduled visit may be rescheduled within the allowed time range of ±3 weeks (Month 2) or ±4 weeks (Months 6, 12, and 18). The interval between the Month 6 and Month 7 visit should be a minimum of 3 weeks and a maximum of 7 weeks from the previous vaccination. For study visits that include vaccinations, study personnel should verify by verbal history that:

1) Subjects have not had a temperature of ≥100°F or 37.8°C (oral) within 24 hours prior to each injection. If the subject had a temperature ≥100°F or 37.8°C (oral) within 24 hours prior to an injection, the injection will be postponed.

2) Subjects must not have received a course of systemic corticosteroids or any other immunosuppressive agent before a vaccination is due. If systemic corticosteroids or other immunosuppressive treatment have been received, vaccination should be postponed for at least 2 weeks after completion of the medication regimen.

e. Collection and Handling of Specimens Obtained During Scheduled Visits

Procedures should be conducted in the order listed in Appendix 2, Study Procedures by Visit. The Chart identifies each study procedure and the documentation needed to complete each study visit. The following are the step-by-step procedures for collecting specimens for the mandatory protocol-specified tests, the supplies needed to perform these examinations, and the procedures for handling and transporting the specimens for processing and/or testing.

1) Serum or Urine Specimen for Pregnancy Test

Procedure should be performed as per the manufacturer's instructions at the investigative site at the Day 1, Month 2, and Month 6 visits (prior to study vaccination).

2) Serum for Antibody Measurements

Luminex Assay (a competitive immunoassay developed by Merck Research Laboratories using technology from the Luminex Corporation, Austin, TX, hereafter referred to as the Luminex assay) for Quantitation of Antibodies to HPV 6, 11, 16 and 18:

Serum will be collected from all subjects at Day 1 and Months 7 and 18. A 10-mL blood specimen (in nonheparinized, red top tubes without a serum separator) will be collected and serum separated, avoiding any hemolysis. A minimum of 3.0 mL of serum should be aliquotted to a labeled vial for testing of antibodies by the SPONSOR.

All sera should be stored in the labeled vials provided by the SPONSOR in a freezer at -20°C or below until shipped frozen on dry ice to the address noted on SPONSOR Contact Information page. The freezer must be a non-frost-free freezer.

Retention serum: An additional 1.5 mL of serum, at the same time points as above, is to be stored at the investigative site. This retention serum should be stored in a labeled vial provided by the SPONSOR in a freezer at -20°C or below until shipped frozen on dry ice to the address of the SPONSOR upon request only. The SPONSOR will notify the site when the retention samples can sent to the SPONSOR.

f. Assignment of Allocation Number and Vaccine

Randomization

For study randomization, an allocation schedule will be generated by the Clinical Biostatistics department of the SPONSOR. Throughout this study and across all study sites, there will be no repetition of an allocation number. Subjects will be assigned an allocation number at the time of randomization on Day 1. This department will also generate a schedule for the component identification numbers that will be used to identify the vials of vaccine or placebo that correspond to the subject's treatment group for the purpose described below.

An Interactive Voice Response System (IVRS) will be used to allocate clinical subjects and assist with vaccine supplies management at the study site. At the first visit, study personnel will access the IVRS after a subject has signed the consent form and the subject has met the inclusion/exclusion criteria. The IVRS will assign the subject an allocation number and then assign a unique vial identification number for the vial of clinical material the subject should receive at that visit. The IVRS will assign the appropriate clinical material based on the subject's treatment allocation. The study personnel will access IVRS at each subsequent visit when administration of vaccine is to occur for assignment of a unique vial identification number for the clinical material to be administered to the subject.

Once assigned, a subject's allocation number will never change, and that allocation number cannot be reused for any reason. Allocation numbers for subjects who discontinue or withdraw may not be reassigned.

Nonrandomized Subjects

If a subject has signed an informed consent form but the subject is not randomized, the investigator must submit a STATUS form to the SPONSOR for the subject. This form reports basic demographics and the reason(s) for exclusion. The investigator shall also submit an AE form if applicable. Unless otherwise directed, no other data need be submitted for these subjects.

g. Vaccine/Placebo Administration (see details in Vaccine Administration Guideline)

The Roles of Unblinded and Blinded Personnel in Preparation for Administration

Because of the differences in the appearance of the vaccine and placebo, unblinded personnel is required for vaccine/placebo administration in order to minimize bias. The subjects will be seen first by the blinded personnel, who will provide subjects with an informational brochure and obtain eligible subjects' consent/assent. The blinded study personnel will access IVRS, and IVRS will assign the subject with an allocation number and then subsequently assign a unique vial identification number for the vial of clinical material that the subject should receive at that visit. Review of medical history and the physical exam will be also conducted by the blinded personnel; the demographic information needed for vaccine/placebo preparation including the body weight, will be provided to the unblinded personnel. The unblinded third party will be responsible for vaccine preparation and injection, but will not disclose the contents of the syringe to the subject, the parent/legal guardian, the blinded study personnel/ investigator, or SPONSOR'S personnel until all subjects have completed the study, the data have been screened for completeness and accuracy, and protocol violators have been identified. The unblinded study personnel are considered unblinded during the course of the study because of their responsibilities in preparation and administration of the clinical materials, and they are therefore NOT involved with subject management. Subjects will be monitored by the blinded study personnel after vaccination is completed.

1) Preparation and Administration of the Vaccine by Unblinded Personnel

The unblinded study personnel will be responsible for obtaining the allocation number from the blinded study personnel, selecting the appropriate vial from the refrigerator, withdrawing, and verifying the volume and contents of the syringe. The unblinded personnel will record the subjects' allocation number, date, and their own initials onto the appropriate worksheet. The unblinded personnel will be responsible for documentation that pertains to vaccine accountability.

The vaccine should be used as supplied. No dilution is required before administration. The vaccine vial should be thoroughly mixed before administration by gently "rolling" the vial between the palms of both hands for 30 seconds before withdrawing the suspension with a syringe. The 0.5-mL dose should be withdrawn from the vial containing 0.75 mL of injectable material.

The unblinded study personnel will then wrap the syringe with the nontransparent label provided by the SPONSOR to mask the slight difference in appearance between vaccine and placebo.

Vaccine should be administered using a 1.0-mL syringe with the following needle length and gauge specifications: 1 to 1.5 inches, 22 to 23 gauge, for males ≤120 kg; 1 inch, 22 to 23 gauge, for females <70 kg; 1.5 inches, 22 to 23 gauge, for females 70 to 100 kg; and 2 inches, 22 to 23 gauge, for males >120 kg and females >100 kg. If the injection is given in the thigh, a 1½-inch needle, 22 to 23 gauge, should be used.

The 0.5-mL injection of vaccine will be administered intramuscularly at Day 1, Month 2, and Month 6 visits. Injections should be administered at a 90° angle into the deltoid muscle using a 1.0-mL syringe with the appropriate needle length and gauge specifications. All vaccinations should be given in the nondominant arm. However, if this is not feasible, the dominant arm may be used. If it is subject's preference, the injection may be given in the thigh. Injections should not be given within 2 cm of a tattoo, scar, or skin deformity. Data with other vaccines suggest that injections given in the buttocks frequently are given in fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate than was expected. Therefore, the vaccine is not to be administered into the buttocks.

After completing vaccine administration, the unblinded study personnel will leave the exam room immediately, and will have no further contact with the subject or parent/guardian during vaccination or during the 15-day follow-up period.

2) **Observing Subjects After Vaccination by Blinded Personnel**

The blinded study personnel should wait outside the exam room while the unblinded personnel administer the vaccine. The blinded study personnel will enter the exam room as soon as the unblinded personnel leaves. All subjects will be observed for at least 30 minutes following each injection by the blinded study personnel. This period of observation should be documented after each vaccination for any immediate reaction with particular attention to any evidence of allergic phenomena.

h. Optional VAQTA™ Vaccine Administration for Subjects in Spain

VAQTA™ will be provided to all subjects at the Month 18 study visit after all study procedures for that visit have been completed and at an additional Month 24 study visit which will consist only of the administration of the booster dose of VAQTA™ and follow-up for Serious Adverse Experience (SAE) events. All subjects in Spain are eligible to receive VAQTA™. Subject participation is voluntary.

Refer to Appendix 3, "VAQTA™ [Hepatitis A Vaccine, Purified Inactivated]" Product Monograph for vaccine dosage and administration details. Subjects will receive a single 0.5-mL (~25U) dose of VAQTA™ at their Month 18 visit and a booster dose of 0.5-mL (~25U) at an additional Month 24 visit. VAQTA™ is for intramuscular injection; the deltoid muscle is the preferred site for intramuscular injection.

All subjects will be observed for at least 30 minutes after administration of VAQTA™. This period of observation should be documented after each vaccination for any immediate reaction, with particular attention to any evidence of allergic phenomena.

i. Clinical Follow-Up

The parent/guardian of the subject will be given a Vaccine Report Card (VRC) following each vaccination. The parent/guardian of the subject is to record injection-site reactions, systemic reactions, and monitor the subject's temperature daily on the VRC for Day 1 (the day of vaccination, beginning 4 hours after each injection) and daily thereafter for 4 additional calendar days. Temperatures should be taken approximately at the same time each day. The parent/guardian of the subject is to record all adverse experiences that occur during the 15-day period (day of vaccination plus 14 calendar days) after each injection. Follow-up at Months 2, 6, 7, 12, and 18 after the first injection will include an in-person or telephone interview to assess general safety. The interview will solicit any serious AEs that the subject may have encountered. The parent/guardian of the participant will be instructed to notify the study physician immediately if any unexpected or severe reaction occurs.

All injection-site reactions and systemic adverse experiences (AEs), regardless of severity, as well as reasons for premature withdrawal from the study, will be reported on the appropriate case report forms. Any elevated temperature (≥100°F, ≥37.8°C oral) will be recorded as an adverse experience.

The VRC should be reviewed for completeness by the study site personnel at the Month 2 visit, Month 6 visit, and Month 7 visit, or by phone if the VRC was mailed back to the site and no timely visit is scheduled. All comments are to be reviewed by the study personnel and discussed with the parent/guardian of the participant for clarification if necessary. The information on the VRC should be generated only by the parent/guardian of the subject and is to be signed and dated by the parent/guardian of the subject to confirm the accuracy of the recorded information. No original information recorded by the parent/guardian of the participant should be altered by study personnel. Any information gained by phone contact with the parent/guardian of the subject should be clearly documented, initialed, and dated on the subject workbooklet or source documentation, other than the VRC. Discrepancies between information obtained during the telephone contact and the VRC need to be resolved; however, information on the VRC will be accepted over the telephone contact in the event that discrepancies cannot be resolved. At Month 12, subjects and their parents will receive a telephone call to review any new medical conditions, any health concern or events that meet protocol-defined SAE. At the Month 18 visit, a medical history and physical exam will be performed on all study subjects.

All subjects in Spain receiving VAQTA™ will be followed for Serious Adverse Experience (SAE) events for 14 days following each vaccination. All SAE events will be collected on the appropriate SAE worksheet. At 14 days following the VAQTA™ (Months 18 and 24) vaccinations, the subject's parent/guardian will receive a telephone call to determine if any SAEs occurred during the follow-up period. Any information gained by phone contact with the parent/guardian of the subject should be clearly documented, initialed, and dated on the subject workbooklet or source documentation.

Serum samples will be tested for antibodies against the 4 HPV types contained in the vaccine. Anti-HPV serology results from the Day 1 samples will be used to determine whether subjects have been exposed to any of the 4 vaccine HPV types. If a serology test result is above the **lower** cutoff in a subject at Day 1 (prevaccination), that result will be communicated to the primary investigator who enrolled that subject. The investigator will then communicate that result to the subject and the subject's parent/guardian, together with appropriate counseling regarding what the result may mean in terms of current or previous HPV infection and how such infection may have occurred, as well as what follow-up may be necessary.

Since there were no commercially-available anti-HPV detection assays, the SPONSOR developed sensitive, reproducible, and type-specific serology assays for the HPV vaccine program. The cutoff for the HPV 6, 11, 16, and 18 serology tests (i.e., the values that distinguished "HPV negative" sera from "HPV positive" sera) were set to maximize the assay's sensitivity for detecting preexisting anti-HPV antibodies at enrollment, and are referred as "lower cutoff" in the protocol. High sensitivity cutoffs ensured that HPV-naïve subject subcohorts could be identified within the cohorts enrolled in clinical trials. Such subcohorts would be used for the primary evaluation of the immunogenicity and efficacy of candidate prophylactic HPV vaccines. Consequently, the specificity of a low-positive result may be low. Thus, a low-positive result may actually be a false-positive.

The need for a highly sensitive cutoff for the HPV 6, 11, 16, and 18 serology assays complicates the parental/guardian notification of results. A high degree of certainty that a positive HPV assay result represents a true finding (rather than a false positive) is needed for parental/guardian notification of a positive HPV result. Thus, the SPONSOR **developed** a second, higher cutoff, referred to as "higher cutoff" in this protocol, that will reduce false-positive results (such a cutoff will reduce each assay's sensitivity for detecting presence of anti-HPV). See Section I.F. Efficacy/Pharmacokinetic/ Imunogenicity, Etc., Measurements.

j. Laboratory Measurements

Blood or urine specimens will be obtained at Day 1, Month 2, and Month 6 for pregnancy testing in all female subjects.

A 10-mL blood specimen will be obtained from each study participant at Day 1 and Months 7 and 18 visits. All blood specimens will be collected in a red top collection tube (not a serum-separator tube). If a serum specimen is to be sent for optional testing (hepatitis B, hepatitis C, HIV, syphilis), then draw additional blood as per requirements of the investigative site.

Assay descriptions are provided in Protocol Section I.F. Efficacy/Pharmacokinetic/Imunogenicity, Etc., Measurements.

Subjects may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject has been discontinued/withdrawn due to an adverse experience (telephone or FAX). When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Sections I.G.2.a. and b.

A single subject cannot be assigned more than one allocation number.

F. EFFICACY/PHARMACOKINETIC/IMUNOGENICITY, ETC., MEASUREMENTS

Immunogenicity

Luminex Assay for Serum Antibody Response to HPV

The purpose of the quadrivalent human papillomavirus (HPV)-Luminex assay is to detect antibody to HPV virus-like particles (VLPs), Serotypes 6, 11, 16, 18 before and after vaccination with the HPV quadrivalent vaccine. This is the primary assay used by the Virus and Cell Biology serology laboratory of Merck Research Laboratories (MRL) to evaluate the serological response to the vaccine. Yeast-derived VLPs are coupled to a set of 4 distinct fluorescent Luminex microspheres. Antibody titers are determined in a competitive format, where known type-specific phycoerythrin (PE)-labeled neutralizing monoclonal antibodies (mAbs) compete with the subject's serum antibodies for binding to conformationally sensitive neutralizing epitopes on the VLPs. The fluorescent signals from the bound HPV-specific detection mAbs are inversely proportional to the subject's neutralizing antibody titers. Fluorescent value readings for clinical samples are referenced against a monkey reference serum standard curve and the concentration of anti-HPV present are reported in milli-Merck Units per milliliter (mMU/mL).

Extensive validation studies of the serology assays will be used to define categories of test results that will fulfill the clinical need to provide accurate information regarding the presence of anti-HPV. The cutoffs are derived by repeatedly testing a panel of positive and negative samples against the standard curve. Since 2 cutoffs will be used, test results will be reported within one of the following 3 categories:

Negative (below lower cutoff): A negative result indicates that there were no detectable antibodies to HPV.

Positive (above higher cutoff): A positive result indicates that it is reasonably likely that a subject had an HPV infection sometime in the past, or that a subject may be currently infected with HPV. A result is considered positive based on a high probability that it reflects the true presence of antibodies against a particular HPV type, consequent from a prior/current infection to that type. From an assay perspective, all values above the second, higher assay cutoff will be called positive.

Indeterminate (between higher and lower cutoffs): An indeterminate result falls between the first (lower) cutoff and second (higher) cutoff. Antibody titers are detectable but low. The result may not be due to HPV infection. It cannot be determined with a reasonable degree of certainty that a subject has been infected with HPV in the past, or is currently infected with HPV.

Only the lower of the 2 cutoffs will be relevant to the analysis of immunogenicity results. A subject who is above the lower cutoff for a given HPV type at Day 1 will be excluded from the primary analysis of immunogenicity for that HPV type at Month 7. See Section I.I.4. for details of excluding subjects based on pre-positivity.

At completion of the study, subjects' addresses and telephone numbers will be updated by the study site investigator to ensure that the subjects will receive proper notification of test results described above. Samples are read from a standard curve, corrected for dilution as needed, and reported in milli-Merck Units per milliliter (mMU/mL). The lower cutoffs for the HPV 6, 11, 16, and 18 competitive Luminex Assay are 20 mMU/mL, 16 mMU/mL, 20 mMU/mL and 24 mMU/mL, respectively [15]. **The higher cutoffs for the HPV 6, 11, 16, and 18 competitive Luminex Assay are 65 mMU/mL, 65 mMU/mL, 100 mMU/mL, and 65 mMU/mL, respectively [16].**

G. SAFETY MEASUREMENTS

1. Evaluating and Recording Adverse Experiences

All adverse experiences will be collected from the time the consent form is signed through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, and such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets. Serious adverse experiences will be collected as described in Section I.G.2.a., for Quadrivalent HPV L1 VLP Vaccine/Placebo vaccination(s) and VAQTA™ optional vaccination(s) offered to subjects in Spain.

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR'S product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR'S product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

- Maximum intensity:

  For pediatric trials (<13 years of age).

  — Mild is awareness of symptom, but easily tolerated;

  — Moderate is definitely acting like something is wrong;

  — Severe is extremely distressed or unable to do usual activities.

  Injection site redness or swelling beginning from the day of vaccination through Day 4 post-vaccination will be evaluated by maximum size.

- Seriousness:

  A serious adverse experience is any adverse experience occurring at any dose that:

  —†Results in death; or

—†Is life threatening (places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]); or

—†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or

—†Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or

—†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or

— Is a cancer; or

— Is an overdose (whether accidental or intentional). **In this study, an overdose is defined as a subject receiving >3 doses (0.5 mL) of vaccine throughout the study or receiving ≥0.75 mL of vaccine in any one dose.**

N.B. Any overdose whether or not associated with an adverse experience must be reported within 24 hours to one of the individuals on the Contact Information Page.

ALSO:

Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).

- Duration:

  Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units.

- Action taken (Did the adverse experience cause the test vaccine to be discontinued?); and

- Relationship to test vaccine (Did the test vaccine cause the adverse experience?):

The determination of the likelihood that the test vaccine caused the adverse experience will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials and date on the source document or worksheet, that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse experience based upon the available information.

The following components are to be used to assess this relationship; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse experience (AE):

— Exposure:
Is there evidence that the subject was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g., diary), seroconversion or identification of vaccine virus in bodily specimen?

— Time Course:
Did the AE follow in a reasonable temporal sequence from administration of the test vaccine?

Is the time of onset of the AE compatible with a vaccine-induced effect?

— Likely Cause:
Is the AE not reasonably explained by another etiology such as underlying disease, other vaccine(s), or other host or environmental factors?

— Rechallenge:
Was the subject re-exposed to the test vaccine in this study?
If yes, did the AE recur or worsen?
If yes, this is a positive rechallenge.
If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study or a single-dose vaccine study.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT

RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD.

— Consistency With Test Study Vaccine Profile:
Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?

The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship):

— Definitely related to test vaccine:
There is evidence of exposure to the test vaccine.
The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable.
The AE is more likely explained by the test vaccine than by another cause.
Rechallenge (if feasible) is positive.
The AE shows a pattern consistent with previous knowledge of the test vaccine or test vaccine class.

— Probably related to test vaccine:
There is evidence of exposure to the test vaccine.
The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable.
The AE is more likely explained by the test vaccine than by another cause.

— Possibly related to test vaccine:
There is evidence of exposure to the test vaccine.
The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable.
The AE could have been due to another equally likely cause.

— Probably not related to test vaccine:
There is evidence of exposure to the test vaccine.
There is another more likely cause of the AE.
Rechallenge (if performed) is negative or ambiguous.

— Definitely not related to test vaccine:
The subject did not receive the test vaccine.

OR

Temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable.

OR

There is another obvious cause of the AE.

2. Immediate Reporting of Adverse Experiences to the SPONSOR

a. Serious Adverse Experiences

ANY SERIOUS ADVERSE EXPERIENCE, INCLUDING DEATH DUE TO ANY CAUSE, WHICH OCCURS TO ANY SUBJECT FROM THE TIME THE CONSENT IS SIGNED THROUGH 14 DAYS FOLLOWING THE FIRST VACCINATION(S) AND FROM THE TIME OF ANY SUBSEQUENT VACCINATION(S) THROUGH 14 DAYS THEREAFTER, WHETHER OR NOT RELATED TO THE INVESTIGATIONAL PRODUCT, MUST BE REPORTED WITHIN 24 HOURS TO ONE OF THE INDIVIDUAL(S) LISTED ON THE SPONSOR CONTACT INFORMATION PAGE.

ALL SUBJECTS IN SPAIN THAT RECEIVE OPTIONAL VAQTA™ WILL BE FOLLOWED FOR SERIOUS ADVERSE EXPERIENCES FROM THE TIME OF EACH VACCINATION(S) THROUGH 14 DAYS THEREAFTER.

ADDITIONALLY, ANY SERIOUS ADVERSE EXPERIENCE BROUGHT TO THE ATTENTION OF AN INVESTIGATOR WHO IS A QUALIFIED PHYSICIAN AT ANY TIME OUTSIDE OF THE TIME PERIOD SPECIFIED IN THE PREVIOUS PARAGRAPH ALSO MUST BE REPORTED IMMEDIATELY TO ONE OF THE INDIVIDUALS LISTED ON THE SPONSOR CONTACT INFORMATION PAGE IF THE EVENT IS EITHER:

1. A DEATH WHICH RESULTED IN THE SUBJECT DISCONTINUING THE STUDY

OR

2. A SERIOUS ADVERSE EXPERIENCE THAT IS CONSIDERED BY AN INVESTIGATOR WHO IS A QUALIFIED PHYSICIAN TO BE POSSIBLY, PROBABLY, OR DEFINITELY VACCINE RELATED.

ALL SUBJECTS WITH SERIOUS ADVERSE EXPERIENCES MUST BE FOLLOWED UP FOR OUTCOME.

b. Selected Nonserious Adverse Experiences

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page. (See Appendix 1, "Pregnancy Reporting and Follow-Up HPV Vaccine Clinical Program.")

3. Unblinding of Serious Adverse Experiences

In order to protect the integrity of the study, reports of Serious Adverse Experiences (SAE) will not be unblinded prior to study completion. At the termination of the study, all such reports will be unblinded and distributed to investigators. In this study of a prophylactic vaccine, unblinding of treatment allocation is unlikely to be considered necessary for purposes of subject management. This is in contrast to studies of investigational therapeutic agents that continue to be administered for treatment of a disease state. The independent Safety Monitor will have access to the unblinded data from the study on an ongoing basis throughout the study to ensure that the safety of the participants will not be affected. Should the need arise, regulatory agencies may request the treatment assignment of individual subjects on a case-by-case basis. Study sites may request treatment assignment of individual subjects in the case of medical necessity.

H. STUDY DURATION AND SUBMISSION OF DATA

For each subject enrolled, the duration of the study will be 18 months. Enrollment is expected to be completed ~6 months after the first subject is enrolled at the first site. The primary Clinical Study Report for this study will be written after only 12 months of follow-up and will include the primary safety analyses and immunogenicity analyses. An addendum to the primary Clinical Study Report will include safety data through Month 18. For the purposes of subject accounting, subjects will be regarded as ongoing in the study at Month 12 if they have completed the full vaccination regimen (3 doses) and they have completed the follow-up visits through Month 12. This includes safety measurements, serum collection and pregnancy testing. For the end-of-study addendum, subjects will be regarded as having completed the study if they were classified as ongoing at Month 12 and have completed the follow-up visits through Month 18.

Subject Relocation

Given the duration of the study, it can be expected that subjects may temporarily or permanently relocate during the study. The SPONSOR must be contacted for each temporary (>3 months) and permanent relocation as soon as the situation is known. Every effort should be made to adjust study visits around a subject's temporary absence (summer vacations). Every effort should be made to have a permanently or temporarily relocated subject seen at another site participating in this study so they can remain in the study.

I. DATA ANALYSIS

1. Responsibility for Analyses

The data collected under this protocol will be analyzed by the Clinical Biostatistics Department of Merck Research Laboratories. A comprehensive Data Analysis Plan will be provided prior to statistical analysis. This study will be conducted using in-house blinding procedures. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed, data has been declared complete, and all protocol violators have been identified.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these changes will be listed, along with explanations, in the Data Analysis Plan and/or the Clinical Study Report, as appropriate.

2. Hypotheses

Primary

The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents.

Secondary

The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine induces noninferior immune responses with respect to each of the vaccine components individually at Week 4 Postdose 3 in preadolescent and adolescent boys who are seronegative at Day 1, relative to preadolescent and adolescent girls who are seronegative to the relevant HPV type at Day 1.

(The statistical criterion for noninferiority requires that the lower bounds of the 95% confidence intervals for the fold difference in GMTs (boys/girls) exclude a decrease of 2-fold or more. Each vaccine HPV type will be analyzed separately.)

3. Variables and Time Points

The primary variables of interest for safety/tolerability are the incidences of clinical adverse experiences reported Days 1 to 15 following each vaccination and elevated temperatures (≥100°F, oral equivalent) for Days 1 to 5 following each vaccination. Prespecified adverse experiences are vaccine-related adverse experiences, VRC-prompted injection-site adverse experiences (swelling/redness or pain/tenderness/soreness), VRC-prompted systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), severe adverse experiences, and fever.

Serum samples will be obtained immediately prior to the first injection (Day 1), as well as 1 month following the third injection and 18 months following the first injection.

For immunogenicity, the main endpoint is the GMT for each vaccine HPV type at 4 weeks after the third dose. In addition, the associated 95% confidence intervals, and Reverse Cumulative Distributions (RCDs) will be provided.

4. Approach to Analyses

All subjects who received at least 1 injection and have follow-up data will be included in the primary safety analysis.

The main immunogenicity analysis will be performed on a per-protocol basis. All subjects who complete the vaccination regimen within acceptable day ranges, have at least 1 valid serology result after the third injection (within an appropriate day range), do not receive any other inactivated vaccines within 14 days before or after any HPV vaccine injection or live virus vaccines with 21 days before or 14 days after any HPV vaccine injection, do not receive immunosuppressives or have an immune disorder considered by the Clinical Monitor to potentially interfere with the subject's response to the vaccine, and who do not receive immune globulin-containing injections during the vaccination series and for 1 month after the last injection, will be eligible for the immunogenicity analysis in this study. **The main immunogenicity analysis will be performed on the combined age strata.**

The immunogenicity analysis will be conducted on a component-wise basis. To be included in the immunogenicity analyses for the each of the HPV 6 and HPV 11 components, subjects must be seronegative to both HPV 6 and 11 at baseline. In order to be included in the analysis for the HPV 16 component, subjects must be seronegative to HPV 16 at baseline, and to be included in the analysis for the HPV 18 component, subjects must be seronegative to HPV 18 at baseline.

Baseline seropositivity will be determined based on the lower cutoff; i.e., subjects considered "indeterminate" for the purposes of informing investigators and subjects/parents of possible HPV infection will be considered seropositive for the purposes of the immunogenicity analyses. (See Section I.F. Efficacy/Pharmacokinetic/Imunogenicity, Etc., Measurements.) A listing of subjects excluded from the per-protocol summaries will be provided. Supporting analyses including all eligible subjects with serology will be conducted as well.

5. Statistical Methods

Incidences of all adverse events reported Days 1 to 15 and elevated temperatures (≥100°F, oral equivalent) reported Days 1 to 5 following each injection and any injection will be summarized by treatment group.

The 2 treatment groups will be compared with respect to the incidences of VRC-prompted AEs and other AEs which occur in ≥1% of subjects in either treatment group. Comparisons will be made using risk differences and associated 95% confidence intervals; in addition, p-values will be provided for VRC-prompted AEs (vaccine-related adverse experiences, VRC-prompted injection-site adverse experiences (swelling/redness or pain/tenderness/soreness), VRC-prompted systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), severe adverse experiences, and fever. Site specific summaries of the incidences of SAEs will be provided by treatment group (Quadrivalent HPV Vaccine or Placebo) at the 14-day post Month 18 and 14-day post Month 24 time points for those subjects at sites in Spain where VAQTA™ is administered at Month 18 and Month 24 visits.

In order to provide a basis for bridging the large safety database acquired in previous HPV studies for female subjects to the safety profiles for male subjects, adverse experiences will be summarized separately for boys and girls.

For the secondary analysis of immunogenicity, for each HPV type, the null hypothesis is that the fold difference in GMTs between genders (boys/girls) is ≤0.5, and it will be tested against the alternative hypothesis that the fold difference in GMTs between genders (boys/girls) is >0.5. The threshold value of 0.5 was chosen to maintain consistency within the Phase II/III program. A one-sided test at the α=0.025 significance level will be used to test the hypothesis for each HPV type. The statistical analysis will be based on the confidence interval for the fold difference. For each HPV type, a lower bound on the two-sided 95% confidence interval >0.5 will lead to a conclusion of noninferiority with respect to that type. The vaccine must meet the noninferiority criterion for all 4 vaccine HPV types for success to be declared.

In addition, reverse cumulative distribution functions (RCDFs) for Month 7 serum samples will be provided for each treatment group.

The immunogenicity analysis will be performed on the combined age strata; immune responses will be summarized separately by age stratum, but no formal comparisons will be performed. Immune responses may also be compared observationally to those in other Phase II/III studies in which efficacy has been shown, if data from those studies are available at the time of this analysis. This will serve to bridge immune responses from adolescents to levels in young adults that are associated with efficacy. In addition, immunogenicity data from this study will also be evaluated in the context of the other Phase II/III studies in the Integrated Summary of Immunogenicity.

Persistence of immune response will be evaluated based on serology results from the Month 18 visit.

6. Multiplicity

In order to reject the overall null hypothesis for immunogenicity, the statistical criterion must be met for each HPV type separately; therefore, no multiplicity adjustment is necessary to maintain the overall type I error rate at 0.025 (one-sided).

7. Sample Sizes and Power Calculations

The sample size for this study was chosen in order to provide a large number of vaccinees for the assessment of safety. The primary hypothesis in this study relates to the tolerability of the quadrivalent HPV vaccine. If no vaccine-related SAEs are observed among 1100 vaccinated subjects, this study will provide 95% confidence (one-sided) that the true incidence is no greater than 0.27% and 80% confidence (one-sided) that the true incidence is no greater than 0.15%.

For safety comparisons between the vaccine and placebo groups, risk differences between the 2 groups that could be detected with an 85% chance are summarized in Table 2 for a variety of hypothetical true incidence rates. These calculations assume that the numbers of subjects evaluable for safety in the vaccine and placebo groups are 1100 and 550, respectively, and are based on a two-sided significance level of α=0.05. No multiplicity adjustment was performed for these calculations.

Table 2

Differences in Incidence Rates of Adverse Experiences Between the Vaccine and Placebo Groups That Can Be Detected With ~85% Power With 1100 Subjects in the Vaccine Group and 550 Subjects in the Placebo Group (α=0.05, two-sided)

True Incidence Rate of Adverse Experience Among Quadrivalent HPV L1 Vaccine Recipients (%)	True Incidence Rate of Adverse Experience Among Placebo Recipients (%)	Detectable Percentage Point Difference in Incidence Rates of Adverse Experience
2.5	0.5	2.0
3.3	1.0	2.3
9.1	5.0	4.1
15.3	10.0	5.3
21.0	15.0	6.0
26.7	20.0	6.7
37.5	30.0	7.5
Note: The incidence rates in this table are hypothetical.		

For example, for an adverse experience with a true incidence rate of 5% among placebo recipients, this study has ~85% power to detect a 4.1 percentage point increase in vaccine recipients.

The secondary hypothesis is that the quadrivalent HPV vaccine will induce noninferior immune responses to each of the HPV types in the vaccine in boys relative to girls. In order to be declared noninferior, the statistical criterion must be met for each HPV type individually.

Based on previous Phase II studies, it is assumed that the standard deviations of the natural logarithm of the Month 7 titers will be no more than 1.2 for each HPV type. Further assuming baseline seropositivity rates of 8% for the combined Types 6 and 11, and 9% for each individual type of 16 and 18 (approximately half the baseline positivity rates observed in young adult women), and that 15% of subjects will be lost to follow-up by Month 7 (resulting in 847 evaluable subjects for Types 6 and 11, and 836 evaluable subjects for Types 16 and 18), **this study will have >99% power overall to declare noninferiority of the immune response in boys relative to girls.**

8. Interim Analysis

The main analysis of immunogenicity and safety for this study will be based on data collected up to 6 months Postdose 3 (i.e., the Month 12 visit); safety and immunogenicity measurements obtained following Month 12 will be included in a separate analysis. No new interim analyses are planned. In order to conduct the Month 12 analysis, in-house Merck personnel will be unblinded to treatment group after the Month 12 data are reviewed and the database is frozen. Investigators and site personnel will remain blinded until the completion of all safety and immunogenicity evaluations at Month 18.

II. ADMINISTRATIVE AND REGULATORY SECTIONS

A. LABELING, PACKAGING, STORAGE, AND RETURN OF CLINICAL SUPPLIES

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be administered only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount administered to the subjects, and the amount remaining at the conclusion of the study. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all unused clinical supplies must be returned as indicated on the Contact Information page(s). U.S. sites should follow instructions for the Clinical Supplies Return Form (V464) and contact your SPONSOR representative for review of shipment and form before shipping. Sites outside of the United States should check with local country Merck personnel for appropriate documentation that needs to be completed for vaccine accountability.

1. Patient and Replacement Information

Clinical supplies will be packaged for ~1650 subjects. Additional supplies will be packaged to account for replacement subjects, storage temperature excursions, and other unplanned losses.

Study personnel will have access to an Interactive Voice Response System (IVRS) to allocate subjects, to assign drug to subjects and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule generated by the SPONSOR. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

2. Product Descriptions

Investigational materials will be provided by the SPONSOR as summarized in Table 3.

Table 3

Product Descriptions

Product	Potency	Dosage form	Dose	Storage
Quadrivalent HPV VLP Vaccine	40/80/80/40 mcg/mL	Sterile Solution for IM Injection	0.5 mL	Store refrigerated at 2 to 8°C. Protect from light. DO NOT FREEZE.
Placebo for Quadrivalent HPV VLP Vaccine	N/A	Sterile Solution for IM Injection	0.5 mL	Store refrigerated at 2 to 8°C. Protect from light. DO NOT FREEZE.

3. Primary Packaging and Labeling Information

Supplies will be packaged in 3-mL glass vials. Each vial will be labeled with a double-panel, blinded label. Container label text may include the following:

• Component ID #	• Route of Administration
• Packaging Control #	• Storage Conditions
• Protocol #	• Country regulatory requirements
• Dosing Instructions	• SPONSOR address

Panel 2 of the label should be removed from the primary label at the time of dispensing and be applied to the appropriate case-report form (CRF).

4. Storage Requirements

All vaccine supplies will be shipped to the sites as a refrigerated solution to be stored at 2 to 8°C. A temperature-monitoring device will be sent with each shipment. Upon receipt at the investigational site, the vaccine/placebo vials should be placed immediately into the refrigerator. Vials should be stored in the primary shipping box with the lid closed to minimize exposure to light.

A refrigerator temperature log must be maintained at the site. The temperature log will be reviewed by the Merck Research Associate (MRA) throughout the study. An appropriate back up system (i.e., alarm, generator, and study site personnel telephone numbers) should be in place in the event of a refrigerator failure.

5. Distribution

Distribution of clinical supplies will be managed through the IVRS.

Used and unused vaccine vials should be retained at the site until the MRA is able to account for all of the vials originally shipped to the sites. After all of the vials have been accounted for, the used vials may be discarded according to the procedures of the site. The unused vials should be returned to the SPONSOR by the MRA at the completion of the study.

6. Clinical Supplies Disclosure

The IVRS may be used in order to unblind patients and to unmask drug identity in the event of an emergency. The preferred method is prior to unblinding through the IVRS, the investigator will attempt to contact the clinical monitor. The SPONSOR will not provide a disclosure envelope with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Any unblinding that occurs at the site must be documented.

7. Standard Policies/Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be administered only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount administered to the subjects/patients, and the amount remaining at the conclusion of the study. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all unused clinical supplies must be returned as indicated on the Contact Information page(s). U.S. sites should follow instructions for the Clinical Supplies Return Form (V464) and contact your SPONSOR representative for review of shipment and form before shipping. Sites outside of the United States should check with local country Merck personnel for appropriate documentation that needs to be completed for vaccine accountability.

B. BIOLOGICAL SPECIMENS

The laboratory that is analyzing any clinical samples should be blinded to the subject's treatment.

It is the responsibility of the primary investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.

1. Labeling of Specimens

All specimens shipped to Merck Research Laboratories will be labeled with preprinted computer-generated labels provided by SPONSOR. Labels can only be affixed to dry surfaces. However, they can be used on polypropylene or polyethylene and will survive freezing and thawing. The labels will contain the following information:

a. Protocol and site number
b. Subject allocation number (pre-printed on all labels after Day 1)
c. Subject initials (to be completed by study personnel in waterproof ink)
d. Study day or study month
e. Sample date (to be completed by study personnel in waterproof ink)
f. Sample I.D. (serum, retention)
g. Project number (V501)

Specimens must have allocation numbers displayed on the label.

2. Shipment of Specimens

Properly labeled specimens will be shipped according to instructions summarized by the SPONSOR. Inventory forms, tubes for freezing/shipping specimens, and shipping containers will be provided by SPONSOR or SPONSOR's representative.

C. CLINICAL AND LABORATORY DATA COLLECTION

1. Data Entry by Merck Personnel

Workbooklets/worksheets will be provided by the SPONSOR to record data in the clinic. Data on workbooklets/worksheets may be handwritten. For all other protocol required information that is originally recorded elsewhere (e.g., x-ray, lab results, diary cards), either a copy will be sent to the SPONSOR directly, or hand transcribed onto worksheets (as directed by the study procedures). In this instance, the actual date of an examination (e.g., x-ray, phlebotomy) should be reported on the worksheets; this may be different from that of the office or clinic visit. Whenever possible, all information requested on a worksheet should be completed. If information is not available, it should be documented as such (e.g., permanently missing).

After preliminary review of these worksheets by the Investigator/study staff, the worksheets are entered into a database by SPONSOR personnel. Entry by the SPONSOR may occur by local SPONSOR representatives, or upon submission of the data to the SPONSOR via fax or courier (e.g., Federal Express). Section I.H. STUDY DURATION AND SUBMISSION OF DATA of the Protocol defines the timelines in which data are to be submitted to the SPONSOR for data entry. Original worksheets will remain at the site as source/support documents.

Periodically, a representative of the SPONSOR will review study documents (see Protocol Section II.D., Study Documentation and Records Retention) to verify compliance with the protocol. The SPONSOR representative will also review the accuracy of the data compared to source documents.

As a result of the SPONSOR data review process, corrections or changes to data may be required. Discrepancies or questions concerning the data will be sent to the Investigator. The discrepancy reports should be resolved by the Investigator/study staff, signed and dated, and a copy returned to the SPONSOR. The original discrepancy report must be retained in the subject binder as a record of changes or acknowledgment of the receipt of queries on the data.

Shortly after the last patient visit has been completed and the data have been entered into the SPONSOR database, the SPONSOR will send a "Declaration by Investigator" form ("Signature Page") identifying the patient allocation numbers/visits for the study. The original signed and dated signature page and label page (if applicable) must be sent to the SPONSOR at the specified address on the SPONSOR Contact page of the Protocol. A photocopy of the signature page and label page (if applicable) is retained at the site. The worksheets, final data handling and entry guidelines, and discrepancy forms will serve as the site's record of the final study data and will be retained at the site along with the source documents.

2. Laboratory Results

All assay results will be entered into the MRL clinical database.

3. Vaccine Report Cards

The parent/guardian of the subject will be given a vaccine report card (VRC) on which to record all adverse experiences that occur during the 15-day period (day of vaccination plus 14 calendar days) after each injection. All local and systemic reactions will be reported, regardless of severity, as well as reasons for premature withdrawal from the study, on the appropriate case report forms. Any elevated temperature (≥100°F or ≥37.8°C oral) will be recorded as an adverse experience.

The VRC should be reviewed for completeness by the study site personnel at the Month 2 visit, the Month 6 visit, and the Month 7 visit or by phone if the VRC was mailed back to the site and no timely visit is scheduled. All comments are to be reviewed by the study personnel and discussed with the parent/guardian for clarification if necessary. The information on the VRC should be generated only by the subject's parent/guardian and is to be signed and dated by the subject's parent/guardian to confirm the accuracy of the recorded information. Original information recorded by the participant's parent/guardian should never be altered by study personnel. Any information gained by phone contact with the subject's parent/guardian should be clearly documented, initialed, and dated on the subject workbooklet or source documentation, other than the VRC. Discrepancies between information obtained during the telephone contact and the VRC need to be resolved; however, information on the VRC will be accepted over the telephone contact in the event that discrepancies cannot be resolved.

4. Follow-up Telephone Calls

Telephone interview will be conducted at Month 12 with all participating subjects. Any new medical condition, health concern, or vaccine-related adverse experience will be reviewed.

D. STUDY DOCUMENTATION AND RECORDS RETENTION

Study documentation includes all workbooks/worksheets/case report forms/signature pages, data correction forms, data handling and entry guidelines, source documents, monitoring logs and appointment schedules, SPONSOR-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Independent Ethics or Institutional Review Committee correspondence and approval, approved and signed subject consent forms, Statement of Investigator form, clinical supplies receipts, and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, x-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Source documents may also include SPONSOR workbooks/worksheets, CRFs, or electronic devices when information is recorded directly onto such forms or devices. The investigator should identify to the SPONSOR which data will be directly recorded onto workbooks, CRFs, or electronic devices. A form will be supplied by the SPONSOR for this identification. This source document identification form should be maintained in the site's Regulatory Binder. Any document which serves as a source document should be signed or initialed and dated by the individual making the observation/recording. Study related observations within the patient charts and/or workbook/worksheet/collector questions which inherently require "medical judgment" (e.g., "Does this represent a clinically significant change from baseline?", adverse experience causality, clinical significance of out-of-range laboratory values) require the signature/initials and date of a "qualified" physician (or dentist/podiatrist, etc., when appropriate) investigator or subinvestigator. This practice most clearly demonstrates that the appropriate medical input has been provided. Co-signatures by a qualified physician may therefore be necessary and appropriate on those source documents which capture both medical and non-medical related observations and assessments.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator. They shall be retained until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region. or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. The SPONSOR will notify the investigator in writing when retention is no longer necessary.

E. INFORMED CONSENT

The investigator must obtain documented consent from each potential subject in biomedical research or when an investigational vaccine is administered to subjects in a clinical study.

Consent must be documented by the subject's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion.

If the subject is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the subject should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., study staff personnel).

If the subject is legally incompetent (i.e., a minor or mentally incapacitated), the written consent of a parent, legal guardian or legal representative must be obtained. Depending on local law or review committee requirements such consent may also need to be signed by an impartial witness.

When the study population includes non-English speaking people, the information in the consent form should be translated and communicated to the subject in language understandable to the subject. Either the investigator or Merck may take the responsibility for the translation; however, documentation must exist to demonstrate who performed the translation and that the translation was verified by an individual other than the person who performed the translation. An accurately translated consent form should be provided with a written statement by the translator (whether the translator is the investigator, the Clinical Monitor, or a professional translator), indicating that the consent form is an accurate translation of the accompanying English version.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form and any subsequent revised written informed consent form, and any written information provided to the subject must receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form.

A copy of the FDA Regulations Regarding Informed Consent, and the World Medical Association Declaration of Helsinki are attached to this protocol.

F. INSTITUTIONAL REVIEW BOARD (IRB)/INDEPENDENT ETHICS COMMITTEE (IEC)

For Studies Conducted Under the U.S. IND

The investigator is responsible for obtaining Review Board approval of the protocol, as well as approval of all subsequent major changes, in compliance with local law. Copies of these approvals must be forwarded to the SPONSOR. The IRB will comply with all federal, state, and local laws. Particular attention is drawn to the Food and Drug Administration Regulations for Institutional Review Boards (21 CFR, Part 56), and the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices for IRB/IEC Committees. Copies of relevant information derived from these guidelines are attached to this protocol. The investigator is responsible for obtaining initial and continuing review (at intervals not less than once per year) of the study by an IRB. Written approval from the IRB must be forwarded to the SPONSOR before clinical supplies will be shipped. For continuing studies, written approval from the IRB must be sent to the SPONSOR at intervals not to exceed 1 year.

The investigator shall also obtain from the IRB and submit to the SPONSOR, a signed statement indicating that it complies with Good Clinical Practices. A sample IRB Compliance letter is attached to this protocol.

The SPONSOR will promptly be advised of any IRB/IEC inspection of the investigator for a Merck-sponsored study during the course of this trial. The notification and outcome [written report(s) and response(s) when available] of such inspections should be promptly communicated to the SPONSOR by the investigator. The investigator will maintain copies of all IRB/IEC inspection reports and responses in the corresponding study file(s).

For Studies Not Conducted Under the U.S. IND

The investigator is responsible for obtaining Review Board approval of the protocol, as well as approval of all subsequent major changes, in compliance with local law. Copies of these approvals must be forwarded to the SPONSOR. Particular attention is drawn to the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices for Institutional Review Board/Independent Ethics Committees, and a copy of the guidelines is attached to this protocol.

The investigator shall also obtain from the IEC and submit to the SPONSOR, a signed statement indicating that it complies with Good Clinical Practices. A sample IEC Compliance letter is attached to this protocol.

The SPONSOR will promptly be advised of any IRB/IEC inspection of the investigator for a Merck-sponsored study during the course of this trial. The notification and outcome [written report(s) and response(s) when available] of such inspections should be promptly communicated to the SPONSOR by the investigator. The investigator will maintain copies of all IRB/IEC inspection reports and responses in the corresponding study file(s).

G. CONFIDENTIALITY

1. Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

By signing this protocol, the investigator affirms to the SPONSOR that information furnished to the investigator by the SPONSOR will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethics Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in Section II.K., Publications.

2. Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC) or Regulatory Agency representatives may consult and/or copy study documents (see Protocol Section II.D., Study Documentation and Records Retention) in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

3. Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the SPONSOR, and subsidiaries, affiliates and agents of the SPONSOR, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

H. COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck & Co., Inc., is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from patients, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the SPONSOR.

The investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

Study documentation (see Protocol Section II.D., Study Documentation and Records Retention) will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the SPONSOR as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a Sponsor must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes the conduct and results of the study. The Sponsor may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the SPONSOR prematurely terminates a particular trial site, the SPONSOR will promptly notify that site's IRB/IEC.

I. COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck & Co., Inc. in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

J. QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

K. PUBLICATIONS

This is an exploratory study to develop data for possible future studies. It is not intended to be published, unless important new information or data concerning the safety of a marketed product is obtained, in which case the SPONSOR will work with the investigator(s) to publish the data appropriately.

L. COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

III. SIGNATURES—U.S. SITE(S)

A. SPONSOR'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

B. INVESTIGATOR

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section I.G. of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information.

TYPED NAME	SIGNATURE	DATE

IV. SIGNATURES—NON-U.S. SITE(S)

A. SPONSOR'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

B. INVESTIGATOR

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section I.G. of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information.

TYPED NAME	SIGNATURE	DATE

LIST OF REFERENCES

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ATTACHMENTS

Merck & Co., Inc
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck & Co., Inc. ("Merck") conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these studies in compliance with the highest ethical and scientific standards. Protection of patient safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical studies will be consistent with standards established by the Declaration of Helsinki and in compliance with all local and/or national regulations and directives.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to studies which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated studies (e.g., Medical School Grant Program), which are not under the control of Merck.

II. Scientific Issues

A. Study Conduct

1. Study Design

Except for pilot or estimation studies, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, studies to assess or validate various endpoint measures, or studies to determine patient preferences, etc.

The design and conduct of a study (i.e., patient population, duration, statistical power) must be adequate to address the specific purpose of the study. Research subjects must meet protocol entry criteria to be enrolled in the study, unless specifically exempted by the Merck study monitor.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate patients, adequacy of facilities and staff, previous performance in Merck studies, as well as budgetary considerations. Prior to study initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Study sites are monitored to assess compliance with the study protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency; data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud and/or misconduct are suspected, the issue is investigated; when necessary, the clinical site will be closed and, if appropriate, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of studies it conducts. Some early phase or pilot studies are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the study, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the study results and conclusions. Merck funding of a study will be acknowledged in publications.

III. Patient Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect patient safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or local medical director (non-U.S. studies) will approve the patient informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that patient welfare is of primary importance. Potential patients will be informed of the risks and benefits of, as well as alternatives to, study participation. At a minimum, study designs will take into account the local standard of care. Patients are never denied access to appropriate medical care based on participation in a Merck clinical study.

All participation in Merck clinical trials is voluntary. Patients are enrolled only after providing informed consent for participation. Patients may withdraw from a Merck study at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding patient confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. DNA Research

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck studies. Merck does not pay incentives to enroll patients in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for patient referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible patients.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the study. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck studies will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g. to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an attachment to the study protocol, and in signing the protocol, agree to support these ethical and scientific standards.

Date:_____

(insert Primary Investigator's name and address below)

_____

_____

_____

RE: Insert title of protocol and protocol number

Dear Dr. _____(insert name of Primary Investigator):

My signature below verifies that the IRB/IEC listed below operates in accordance with applicable national/local and institutional regulations and guidelines which govern IRB/IEC operations.

_____ _____ _____

Printed Name, IRB/IEC Chairperson Signature, IRB/IEC Chairperson Date

(insert name and address of IRB/IEC here)

_____

_____

_____

_____

IRB's Federal Assurance number is:_____ (optional)

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE

Section 3: INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:

trial protocol(s)/amendments(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfill its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

-approval/favourable opinion;

-modifications required prior to its approval/favourable opinion;

-disapproval/negative opinion; and

-termination/suspension of any prior approval/favourable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but a least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trail is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other documents) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a nonscientific area.

(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite non-members with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2)

(c) All adverse drug reactions (ADRs that are both serious and unexpected.)

(d) New information that may affect adversely the safety of the subjects of the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., write procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

FDA REGULATIONS REGARDING INFORMED CONSENT (CODE OF FEDERAL REGULATIONS, TITLE 21, PART 50)

50.20 General Requirements for Informed Consent

Except as provided in 50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

50.25 Elements of Informed Consent

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:
- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:
- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- (3) Any additional costs to the subject that may result from participation in the research.
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- (6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

50.27 Documentation of Informed Consent

(a) Except as provided in §56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in §56.109(c), the consent form may be either of the following:
- (1) A written consent document that embodies the elements of informed consent required by § 50.25. This form may be read to the subject or the subject's legally authorized representative but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.
- (2) A "short form" written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

FOOD AND DRUG ADMINISTRATION REGULATIONS FOR INSTITUTIONAL REVIEW BOARDS (CODE OF FEDERAL REGULATIONS, TITLE 21, PART 56)

Subpart B — Organization and Personnel

56.107 IRB Membership

a. Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.
b. Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.
c. Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.
d. Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
e. No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
f. An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Subpart C — IRB Functions and Operations

56.108 IRB Functions and Operations

In order to fulfill the requirements of these regulations, each IRB shall:

a. Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity, and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.
b. Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.
c. Except when an expedited review procedure is used (see § 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

56.109 IRB Review of Research

a. An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.
b. An IRB shall require that information given to subjects as part of informed consent is in accordance with § 50.25. The IRB may require that information, in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.
c. An IRB shall require documentation of informed consent in accordance with § 50.27, except that the IRB may, for some or all subjects, waive the requirement that the subject or the subject's legally authorized representative sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.
d. An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.
e. An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations Guiding Medical Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and amended by the 29th World Medical Assembly Tokyo, Japan, October 1975, 35th World Medical Assembly Venice, Italy, October 1983, and the 41st World Medical Assembly Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

I. **BASIC PRINCIPLES (CONT.)**

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, the informed consent should be obtained from the legal guardian in accordance with the national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principals enunciated in the present Declaration are complied with.

II. **MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)**

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic method.
3. In any medical study, every patient (including those of a control group, if any) should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1,2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that the medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. **NONTHERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NONCLINICAL BIOMEDICAL RESEARCH)**

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers; either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. The research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

APPENDICES

1. Pregnancy Reporting and Follow-Up HPV Vaccine Clinical Program
2. Study Procedures by Visit
3. VAQTA® (Hepatitis A Vaccine, Purified Inactivated) Product Monograph

APPENDIX 1

Pregnancy Reporting and Follow-Up HPV Vaccine Clinical Program

Subject: Pregnancy Reporting and Follow-up HPV Vaccine Clinical Program	**Dept.:**	**976**
	Rev.:	**02**
	Effective Date:	**22-Feb-00**

	Name	Signature	Date
Written By:	s47F(1)		
Approved By: Clinical	E. Barr, M.D.		
Approved By: Clinical	s47F(1)		
Approved By: Regulatory	s47F(1)		
Approved By: WPS&E	s47F(1)		
Reviewed by CQA:	s47F(1)		

Subject: Pregnancy Reporting and Follow-up HPV Vaccine Clinical Program	**Dept.:**	**976**
	Rev.:	**02**
	Effective Date:	**22-Feb-00**

I. INTRODUCTION

Females of childbearing potential are being enrolled in the HPV vaccine program. Pregnancy tests are performed prior to each vaccination. Subjects are excluded from enrollment in the clinical studies if they are pregnant. In addition, subjects who are enrolled and become pregnant are excluded from subsequent vaccination. Any subject with a positive pregnancy test must not be vaccinated.

Whether or not associated with an adverse event, all reports of use of a Merck product during pregnancy are reportable to WPS&E. Since studies within the HPV vaccine program include enrollment of women of childbearing potential, the following paragraph is included in the protocols:

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient (spontaneously reported to them) which occurs during the safety follow-up period (through Month 7 of the study). All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page.

II. PURPOSE

The purpose of this document is (1) to describe the procedures for the reporting of all pregnancies that occur during the safety follow-up period (through Month 7 of the study) and (2) to describe the procedures for following all reported pregnancies that occur prior to the Month 7 study visit for outcome (completion/termination).

This document will be sent to each HPV vaccine investigative site for incorporation into the standard study-related procedures at the site (administrative binder).

III. DEFINITIONS

ADVERSE EXPERIENCE (AE) - An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR'S product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR'S product, is also an adverse experience. Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

ADVERSE EXPERIENCE REPORT FORM – (Attachment 1) Form used by the clinical team to report serious adverse experiences and pregnancies to WPS&E

HPV – Human Papillomavirus

LMP – Last menstrual period

MERCK PRODUCT – Any pharmaceutical product, biological product, device or diagnostic agent, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by, or distributed by Merck and Co., Inc., for human use

SAFETY FOLLOW-UP PERIOD – Period from the time the consent form is signed through Month 7 of the study

SERIOUS ADVERSE EVENT - A serious adverse experience is any adverse experience occurring at any dose that:

*Results in death;

*Is life-threatening (places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]);

*Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions);

*Results in or prolongs an existing inpatient hospitalization (an overnight stay in the hospital, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.);

*Is a congenital anomaly/birth defect (in offspring of subject/patient taking the product regardless of time to diagnosis);

Is a cancer; or

Is the result of an overdose (whether accidental or intentional).

ALSO:
Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the starred (*) outcomes listed previously.

SPONSOR – Merck & Co., Inc.

WPS&E – Worldwide Product Safety & Epidemiology; Department within Merck & Co., Inc. responsible for collection of all AE information and reporting to regulatory agency(ies) as required

IV. PROCEDURES

RESPONSIBILITY OF THE INVESTIGATOR/DESIGNEE
Pregnancy Reporting (Initial Report)

1. Any pregnancy in a subject (either detected by a study pregnancy test or spontaneously reported to study site personnel) which occurs during the safety follow-up period (through Month 7 of the study) must be reported to one of the individuals (Clinical Monitor or Medical Program Coordinator [MPC]) on the SPONSOR Contact Information page.
2. The following initial report information is required:
   a) Name – provide the initials of the subject in accordance with local confidentiality regulations.
   b) Allocation Number – Provide the allocation number of the subject.
   c) Age – Provide the subject's age at the onset of the pregnancy and/or subject's date of birth

d) Sex – Female (given)
e) Weight – Provide the weight with the appropriate units (LB or KG).
f) Weeks Gestation– Provide the weeks of gestation at the time of reporting and/or provide date of LMP.
g) Complete study title (including protocol number)
h) Provide any recent/concomitant therapy given within 14 days prior to onset of the pregnancy (to include daily dosage, start date, stop date and indication for usage). Receipt of HPV vaccine/placebo should also be listed in this section. Indicate date(s) any dose(s) of vaccine received.
i) List any concurrent conditions that developed prior to the vaccination and were still present at the time of the pregnancy (e.g., diabetes mellitus, carcinoma).
j) List any other relevant medical history.
k) Provide any laboratory test or diagnostic test results which would add meaningful information regarding the pregnancy.
l) A description of the event (narrative) and any comments (which may include the action taken, i.e. discontinued, and information concerning follow-up activity)
m) Name of primary investigator and, if not reported by the PI, the name and address of study personnel reporting the pregnancy

3. Pregnancies should be reported to the SPONSOR via telephone and fax as soon as the situation becomes known. The investigator/designee should telephone the appropriate contact person at the SPONSOR to give notice of a pregnancy that has been reported in a study subject. The investigator/designee should then complete an Adverse Event Report form (blank copy can be found in the administrative binder for the study or can be sent upon request) with the information listed above. When complete, the Adverse Event Report form should be faxed to the appropriate contact person at the SPONSOR.

   NOTE: As per the standard protocol language, a pregnancy is not considered an adverse experience. Therefore, the questions on the adverse event report form asking "Did the AE result in: Death, Hospitalization (or prolong existing hospitalization), Persistent or significant disability, Life threatening, Cancer, Due to overdose, Congenital anomaly, Other important medical event" do not need to be addressed by the investigator/designee.

   Any new information received regarding the reported pregnancy should be forwarded to the SPONSOR (via telephone and/or fax) so that a follow-up report can be filed.

4. For studies with a duration of 7 months:

   All pregnancies during the study (through and including the Month 7 study visit) must be reported to one of the individuals listed on the SPONSOR Contact Information page as outlined previously.

5. For studies with a duration of >7 months:

   Any subject who reports being pregnant at the next subsequent study visit after Month 7 (e.g. Month 12), or reports being pregnant anytime between the Month 7 and next subsequent study visit, should be questioned as to the estimated date of conception. If a subject reports that they are ≥ 4 months pregnant and/or if a subject reports that the date of conception was prior to the Month 7 visit, the pregnancy must be reported to one of the individuals listed on the SPONSOR Contact Information page as outlined previously.

6. For all studies:

   Any pregnancy that is spontaneously reported to study site personnel in a subject who has discontinued from the study prior to receiving all doses of vaccine/placebo and becomes pregnant within one month following her last dose of study vaccine/placebo, must be reported to one of the individuals listed in the SPONSOR Contact Information page. If the pregnancy occurred greater than one month following the last dose of study vaccine/placebo, the pregnancy does not need to be reported or followed for outcome.

Follow-up for Outcome

7. When a subject is discontinued from the study due to pregnancy prior to the Month 7 study visit, the investigator/designee should obtain contact information. This contact information should include current address and phone number, as well as the name, address, and phone number of a friend or relative who may be contacted in case attempts to contact the subject fail (if possible). Study sites may also consider collecting the name and phone number of the subject's primary care physician and/or obstetrician (if possible).
8. Subjects discontinued from the study due to pregnancy should be instructed to inform the sites of any change in address or phone number.
9. Subjects discontinued from the study due to pregnancy should be informed of the need and importance of maintaining contact with the study site personnel in order to report the outcome of the pregnancy. Study sites may consider placing periodic phone calls to subjects who have been discontinued from the study due to pregnancy in order to maintain current contact information.

10. Outcome (completion/termination) of the pregnancy must be reported to the SPONSOR using the Pregnancy Outcome Questionnaire (Attachment 2). The final outcome of the pregnancy should be reported as close to the estimated delivery date as possible (not to exceed 1 year after the initial pregnancy report).
11. If the outcome of the pregnancy is associated with a serious adverse event (i.e. congenital anomaly, adverse event associated with termination), an Adverse Event Report Form should be completed. All serious adverse events must be reported to the SPONSOR within 24 hours. Information regarding serious adverse events may be obtained from the subject. Additional information may be obtained from the subject's physician and/or pediatrician, if appropriate and agreed to by the subject. If possible, a discharge summary should accompany the Adverse Event Report.
12. If the subject can not be reached to report the outcome of the pregnancy, this information should be documented and reported to the SPONSOR.

RESPONSIBILITY OF THE CLINICAL TEAM

1. Once a pregnancy is reported to the SPONSOR from a clinical study site, the event must be reported to WPS&E via an Adverse Event Report Form (within 2 working days if associated with a serious outcome and within 10 working days if no known serious outcome, or the outcome is as yet unknown). The report will include all the previously mentioned information.
2. Information from the initial report will be entered into a tracking database (information to include protocol number, study site number, name of primary investigator, allocation number, subject ID [initials], and estimated delivery date [EDD])
   Note: If EDD is not given, it will be estimated to be ~36 weeks from the date of the initial report.
3. Once the EDD has arrived, a letter will be sent to the primary investigator at the reporting study site as a reminder to obtain outcome information using the questionnaire.
4. The tracking database will then be checked monthly to ensure outcome information has been received. A follow-up phone call will be placed to sites where outcome information is still outstanding.
5. Any new information, regarding the pregnancy, reported from the clinical study sites will be reported to WPS&E in a follow-up report.
6. Once the outcome of a pregnancy is reported to the clinical team, a final report will be sent to WPS&E using the information recorded on the Pregnancy Outcome Questionnaire. If a subject can not be reached in order to report the outcome of the pregnancy (i.e. lost to follow-up), a report should be filed with WPS&E indicating this fact.

7. The clinical team will ensure that copies of all reports are sent to the appropriate personnel (i.e. original to WPS&E, copy to site, study file, MRA, RIBL).
8. The final outcome of the pregnancy should be reported as close to the estimated delivery date as possible (not to exceed 1 year after filing of the initial pregnancy report).

ATTACHMENTS

Attachment 1 – Adverse Event Report Form
Attachment 2 – Pregnancy Outcome Questionnaire
Attachment 3 – Sample Reminder Letter

Attachment 1

MERCK RESEARCH LABORATORIES
ADVERSE EVENT REPORT

PATIENT INFORMATION — FIRST NAME OR INITIALS _____ LAST _____ ALLOCATION NO. _____ AGE _____ SEX _____ WEIGHT _____ KG _____ LB PREGNANT _____ WKS. GEST. _____

COMPLETE STUDY TITLE:

_____
_____
_____
_____

ADVERSE EVENT(S)	IS AE IN LABELING (Y / N)	ONSET DATE	CAUSALITY[a] Y OR N	OUTCOME[b]	DID AE RESULT IN: DEATH*	HOSPITALIZATION OR PROLONG EXISTING HOSPITALIZATION	PERSISTENT OR SIGNIFICANT DISABILITY	WAS AE LIFE THREATENING	IS AE CANCER	IS AE DUE TO	IS AE OVERDOSE	IS AE CONGENITAL	IS AE ANOMALY	IS AE OTHER MED EVENT
					ENTER Y FOR YES OR N FOR NO FOR EACH AE									

*If patient died, record death as an adverse event, specify date, complete item (a) above, and record probable cause(s) of death here.

PROBABLE CAUSE(S) OF DEATH
1. _____
2. _____
3. _____

PRIMARY SUSPECT DRUG	FORMULATION (e.g. Tablet)	ROUTE	INDICATION FOR USE	STRENGTH (mg or specify units)	FREQUENCY	TOTAL DAILY DOSE AT TIME OF AE (mg or specify units)	START DATE	STOP DATE	ACTION TAKEN[c]
SECONDARY SUSPECT DRUG AND OTHER MERCK THERAPY									

DID ADVERSE EVENT (AE) DIMINISH AFTER STOPPING SUSPECT DRUG?	___ YES	___ NO	___ NOT APPLICABLE (Suspect drug not stopped)	If 'YES' specify AE(s)	_____
DID ADVERSE EVENT REAPPEAR AFTER RESTARTING SUSPECT DRUG?	___ YES	___ NO	___ NOT APPLICABLE (Suspect drug not restarted)	If 'YES' specify AE(s)	_____

RECENT / CONCOMITANT THERAPY (WITHIN 14 DAYS OF ONSET OF AE)	DAILY DOSAGE (mg or specify units)	START DATE	STOP DATE	INDICATION FOR USE

a) **CAUSALITY**
Was there a reasonable possibility that the adverse experience may have been caused by the suspect drug?

b) **OUTCOME**
1 = Recovered
2 = Not Recovered

c) **ACTION TAKEN REGARDING SUSPECT DRUG**
1 = None
2 = Discontinued
3 = Dosage Reduced
4 = Dosage Interrupted

NOTE: COMPLETE PAGE 2

cc:

WAES-USA

ALLOCATION NO. _____

MEDICAL HISTORY (RELEVANT TO AE)	
CONCURRENT CONDITIONS (ONSET PRIOR TO SUSPECT THERAPY)	OTHER MEDICAL HISTORY

LABORATORY RESULTS / DIAGNOSTIC TESTS (RELEVANT TO AE)	DATE	VALUE	UNITS	COMMENTS (NORMAL / ABNORMAL)

NARRATIVE AND COMMENTS

FULL NAME OF PRIMARY INVESTIGATOR _____

NAME AND ADDRESS OF REPORTING PHYSICIAN _____

STUDY NO. _____ COMPASSIONATE USE _____ MK/V# _____ MISC CRF

EXTENSION NO. _____ AMENDMENT NO. _____

IND NO. _____ IIN NO. _____ INITIAL REPORT ___ OR FOLLOW-UP ___

DATE MERCK RECEIVED DATA RECORDED ON **THIS** REPORT _____

PERSON REPORTING: NAME _____

PHONE NUMBER: _____

SIGNATURE _____ DATE: _____

Product: V501
Protocol/Amendment No.: 018-04
Appendix: 1

Attachment 2

MERCK Research Laboratories
Vaccine

Pregnancy Outcome Questionnaire - HPV

Merck & Co., Inc. is committed to the CONFIDENTIAL collection of patient information. In order to allow for the collection of pregnancy outcome data, minimize duplicate reporting, and prevent loss to follow-up, please COMPLETE ALL SECTIONS below. Please correct any inaccurate pre-filled information.

Subject ID (initials and allocation number): _____

Pregnancy Outcome (**If multiple birth**, please photocopy and complete a form for each infant)

☞❑ Liveborn infant: Birthdate ___/___/___ Sex _____ Weight _____
Weeks from LMP _____
Was the infant normal? ❑yes ❑no
Were there congenital anomalies? If so, describe
_____
Were there other complications or abnormalities? If so, describe
_____
_____
_____

☞❑ Elective termination ❑ Spontaneous abortion (<20 weeks)
❑ Fetal death/stillbirth (≥20 weeks)
Date ____/____/____ Weeks from LMP _____
Were the products of conception examined? ❑yes ❑no ❑unknown
Was the fetus normal? ❑yes ❑no ❑unknown
If no, describe
_____
_____

Obstetric Information
❑no ❑yes Complication during pregnancy, specify
_____
❑no ❑yes Complication during labor/delivery, specify
_____
❑no ❑yes Diagnostic test during pregnancy. If yes, dates and test results:
_____
_____
_____
❑no ❑yes Infections or illnesses during pregnancy, specify
_____
❑no ❑yes Concurrent medical conditions, specify
_____
_____

Product: V501
Protocol/Amendment No.: 018-04
Appendix: 1

Other Medication Used During This Pregnancy

Name of medication	Date(s) of use	Strength (eg. 5 mg)	Number of doses taken	Reason for Use

Infant Adverse Event

❑no ❑yes If yes, describe

_____
_____
_____
_____
_____

Questionnaire was completed by: _____ **Date:** _____

Merck Use Only	WAES Number - _____

Product: V501
Protocol/Amendment No.: 018-04
Appendix: 1

Attachment 3
Sample Reminder Letter

Date

Name
Address
Address
Address

Subject: Merck & Co., Inc. HPV Vaccine Protocol _____
Study _____-_____
Pregnancy Outcome (initials/allocation number)

Dear Dr. _____,

The purpose of this letter is to remind you that a report documenting the outcome of the reported pregnancy for subject (initials/allocation number) is now due. Please complete the Pregnancy Outcome Questionnaire and return, via fax, to the Medical Monitor/MPC assigned to your study site.

Very truly yours,

MPC

Product: V501
Protocol/Amendment No.: 018-04
Appendix: 2

APPENDIX 2

Study Procedures by Visit

	PERIOD:								
Compound No: V501 **Protocol No:** 018	**TIME FRAME** *(Day, Week, Month)*:	Day 1	Month 2	Month 6	Month 7	Month 12[†]	**Month 18**	**Month 24**	UNS
	VISIT:	1	**2**	**3**	**4**	**5**	**6**	**7**	**U**
Procedure	**Worksheet ID**								
Informational brochure/prescreening	Brochure	x							
Informed consent/assent	Worksheet	x							
Inclusion criteria	INCL	x							
Exclusion criteria	EXCL	x							
Demographics	D	x							
Telephone contact log	Worksheet					x			
Subject telephone contact	STC					x			
Temperature (pediatric)	TEMPp		x	x	x				x
Adverse experience	NSAEv/SAEv/AEOS		x	x	x	x	x		x
Serious Adverse Experience (Vaqta™)	SAEv/AEOS						**x**	**x**	**x**
Concomitant therapies (special medications)	CRX1		x	x	x				x

Product: V501
Protocol/Amendment No.: 018-04
Appendix: 2

Study Procedures by Visit (Cont.)

	PERIOD:								
Compound No: V501 **Protocol No:** 018	**TIME FRAME** *(Day, Week, Month)*:	Day 1	Month 2	Month 6	Month 7	Month 12[†]	**Month 18**	**Month 24**	UNS
	VISIT:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**U**
Procedure	**Worksheet ID**								
Concomitant therapies (other medications)	CRX2		x	x	x				x
Concomitant nonstudy vaccine	CVX		x	x	x				x
Safety follow-up question	SFUQ		x	x	x				x
Vital signs	V	x	x	x	x		x		x
Medical history	MH	x	x	x	x	x	x		x
Prior therapies (special medications)	PRX1	x	x	x					x
Prior therapies (other medications)	PRX2	x	x	x					x
Prior nonstudy vaccine	PVX	x	x	x					x
Urine pregnancy test	UPT	x	x	x			x	x	x
Serum pregnancy test	SPT	x	x	x			x	x	x
Specimen collection	SCV	x			x		x		x
Supplemental lab tests	SLAB	x	x	x	x		x		x
Vaccine administration	Worksheet	x	x	x					
Study vaccinations(s)	RXV	x	x	x					x
Pregnancy status	PSTAT								x

Study Procedures by Visit (Cont.)

	PERIOD:								
Compound No: V501 **Protocol No:** 018	**TIME FRAME** *(Day, Week, Month)*:	Day 1	Month 2	Month 6	Month 7	Month 12[†]	**Month 18**	**Month 24**	UNS
	VISIT:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**U**
Procedure	**Worksheet ID**								
Maternal information (women of child bearing) (study binder)	MPREG								x
Previous pregnancy outcome/outcome of pregnancy/(women of child bearing) (study binder)	PPREG/OPREG								x
Pregnancy worksheet – trimester update (study binder)	Worksheet								x
Patient (or subject) status	STATUS	x	x	x	x	x	x		x
Vaqta® Vaccination	**To be determined**						**x**	**x**	
Vaccination report cards	VRC	x	x	x					

Product: V501
Protocol/Amendment No.: 018-04
Appendix: 3

APPENDIX 3

VAQTA® (Hepatitis A Vaccine, Purified Inactivated) Product Monograph

PRODUCT MONOGRAPH

VAQTA®

(hepatitis A vaccine, purified inactivated)

Suspension for Injection

THERAPEUTIC CLASSIFICATION

Active Immunizing Agent against hepatitis A virus

ACTION AND CLINICAL PHARMACOLOGY

VAQTA® (hepatitis A vaccine, purified inactivated) is an inactivated whole virus vaccine which has been shown to induce antibody to hepatitis A virus protein.

Disease Epidemiology

Hepatitis A virus is one of several hepatitis viruses that cause a systemic infection with pathology in the liver. The incubation period ranges from approximately 20 to 50 days. While the course of the disease is generally benign and does not result in chronic hepatitis, infection with hepatitis A virus remains an important cause of morbidity and occasional fulminant hepatitis and death.

Hepatitis A is transmitted most often by the fecal-oral route, with infection occurring within private households, day-care centers, neonatal intensive care units, and chronic-care hospitals. Common-source outbreaks due to contaminated food and water supplies have occurred following consumption of certain foods such as raw shellfish, and uncooked foods prepared by an infected food-handler or otherwise contaminated prior to ingestion (salads, sandwiches, frozen raspberries, etc). Bloodborne transmission, while uncommon, is possible via blood transfusion, contaminated blood products, or from needles shared with an infected viremic individual. Sexual transmission has also been reported.[1-5]

The disease burden due to hepatitis A in the United States has been estimated to be approximately 75,800 cases of clinical hepatitis each year, resulting in 11,400 hospitalizations, and 80 deaths due to fulminant hepatitis. Worldwide, it has been estimated that 1.4 million cases occur annually.[2] The clinical manifestations of hepatitis A infection often pass unrecognized in children ≤ 2 years of age whereas overt hepatitis develops in the majority of infected older children and adults. Symptoms and signs of hepatitis A infection are similar to those associated with other types of viral hepatitis and include anorexia, nausea, fever/chills, jaundice, dark urine, light-colored stools, abdominal pain, malaise, and fatigue.

Clinical Evaluation

Clinical trials conducted worldwide with several formulations of the vaccine in 9181 healthy individuals ranging from 2 to 85 years of age have demonstrated that VAQTA® is highly immunogenic and generally well tolerated.

Protection from hepatitis A disease has been shown to be related to the presence of antibody; an anamnestic antibody response occurs in healthy individuals with a history of infection who are subsequently re-exposed to hepatitis A virus.[5] Similarly, protection after vaccination with VAQTA® was associated with the onset of seroconversion (≥ 10 mIU/mL of hepatitis A antibody, measured by a modification of the HAVAB* radioimmunoassay [RIA][6]) and with an anamnestic antibody response following booster vaccination with VAQTA®.

In a post-marketing safety study, conducted at a large health maintenance organization in the United States, a total of 42,110 individuals ≥2 years of age received 1 or 2 doses of VAQTA®. Safety was monitored by reviewing medical records that tracked emergency room and outpatient visits, hospitalizations and deaths. There was no serious, vaccine-related, adverse event identified among the 42,110 individuals in this study. There was no nonserious, vaccine-related, adverse event resulting in outpatient visits, with the exception of diarrhea/gastroenteritis in adults at a rate of 0.5%. There was no vaccine-related, adverse event identified that had not been reported in earlier clinical trials with VAQTA®.

Clinical Studies

In combined clinical studies, 97% of 1214 children and adolescents 2 to 17 years of age seroconverted within 4 weeks after a single ~25 U intramuscular dose of VAQTA®. Similarly, 95% of 1428 adults ≥ 18 years of age seroconverted within 4 weeks after a single ~50 U intramuscular dose of VAQTA®. Immune memory was later demonstrated by an anamnestic antibody response in individuals who received a booster dose.

While a study evaluating VAQTA® alone in a post-exposure setting has not been conducted, the concurrent use of VAQTA® (~50 U) and immune globulin (IG, 0.06 mL/kg) was evaluated in a clinical study involving healthy adults 18 to 39 years of age. Table 1 provides seroconversion rates at 4 and 24 weeks after the first dose in each treatment group and at one month after a booster dose of VAQTA® (administered at 24 weeks).

Table 1

Seroconversion Rates After Vaccination With VAQTA® Plus IG, VAQTA® Alone, and IG Alone

	VAQTA® plus IG	VAQTA®	IG
Weeks	**Seroconversion Rate**		
4	100% (n=129)	96% (n=135)	87% (n=30)
24	92% (n=125)	†97% (n=132)	0% (n=28)
28	100% (n=114)	100% (n=128)	N/A

† Seroconversion rate in the vaccine alone group significantly higher than that in the vaccine plus IG group (p=0.05).

N/A = Not Applicable.

A very high degree of protection has been demonstrated after a single dose of VAQTA® in children and adolescents.[7] The protective efficacy, immunogenicity, and safety of VAQTA® were evaluated in a randomized, double-blind placebo-controlled study involving 1037 susceptible healthy children and adolescents 2 to 16 years of age in a U.S. community with recurrent outbreaks of hepatitis A (The Monroe Efficacy Study). Each child received a single intramuscular dose of VAQTA® (~25 U) or placebo. Among those individuals who were initially seronegative (by modified HAVAB®), seroconversion was achieved in > 99% of vaccine recipients within 4 weeks after vaccination. The onset of seroconversion following a single dose of VAQTA® was shown to parallel the onset of protection against clinical hepatitis A disease.

Because of the long incubation period of the disease (approximately 20 to 50 days or longer in children), analysis of protective efficacy was based on cases of hepatitis A occurring ≥ 50 days after vaccination in order to exclude any children incubating the infection before vaccination. In subjects who were initially seronegative, the protective efficacy of a single dose of VAQTA® was observed to be 100% with 25 cases of clinical hepatitis A occurring in the placebo group and none in the vaccine group ($p<0.001$). No cases of clinical hepatitis A disease occurred in the vaccine group after day 18. In addition, 9 cases of clinical hepatitis A occurred in the placebo group while none occurred in the vaccine group 19 to 49 days after vaccination. Following demonstration of protection with a single dose and termination of the study, a booster dose was administered to most vaccinees 6, 12, or 18 months after the primary dose. The effectiveness of VAQTA® for use in community outbreak control has been demonstrated by the fact that, to date, no cases of hepatitis A disease ≥ 19 days after vaccination have occurred in those vaccinees from The Monroe Efficacy Study monitored for up to 9 years. In contrast, three nearby sister communities to Monroe have continued to experience outbreaks.[7-9]

Persistence

The total duration of the protective effect of VAQTA® in healthy vaccinees is unknown at present. However, seropositivity was shown to persist up to 18 months after a single ~25 U dose in most children and adolescents who participated in The Monroe Efficacy Study. In adults, seropositivity has been shown to persist up to 6 months after a single ~50 U dose.

Persistence of immunologic memory was demonstrated with an anamnestic antibody response to a booster dose of ~25 U given 6 to 18 months after the primary dose in children and adolescents, and to a booster dose of ~50 U given 6 months after the primary dose to adults.

In studies of healthy children and adolescents who received two doses (~25 U) of VAQTA® at 0 and 6 to 18 months, the hepatitis A antibody response to date has been shown to persist for up to 6 years. The GMTs tend to decline over time.

In studies of healthy adults who received two doses (~50 U) of VAQTA® at 0 and 6 months, the hepatitis A antibody response to date has been shown to persist up to 4-6 years. In a follow-up study of 381 vaccinated subjects, after an initial decline over 2 years, the GMTs appeared to plateau during the 2- to 6-year period. It is, however, noted that 6-year antibody persistence samples were available for 171 subjects only.

Studies in healthy children, adolescents and adults are ongoing to evaluate longer-term persistence and the need, if any, for additional booster doses.

In the absence of study data on antibody persistence for vaccine recipients over several decades, an extrapolation from a kinetic model of antibody decay was used to estimate the duration of antibody. Extrapolation of observed antibody titers from year 2 to year 3 in 118 children and adults, most of whom had received 3 injections of 6, 13, or 25 unit vaccine, suggests that detectable levels of antibody may persist after the booster dose for many years. The median duration based on this extrapolation was calculated to be 21 years [95% CI = (14 to 27 years)].

Interchangeability of the Booster Dose

A clinical study in 537 healthy adults, 18 to 83 years of age, evaluated the immune response to a booster dose of VAQTA® and Havrix** (hepatitis A vaccine, inactivated) given at 6 or 12 months following an initial dose of Havrix. When VAQTA® was given as a booster dose following Havrix, the vaccine produced an adequate immune response (see Table 2) and was generally well tolerated (see DOSAGE AND ADMINISTRATION, Interchangeability of the Booster Dose).

Table 2

VAQTA® Versus Havrix Seropositivity Rate, Booster Response Rate† and Geometric Mean Titer at 4 Weeks Postbooster

First Dose	Booster Dose	Seropositivity Rate	Booster Response Rate†	Geometric Mean Titer
Havrix 1440 EL.U.	VAQTA® 50 U	99.7% (n=313)	86.1% (n=310)	3272 (n=313)
Havrix 1440 EL.U.	Havrix 1440 EL.U.	99.3% (n=151)	80.1% (n=151)	2423 (n=151)

† Booster Response Rate is defined as greater than or equal to a tenfold rise from prebooster to postbooster titer and postbooster titer ≥ 100 mIU/mL.

Use With Other Vaccines

A controlled clinical study was conducted with 240 healthy adults, 18 to 54 years of age, who were randomized to receive either VAQTA®, yellow fever and typhoid vaccines concomitantly at separate injection sites; yellow fever and typhoid vaccines concomitantly at separate injection sites; or VAQTA® alone. The seropositivity rate for hepatitis A when VAQTA®, yellow fever and typhoid vaccines were administered concomitantly was generally similar to when VAQTA® was given alone. The antibody response rates for yellow fever and typhoid were adequate when yellow fever and typhoid vaccines were administered concomitantly with and without VAQTA®. The concomitant administration of these three vaccines at separate injection sites was generally well tolerated (see DOSAGE AND ADMINISTRATION, Use With Other Vaccines).

INDICATIONS AND CLINICAL USE

VAQTA® (hepatitis A vaccine, purified inactivated) is indicated for vaccination against infection caused by hepatitis A virus.

VAQTA® is indicated for active pre-exposure prophylaxis against disease caused by hepatitis A virus. Vaccination is recommended in children 2 years of age and older, adolescents, and adults who are at risk of contracting or spreading infection or who are at risk of life-threatening disease if infected, including but not limited to:[1-5,10,11]

A. **Travelers to Endemic or Outbreak Areas**

B. **Frequently Affected Communities**

Members residing in any community with one or more recorded outbreaks within the last five years.

C. **Day-Care**

Children and staff of day-care centers as well as their parents, siblings, and other contacts.

D. **Military Personnel Prior to Departure for Endemic or Outbreak Areas**

E. **Persons for Whom Hepatitis A is an Occupational Hazard**

Health-care workers.

Staff and residents of orphanages, chronic care hospitals and mental health-care facilities.

Sewage workers.

F. **Hemophiliacs and Other Recipients of Therapeutic Blood Products**

G. **People with Chronic Liver Disease (Including Chronic Hepatitis C Infection).**

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People with chronic liver disease who may not be at increased risk of infection but are at increased risk of fulminant hepatitis A.[10,11]

H. **Food Handlers**

I. **Consumers of High-Risk Foods**

e.g,. raw shellfish

J. **Persons at Increased Risk of the Disease Due to their Sexual Practices**

Homosexually-active males.

Persons who repeatedly contract sexually transmitted diseases.

K. **Users of Illicit Injectable Drugs**

VAQTA® will not prevent hepatitis caused by infectious agents other than hepatitis A virus.

Revaccination: See DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

WARNINGS

If VAQTA® (hepatitis A vaccine, purified inactivated) is used in individuals with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

VAQTA® IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 YEARS OF AGE SINCE DATA ON USE IN THIS AGE GROUP ARE NOT CURRENTLY AVAILABLE.

PRECAUTIONS

General

Individuals who develop symptoms suggestive of hypersensitivity after an injection of VAQTA® (hepatitis A vaccine, purified inactivated) should not receive further injections of the vaccine (see CONTRAINDICATIONS).

As with any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

Since there is a possibility that the vaccine may contain trace amounts of neomycin, the possibility of an allergic reaction in individuals sensitive to this substance should be kept in mind when considering the use of this vaccine (see PHARMACEUTICAL INFORMATION, Composition).

As with any vaccine, vaccination with VAQTA® may not result in a protective response in all susceptible vaccinees.

Any acute infection or febrile illness may be reason for delaying use of VAQTA® except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

VAQTA® will not prevent hepatitis caused by infectious agents other than hepatitis A virus. Because of the long incubation period (approximately 20 to 50 days) for hepatitis A, it is possible for unrecognized hepatitis A infection to be present at the time the vaccine is given. The vaccine may not prevent hepatitis A in such individuals.

Use in Children

VAQTA® has been shown to be generally well tolerated and highly immunogenic in individuals 2 to 17 years of age. See DOSAGE AND ADMINISTRATION for the recommended dosage schedule.

Safety and effectiveness in infants below 2 years of age have not been established.

Use in Obstetrics

Animal reproduction studies have not been conducted with VAQTA®. It is also not known whether VAQTA® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VAQTA® should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether VAQTA® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VAQTA® is administered to a woman who is breast-feeding.

Carcinogenesis, Mutagenesis, Reproduction

VAQTA® has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

Drug Interactions

Use With Other Vaccines

VAQTA® may be given concomitantly at separate injection sites with yellow fever and typhoid vaccines.

The inactivated vaccines can be given simultaneously, but at separate anatomic sites, consideration being given to the precautions that apply to each individual vaccine. No inactivated vaccine has been shown to interfere with the immune response to another inactivated vaccine; thus, no particular interval between inactivated vaccines need be respected.[12]

The Advisory Committee on Immunization Practices, has stated that limited data from studies conducted among adults indicate that simultaneous administration of hepatitis A vaccine with diphtheria, poliovirus (oral and inactivated), tetanus, oral typhoid, cholera, Japanese encephalitis, rabies, or yellow fever vaccine does not decrease the immune response to either vaccine or increase the frequency of reported adverse events. Studies indicate that hepatitis B vaccine can be administered with VAQTA® without affecting immunogenicity or increasing the frequency of adverse events.[13]

Use With Immune Globulin

For individuals requiring either post-exposure prophylaxis or combined immediate and longer-term protection (e.g., travelers departing on short notice to endemic areas), VAQTA® may be administered concomitantly with IG using separate sites and syringes.

ADVERSE REACTIONS

Clinical Studies

No serious vaccine-related adverse experiences were observed during clinical trials.

In The Monroe Efficacy Study, 1037 healthy children and adolescents 2 to 16 years of age received either a primary dose of ~25 U of hepatitis A vaccine and a booster 6, 12, or 18 months later, or placebo. Subjects were observed during a 5-day period for fever and local complaints and during a 14-day period for systemic complaints. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Table 3 summarizes the local and systemic complaints (≥1%) reported in this study, without regard to causality. There were no significant differences in the rates of any complaint between vaccine and placebo recipients after Dose 1.

Table 3

Local and Systemic Complaints (≥ 1%)
Healthy Children and Adolescents from The Monroe Efficacy Study

	VAQTA® (hepatitis A vaccine, purified inactivated)		
REACTION	**Dose 1***	**Booster**	**Placebo*,†**
Injection-Site Complaints			
Pain	6.4% (33/515)	3.4% (16/475)	6.3% (32/510)
Tenderness	4.9% (25/515)	1.7% (8/475)	6.1% (31/510)
Erythema	1.9% (10/515)	0.8% (4/475)	1.8% (9/510)
Swelling	1.7% (9/515)	1.5% (7/475)	1.6% (8/510)
Warmth	1.7% (9/515)	0.6% (3/475)	1.6% (8/510)
Systemic Complaints			
Abdominal Pain	1.2% (6/519)	1.1% (5/475)	1.0% (5/518)
Pharyngitis	1.2% (6/519)	0% (0/475)	0.8% (4/518)
Headache	0.4% (2/519)	0.8% (4/475)	1.0% (5/518)

* No statistically significant differences between the two groups.
† Second injection of placebo not administered because code for the trial was broken.

Children/Adolescents - 2 to 17 Years of Age

In combined clinical trials (including Monroe Efficacy Study participants) involving 2595 healthy children and adolescents who received one or more ~25 U doses of hepatitis A vaccine, fever and local complaints were observed during a 5-day period following vaccination and systemic complaints during a 14-day period following vaccination. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Listed below are the complaints (≥ 1%) reported, without regard to causality, in decreasing order of frequency within each body system.

Table 4

Local and Systemic Complaints (≥ 1%) in Healthy Children and Adolescents from Combined Clinical Trials

Localized Injection-Site Reactions (generally mild and transient)	
Pain	18.7%
Tenderness	16.8%
Warmth	8.6%
Erythema	7.5%
Swelling	7.3%
Ecchymosis	1.3%
Body as a Whole	
Fever ≥ 38.9°C, Oral	3.1%
Abdominal pain	1.6%
Digestive System	
Diarrhea	1.0%
Vomiting	1.0%
Nervous System/Psychiatric	
Headache	2.3%
Respiratory System	
Pharyngitis	1.5%
Upper respiratory infection	1.1%
Cough	1.0%

Laboratory Findings

Very few laboratory abnormalities were reported and included isolated reports of elevated liver function tests, eosinophilia, and increased urine protein.

Adults - 18 Years of Age and Older

In combined clinical trials involving 1529 healthy adults who received one or more ~50 U doses of hepatitis A vaccine, fever and local complaints were observed during a 5-day period following vaccination and systemic complaints during a 14-day period following vaccination. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Listed below are the complaints (≥ 1%) reported, without regard to causality, in decreasing order of frequency within each body system.

Table 5

Local and Systemic Complaints (≥ 1%) in Healthy Adults from Combined Clinical Trials

Localized Injection-Site Reactions (generally mild and transient)	
Tenderness	52.6%
Pain	51.1%
Warmth	17.3%
Swelling	13.6%
Erythema	12.9%
Ecchymosis	1.5%
Pain/soreness	1.2%

Table 5 (continued)

Body as a Whole	
Asthenia/fatigue	3.9%
Fever ≥ 38.3°C, Oral	2.6%
Abdominal pain	1.3%
Digestive System	
Diarrhea	2.4%
Nausea	2.3%
Musculoskeletal System	
Myalgia	2.0%
Arm pain	1.3%
Back pain	1.1%
Stiffness	1.0%
Nervous System/Psychiatric	
Headache	16.1%
Respiratory System	
Upper respiratory infection	2.8%
Pharyngitis	2.7%
Nasal congestion	1.1%
Urogenital System	
Menstruation disorder	1.1%

Local and/or systemic hypersensitivity reactions occurred in < 1% of children, adolescents, or adults in clinical trials and included the following regardless of causality: pruritus, urticaria and rash.

As with any vaccine, there is the possibility that use of VAQTA® in very large populations might reveal adverse experiences not observed in clinical trials.

Post-marketing Safety Study

In a post-marketing safety study, a total of 42,110 individuals ≥2 years of age received 1 or 2 doses of VAQTA®. There was no serious, vaccine-related, adverse event identified. There was no nonserious, vaccine-related, adverse event resulting in outpatient visits, with the exception of diarrhea/gastroenteritis in adults at a rate of 0.5%.

Marketed Experience

The following additional adverse reactions have been reported with use of the marketed vaccine.

Nervous System

Very rarely, Guillain-Barré syndrome.

DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR USE ONLY. THE DELTOID MUSCLE IS THE PREFERRED SITE FOR INJECTION.

Do not inject intravenously, intradermally, or subcutaneously.

The vaccination series consists of one primary dose and one booster dose given according to the following schedule:

Pediatric/Adolescent

Individuals 2 to 17 years of age should receive a single 0.5 mL (~25 U) dose of vaccine at elected date and a booster dose of 0.5 mL (~25 U) 6 to 18 months later.

Adult

Adults 18 years of age and older should receive a single 1.0 mL (~50 U) dose of vaccine at an elected date and a booster dose of 1.0 mL (~50 U) 6 months later.

Interchangeability of the Booster Dose

A booster dose of VAQTA® (hepatitis A vaccine, purified inactivated) may be given at 6 to 12 months following the initial dose of other inactivated hepatitis A vaccines.

Use With Other Vaccines

VAQTA® may be given concomitantly with yellow fever and typhoid vaccines. Data on concomitant use with other vaccines are limited. Separate injection sites and syringes should be used for concomitant administration of injectable vaccines.

Known or Presumed Exposure to Hepatitis A Virus, Travel to Endemic Areas, and Use With Immune Globulin

VAQTA® may be administered concomitantly with IG using separate sites and syringes. The vaccination regimen for VAQTA® should be followed as stated above. Consult the manufacturers' Product Monograph for the appropriate dosage of IG. A booster dose of VAQTA® should be administered at the appropriate time as outlined above (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies and PRECAUTIONS, Drug Interactions).

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. After thorough agitation, VAQTA® is a slightly opaque, white suspension.

It is important to use a separate, sterile syringe and needle for each individual to prevent transmission of infectious agents from one person to another.

PHARMACEUTICAL INFORMATION

COMPOSITION

Active Ingredients

VAQTA® (hepatitis A vaccine, purified inactivated) is a sterile suspension for intramuscular injection.

VAQTA® is a highly purified inactivated whole virus vaccine derived from hepatitis A virus grown in cell culture in human MRC-5 diploid fibroblasts. It contains inactivated virus of a strain which was originally derived by further serial passage of a proven attenuated strain. The virus is grown, harvested, purified by a combination of physical and high performance liquid chromatographic techniques, formalin inactivated, and then adsorbed onto amorphous aluminum hydroxyphosphate sulfate. One milliliter of the vaccine contains approximately 50 units (U) of hepatitis A antigen, equivalent to approximately 50 nanograms (ng) of virus protein per mL which is highly purified and is formulated without a preservative. Within the limits of current assay variability, the 50 unit dose of VAQTA® contains less than 0.1 µg (less than 100 ng) of non-viral protein, less than 4×10^{-6} µg (less than 0.004 ng) of DNA, less than 10^{-4} µg (less than 0.1 ng) of bovine albumin, less than 0.8 µg (less than 800 ng) of formaldehyde and a trace of neomycin B sulphate [≤ 0.002 µg (≤ 2 ng)]. Other process chemical residuals are less than 10 parts per billion (ppb).

VAQTA® meets the World Health Organization requirement for biological substances including those for final vaccine residual bovine serum albumin.

VAQTA® is supplied in two presentations:

Pediatric/Adolescent Presentation: Each 0.5 mL dose contains approximately 25 U of hepatitis A virus protein as the active ingredient.

Adult Presentation: Each 1.0 mL dose contains approximately 50 U of hepatitis A virus protein as the active ingredient.

Non-Medicinal Ingredients

Pediatric/Adolescent Presentation: Each 0.5 mL dose contains approximately 0.225 mg of aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 35 µg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

Adult Presentation: Each 1.0 mL dose contains approximately 0.45 mg of aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 70 µg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

STABILITY AND STORAGE RECOMMENDATIONS

Store vaccine at 2°C - 8°C (36°F - 46°F).

DO NOT FREEZE since freezing destroys potency.

Stability studies with VAQTA® show that the potency of unopened vaccine is not significantly affected after exposure at 37°C for up to 6 months. This is **not**, however, a storage recommendation.

AVAILABILITY OF DOSAGE FORMS

VAQTA® (hepatitis A vaccine, purified inactivated) is available as follows:

Pediatric/Adolescent Presentation - 0.5 mL single-use vials containing 25 U of hepatitis A virus protein on an aluminum hydroxide adjuvant packaged in ones.

Adult Presentation - 1.0 mL single-use vials containing 50 U of hepatitis A virus protein on an aluminum hydroxide adjuvant, packaged in ones or fives.

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795-a,10,02

MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

V501
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine, 0.5 mL
Intramuscular Injection
cervixcancer, exgenlesion

PROTOCOL TITLE/NO.: A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents. # 018

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (47)

PRIMARY THERAPY PERIOD: 08-Oct-2003 to 19-Jan-2005. Clean file was achieved on 31-Jan-2005. The database was unblinded on 2-Feb-2005.

CLINICAL PHASE: III

DURATION OF TREATMENT: Vaccination at Day 1, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after administration of each dose. All subjects will be followed for persistence of antibody response and safety evaluation through Month 18.

OBJECTIVE(S): **Primary Safety Objective:** To demonstrate that a 3-dose regimen of quadrivalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents. **Secondary Objectives:** (1) To demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls. (2) To describe the persistence of immune response to the quadrivalent HPV (Types 6, 11, 16, 18) LI VLP vaccine, when given in a 3-dose regimen.

STUDY DESIGN: This study was a randomized, double-blind (operating under third party blinding and in-house blinding procedures), placebo-controlled, multicenter study with a target enrollment of approximately 1650 preadolescent and adolescent subjects.

SUBJECT DISPOSITION:

	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	Non-Alum Placebo	Total
SCREENING FAILURES:			20
RANDOMIZED:	1184	597	1781
Female (age range – years)	617 (9 to 15)	322 (9 to 15)	939
Male (age range – years)	567 (9 to 16)	275 (9 to 15)	842
VACCINATED AT:			
Dose 1	1179	596	1775
Dose 2	1149	573	1722
Dose 3	1123	562	1685
VACCINATION PERIOD (Day 1 Through Month 7)			
ENTERED	1179	596	1775
COMPLETED	1120	560	1680
CONTINUING†	1	0	1
DISCONTINUED	58	36	94
With Long-Term Follow-Up	7	4	11
Clinical Adverse Experience	2	0	2
Other	5	4	9
Without Long-Term Follow-Up	51	32	83
Clinical Adverse Experience	1	0	1
Lost to Follow-up	17	7	24
Moved	4	1	5
Other Reasons	1	2	3
Parent withdrew consent	9	8	17
Withdrew consent	19	14	33

† Subject did not complete Month 7 visit prior to the Month 7 visit date cutoff of 19-Jan-2005.
HPV = Human papillomavirus; VLP = Virus-like particles.

DOSAGE/FORMULATION NOS.: Subjects received one 0.5-mL intramuscular dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine or non-aluminum-containing placebo at Day 1, Month 2, and Month 6. Formulation numbers and dosage for the clinical material can be found in the table that follows:

Formulation Numbers, Dosage, and Package Information for Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine and Placebo

Clinical Material	Formulation Number	Dosage	Package and Storage
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	V501 VAI025T004	40/80/80/40 mcg plus 225 mcg aluminum adjuvant /mL 0.5 mL	0.75-mL single dose vial
Placebo for Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	PV501 VAI036P001	Carrier Solution Only /0.5 mL	0.75-mL single dose vial

HPV = Human papillomavirus; VLP = Virus-like particles.

DIAGNOSIS/INCLUSION CRITERIA: Healthy preadolescent or adolescent subjects between the ages of 9 years and 0 days and 15 years and 364 days; must not yet have had coitarche and did not plan on becoming sexually active through the course of the study; must have agreed to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes; no temperature ≥100°F or ≥37.8°C (oral) within 24 hours prior to the first injection; not pregnant at study start (as determined by a serum pregnancy test or urine pregnancy test sensitive to 25 IU Human Chorionic Gonadotropin [hCG]) or is a male.

EVALUATION CRITERIA: **Immunogenicity**: This study included 2 secondary objectives relating to immunogenicity. The first was to demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 competitive Luminex immunoassay (cLIA) responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls. Two immunogenicity measurements were used to address this objective: (1) geometric mean anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 serum cLIA levels at Month 7; and (2) among subjects who were baseline naïve to HPV 6, HPV 11, HPV 16, and/or HPV 18, the proportion who became seropositive to the relevant vaccine HPV type by Month 7. Serum samples were to be collected from all subjects at Day 1, Month 7, and Month 18. The second immunogenicity objective was to describe the persistence of immune response to a 3-dose regimen of the vaccine. This objective will be addressed in a separate report summarizing immune responses through Month 18. **Safety:** The primary objective of this study related to the safety of the vaccine. The primary hypothesis stated that a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine will be generally well tolerated in adolescents and preadolescents. In order to address this objective, the study called for a detailed tolerability analysis, with emphasis on the following prespecified adverse experiences: vaccine-related adverse experiences, vaccination report card (VRC)-prompted injection-site adverse experiences (swelling/redness and pain/tenderness/soreness), VRC-prompted systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), severe adverse experiences, and fever.

STATISTICAL PLANNING AND ANALYSIS: **Immunogenicity:** The first immunogenicity hypothesis regarding noninferiority of boys to girls with respect to Geometric Mean Titers (GMTs) at Week 4 Postdose 3 was tested using an analysis of variance (ANOVA) model. The natural log of the individual titers of the subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group was modeled as a function of gender, age at enrollment, and geographic region, which were considered fixed effects. The analysis was performed using the Mean Squared Error (MSE) from the ANOVA model as an estimate of variance and a one-sided test for the similarity of two means was performed at the 0.025 level using a t-distribution. The anti-log of the estimated treatment difference in the ANOVA model and the confidence interval associated with this difference was computed.

In order to reject the null hypothesis for a given HPV type, the lower bound of the 95% confidence interval on the ratio of GMTs had to be greater than 0.5 (i.e., to rule out a 2-fold decrease). The null hypothesis for each HPV type had to be rejected in order for boys to be declared noninferior to girls with respect to GMTs. The second immunogenicity hypothesis regarding noninferiority between genders (boys minus girls) with respect to the percentage of subjects who seroconvert for each HPV type by Week 4 Postdose 3 was addressed by 4 one-sided tests of noninferiority (one corresponding to each HPV type) conducted at the 0.025 level. These tests above were conducted based on methods developed by Miettinen and Nurminen for testing the equivalence of 2 proportions, which allows for stratification by age and geographic region. In order to reject the null hypothesis for a given HPV type, the lower bound of the 95% confidence interval on the difference in percentages of seroconverters between boys and girls had to be greater than -0.05. The null hypothesis for each HPV type had to be rejected in order for boys to be declared noninferior to girls with respect to seroconversion rates. In order to declare the immune

responses of boys to the quadrivalent HPV vaccine at Week 4 Postdose 3 noninferior to those of girls, the statistical criterion had to be met for each HPV type and for each endpoint (GMTs and seroconversion rates). The per-protocol population (PPI) was the population from which inference was made.

Safety: All subjects who received at least one injection and had follow-up data were included in the safety summaries. Adverse experiences were summarized descriptively as frequencies and percentages by vaccination group and type of adverse experience, by vaccination visit and across all vaccination visits. Elevated temperatures (≥100° F, ≥37.8° C, oral or oral equivalent) within 5 days following each vaccination were summarized in a similar manner. In addition, risk differences and associated 95% confidence intervals were computed comparing the vaccine and placebo groups across all vaccination visits with respect to adverse experiences with ≥1% incidence in either vaccination group and elevated temperatures. p-Values were computed only for those adverse experiences that were prompted for on the VRC (elevated temperatures, injection-site pain, injection-site swelling, injection-site redness, muscle/joint pain, headaches, hives, rashes, diarrhea). In order to provide a basis for bridging the large safety database acquired in previous HPV studies for female subjects to the safety profiles for male subjects, adverse experiences were also summarized separately for boys and girls (within each vaccination group) and by age group. No formal comparisons were made between boys and girls or age group with respect to adverse experiences. The placebo used in this study contained no aluminum. In order to eliminate the impact of aluminum-containing non-study vaccinations received during the course of this study on the assessment of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine and the non-aluminum-containing placebo groups in terms of the incidence of adverse experiences, summaries of incidence rates of overall adverse experiences, specific adverse experiences that occur in ≥1% of subjects in either vaccination group, and elevated temperatures were also provided, by vaccination group, excluding those subjects who received any aluminum-containing non-study vaccinations during this study. These summaries were provided across all vaccination visits. No formal comparisons were performed in this subset of subjects.

RESULTS:

Immunogenicity: The first secondary immunogenicity objective of this study was to demonstrate that the Week 4 Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are non-inferior to the responses observed in preadolescent and adolescent girls. To address this objective, estimated GMTs at Week 4 Postdose 3 and seroconversion rates by Week 4 Postdose 3 were compared between boys and girls in the PPI population. The tables that follow present the results of these analyses. For both endpoints, the statistical criterion for non-inferiority was met for each vaccine HPV type.

Statistical Analysis of Non-Inferiority of Month 7 HPV cLIA Geometric Mean Titers Comparing Boys With Girls Among Subjects Who Received Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (Per-Protocol Immunogenicity Population[†])

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine					
	Boys (Comparison Group A) (N=564)		Girls (Comparison Group B) (N=615)		Estimated Fold Difference	
Assay (cLIA)	n	Estimated GMT[‡] (mMU/mL)	n	Estimated GMT[‡] (mMU/mL)	Group A/Group B (95% CI)[‡]	p-Value for Non-Inferiority[‡,§]
Anti-HPV 6	471	1,003.7	501	807.7	1.24 (1.03, 1.49)	<0.001
Anti-HPV 11	471	1,333.8	501	1,184.7	1.13 (0.93, 1.36)	<0.001
Anti-HPV 16	471	6,345.1	502	4,513.0	1.41 (1.11, 1.78)	<0.001
Anti-HPV 18	474	1,577.5	503	1,073.8	1.47 (1.17, 1.85)	<0.001

Overall conclusion: Non-Inferior[¶].

[†] The per-protocol immunogenicity population includes all subjects who were not general protocol violators; received all 3 vaccinations within acceptable day ranges; were seronegative at Day 1 for the relevant HPV type(s); and had a Month 7 serum sample collected within an acceptable day range.

[‡] Parameter estimates, confidence intervals, and p-values are based on a statistical model adjusting for region and age.

[§] For the null hypothesis that $GMT_{Boys}/GMT_{Girls} \leq 0.5$ (2-fold decrease), a p-value <0.025 supports a conclusion that the specific type anti-HPV response in Boys is non-inferior to the response in Girls.

[¶] The quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine induces similar immune responses, as measured by the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3, in adolescent boys 9 to 15 years of age, as compared to adolescent girls 9 to 15 years of age.

N = Number of subjects in the respective demographic cohort who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; VLP = Virus-like particles..

Statistical Analysis of Non-Inferiority of Month 7 Anti-HPV Seroconversion Rates Comparing Boys With Girls Among Subjects Who Received Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (Per-Protocol Immunogenicity Population[†])

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine				Estimated Percentage Point Difference Boys minus Girls (95% CI)[‡]	p-Value for Non-Inferiority[‡§]
	Boys (N=564)		Girls (N= 615)			
Anti-HPV Response	n	Estimated Response[‡] (%)	n	Estimated Response[‡] (%)		
HPV 6 cLIA ≥20 mMU/mL	471	99.8	501	99.8	-0.0 (-1.1, 0.9)	<0.001
HPV 11 cLIA ≥16 mMU/mL	471	99.8	501	99.8	-0.0 (-1.1, 0.9)	<0.001
HPV 16 cLIA ≥20 mMU/mL	471	99.6	502	99.8	-0.2 (-1.4, 0.7)	<0.001
HPV 18 cLIA ≥24 mMU/mL	474	99.8	503	99.6	0.2 (-0.8, 1.2)	<0.001
Overall conclusion: Non-inferior[‖]						

[†] The per-protocol immunogenicity population includes all subjects who were not general protocol violators; received all 3 vaccinations within acceptable day ranges; were seronegative at Day 1 for the relevant HPV type(s); and had a Month 7 serum sample collected within an acceptable day range.
[‡] Parameter estimates, confidence intervals, and p-values are based on a statistical model adjusting for region and age.
[§] For the null hypothesis that $p_{Boys}-p_{Girls} \leq -0.05$, a p-value <0.025 supports a conclusion that the specific type anti-HPV seroconversion rate in Boys is non-inferior to the seroconversion rate in Girls.
[‖] The Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine induces similar immune responses, as measured by the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3, in adolescent boys 9 to 15 years of age, as compared to adolescent girls 9 to 15 years of age.
Seropositive is defined as anti-HPV serum cLIA levels ≥20, 16, 20, 24 mMU/mL for HPV types 6, 11, 16, and 18, respectively.
N = Number of subjects in the respective demographic cohort who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units.
VLP = Virus-like particles.

RESULTS:

Safety: The primary safety objective of this study was to demonstrate that the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is well tolerated in preadolescents and adolescents. The table that follows displays a summary of clinical adverse experiences reported from Days 1 through 15 following any vaccination visit by vaccination group. The following observations can be made:

- Overall, a higher proportion of subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group reported one or more adverse experiences compared with subjects in the non-aluminum-containing placebo group.
- The difference between vaccination groups in the proportion of subjects who reported one or more adverse experiences Days 1 to 15 following any vaccination visit was primarily due to a higher proportion of subjects reporting one or more injection-site adverse experiences in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group compared with the non-aluminum-containing placebo group.
- Very few subjects experienced a serious adverse experience. None of the serious adverse experiences reported in the study were judged by the study investigator to be vaccine-related.
- Very few subjects discontinued study participation due to an adverse experience.

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)	
	n	(%)	n	(%)
Subjects in analysis population	1179		594	
Subjects without follow-up	14		10	
Subjects with follow-up	1165		584	
Number (%) of subjects:				
with no adverse experience	202	(17.3)	192	(32.9)
with one or more adverse experiences	963	(82.7)	392	(67.1)
injection-site adverse experiences	877	(75.3)	292	(50.0)
systemic adverse experiences	541	(46.4)	260	(44.5)
with vaccine-related† adverse experiences	913	(78.4)	339	(58.0)
injection-site adverse experiences	877	(75.3)	292	(50.0)
systemic adverse experiences	274	(23.5)	134	(22.9)
with serious adverse experiences	5	(0.4)	0	(0.0)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse experience	3	(0.3)	0	(0.0)
discontinued due to a vaccine-related adverse experience	2	(0.2)	0	(0.0)
discontinued due to a serious adverse experience	1	(0.1)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
‡ Discontinued = Subject discontinued from therapy.
Percentages are calculated based on the number of subjects with follow-up.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

CONCLUSIONS:

1. Administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9- to 15-year-old boys induces anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3 that are at least as robust as those observed 4 weeks following administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9- to 15-year-old girls.
2. Administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9- to 15-year-old boys and girls results in development of detectable anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 at 4 weeks Postdose 3 in over 98% of adolescents.
3. Administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine to 9- to 15-year-old boys and girls is generally well tolerated.
4. Compared with a 3-dose regimen of non-aluminum containing placebo, administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine results in an increase in the proportion of subjects who report one or more injection-site adverse experiences, including an increase in the proportion of subjects who report an injection-site adverse experience of moderate or severe intensity.

AUTHORS:

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PRINCIPAL AUTHORS' SIGNATURES

PRODUCT: V501
PROTOCOL NO.: 018 – Month 12 Safety Report
STUDY TITLE: A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents.

This report completely and accurately describes the conduct and results of the study to the best of our knowledge.

s47F(1)

Suzanne Lukac, B.S.
Associate MPCS
Biologics, Clinical Research

20-July-2005
Date

s47F(1)

Eliav Barr, M.D.
Senior Director
Biologics, Clinical Research

20 July 05
Date

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

MONTH 12

A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents

Was visit completed? **No** ☐ *If **yes**, complete form below.*

Date of visit: _____
DD-Mon-YYYY

WORKSHEETS COMPLETED AT THIS VISIT

Indicate the Source Document below ONLY for those that differ from the Source Document Identification Log

Worksheet	Worksheet ID	Worksheet	VRC	Chart	Other, *specify*:
Telephone contact log	----	☐	☐	☐	_____
Subject telephone contact	STC	☐	☐	☐	_____
Serious adverse experience	SAEv/AEos	☐	☐	☐	_____
Medical history	MH	☐	☐	☐	_____
Concomitant non-study vaccine	CVX	☐	☐	☐	_____
Patient (or subject) status††	STATUS	☐	☐	☐	_____

†† *Complete **STATUS** when **patient** is **excluded, completed or discontinued. Found in STATUS section of patient (subject) binder.***

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording.

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

Source Document - Retain in Patient Binder - Do Not Send to the Sponsor

TELEPHONE CONTACT INSTRUCTIONS

Please use the log below to document all telephone attempts. The timing of the phone call will be twelve months after day one ± 3 weeks. **Information from this log will need to be transcribed onto the Telephone Contact worksheet for the Month 12 visit.**

The following question is asked to the parent/guardian of the subject to record any new/worsening medical conditions, hospitalizations, or additional vaccines received. If the parent/guardian of the subject during the phone call reports a serious adverse event, new medical history or additional vaccine(s) received, study personnel should indicate this new information on the appropriate worksheet (MH, SAEv or CVX).

- Complete SAEv and notify Merck Monitor within 24 hours if the subject has the following condition: death, vaccine related SAE (possible, probable and definite), congenital abnormalities (of the subject's offspring), or cancer.
- Enter information onto MH for all other conditions.
- Enter additional vaccine(s) received on the CVX worksheet.
- The Month 12 phone call should occur 12 months from Day 1 visit ± 3 weeks.

TELEPHONE CONTACT LOG

Since his/her last visit, has the subject:

seen a doctor for any new or worsening medical condition?

No ☐

Yes ☐ *If **yes**, please explain:* _____

_____

been hospitalized?

No ☐

Yes ☐ *If **yes**, please explain:* _____

_____

received any additional vaccines?

No ☐

Yes ☐ *If **yes**, please explain:* _____

Attempt 1: Date _____ (DD-Mon-YYYY)

Attempt 2: Date _____ (DD-Mon-YYYY)

Attempt 3: Date _____ (DD-Mon-YYYY)

Attempt 4: Date _____ (DD-Mon-YYYY)

Attempt 5: Date _____ (DD-Mon-YYYY)

REASON CONTACT NOT COMPLETED

Unable to contact after 5 attempts ☐

No attempts made ☐ *(specify reason)* _____

Other ☐ *(specify)* _____

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording. →

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

STC

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

SUBJECT TELEPHONE CONTACT

51040

Was telephone contact completed?

No ☐ *Complete **Reason Contact Not Completed** section at the bottom of the worksheet.*

Yes ☐ *Complete **Telephone Contact Completed** section .*

Prescribed time: *Month 12*

TELEPHONE CONTACT COMPLETED

Date call completed: _____
DD-Mon-YYYY

Since his/her last visit, has the subject seen a doctor for any new or worsening medical condition?

No ☐

Yes ☐ ***If yes,** complete SAEv and/or MH worksheets.*

Refused to provide information ☐

Since his/her last visit, has the subject been hospitalized?

No ☐

Yes ☐ ***If yes,** complete SAEv and/or MH worksheets.*

Refused to provide information ☐

Since his/her last visit, has the subject received any additional vaccinations?

No ☐

Yes ☐ ***If yes,** complete CVX worksheet.*

Refused to provide information ☐

REASON CONTACT NOT COMPLETED

Unable to contact after 5 attempts ☐

No attempts made ☐ *(specify reason)* _____

Other *(specify)* ☐ _____

DO NOT RECORD ANY CLINICAL INFORMATION ON THIS FORM

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording.

GENERAL INSTRUCTIONS FOR COMPLETING
SERIOUS ADVERSE EXPERIENCE (**SAEv**) REPORT FORM

If the AE ....

- resulted in death
- was immediately life threatening
- resulted in persistent or significant disability/incapacity
- resulted in inpatient hospitalization or the prolongation of an existing inpatient hospitalization
- is a congenital anomaly/birth defect
- is an other important medical event
- is a cancer
- is an overdose (whether accidental or intentional)

Do NOT use THIS form, USE the SAE form.

BLOCK ON SAE FORM	INSTRUCTIONS
Visit # *(Cumulative worksheet ONLY)*	Record the visit number for the period when the SAE started.
Type of SAE	Systemic = any clinical SAE other than injection site SAE. Injection site = occurs at the injection site only. Laboratory = results from laboratory assessment of tissue or other specimen. Other = neither systemic, nor injection site, nor laboratory.
SAE term	List all SAE. If diagnosis is made, the diagnosis should be in lieu of listing the individual symptoms, signs or laboratory data. For laboratory SAE, use the term 'increased' or 'decreased'.
Check if worsening of pre-existing condition	Check if SAE is a worsening of a pre-existing condition. A pre-existing condition is a clinical condition which is diagnosed prior to use of a Merck product or protocol-specific intervention and which is documented as part of the patient's (subject's) medical history.
Onset date *(Lab date if lab SAE)*	Date when SAE began. If laboratory or other SAE enter the date of the laboratory exam or special safety exam on which the SAE was noted.
Stop date *(Not applicable for lab or other)*	Enter last date that SAE or symptoms were present.
Duration (If less than 24 hours) *(Not applicable for lab or other)*	If SAE resolved in less than 24 hours, specify the length of time it was present and check the appropriate unit.
Intensity: *(Not applicable for lab or other)*	
Mild	Aware of symptom, but easily tolerated.
Moderate	Definitely acting like something is wrong.
Severe	Extremely distressed or unable to do usual activities.
Maximum size (1-8) *(Injection site SAE only)*	Record quantitative evaluation provided on vaccination report card for applicable injection site SAE only (redness or swelling).
Injection site *(Injection site SAE only)*	Enter the site at which the injection was given for injection site SAE only.
Did the SAE result in:	
Persistent or significant disability/incapacity?	Substantial disruption of a person's ability to conduct normal life functions.
Hospitalization or prolongation?	New inpatient hospitalization or prolonged existing stay.
Death?	Record death date in the space provided.
Is the SAE:	
Immediately life-threatening?	Places the patient (subject) at **immediate** risk of death from the experience as it occurred.
Cancer?	Malignant process including basal-cell carcinoma.
Due to overdose?	Result of an overdose (whether accidental or intentional).
Congenital anomaly/birth defect?	In offspring of a patient (subject) who has taken the test vaccine regardless of time to diagnosis.
Other important medical event?	May not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the patient (subject) and may require medical or surgical intervention to prevent one of the outcomes listed previously.
Action taken on primary test vaccine due to SAE:	
None	No action was taken with test vaccine(s).
No further test vaccinations given *(Multi-dose studies only)*	Subsequent scheduled study vaccines were not administered due to SAE.
Discontinued from follow-up only	No action was taken with test vaccinations because no subsequent vaccinations were scheduled, but patient (subject) did not complete protocol specified clinical follow-up period.
Did SAE reappear after restarting test vaccine? *(Rechallenge)* *(Multi-dose studies only)*	If SAE reappeared or worsened after the test vaccine was restarted, check **Yes.**
	If SAE did not recur after the test vaccine was restarted or rechallenge was ambiguous, check **No.**
	If not applicable, check **NA.**
Did primary test vaccine cause SAE? *(Refer to Guidelines for Causality, then enter classification)*	Check classification as determined by the Investigator using GUIDELINES FOR CAUSALITY (see reverse side).
NCI common toxicity criteria *(Refer to protocol) (If applicable)*	Toxicity grade should be assigned using Common Toxicity Criteria. ***See the protocol for details***
Check if SAE is an Event of Clinical Interest (ECI)	Check the box if the event is a **Special Interest SAE** *(requires rapid communication to sponsor)* or a protocol defined **endpoint**.

GUIDELINES FOR CAUSALITY:

Assessing the Relationship of Adverse Experiences to Test Vaccine

The assessment of causality is reported according to the investigator's **best** clinical judgement. The confidence in a given **classification increases** as the number **and/or** intensity of its respective **criteria increase**.

NOTE: 1. If test vaccine was discontinued because of AE, the MRL Monitor ***MUST*** approve **all** rechallenges (multi-dose studies only).
2. Test vaccine can be defined as any clinical material, i.e., placebo, comparative agent etc. received in this study.

CRITERIA	CLASSIFICATION
The patient (subject) **did not receive** the test vaccine. **OR** The temporal sequence of the AE onset **relative** to **administration** of the test vaccine is **not reasonable**. **OR** There is **another obvious** cause of the AE.	**1 = Definitely not** related to test vaccine.
There is **evidence of exposure** to the test vaccine. There is **another more likely** cause of the AE. Rechallenge (if performed) is **negative or ambiguous.**	**2 = Probably not** related to test vaccine.
There is **evidence of exposure** to the test vaccine. The temporal sequence of the AE onset relative to **administration** of the test vaccine is reasonable. The AE could have been due to **another equally likely cause**.	**3 = Possibly** related to test vaccine.
There is **evidence of exposure** to the test vaccine. The temporal sequence of the AE onset **relative** to **administration** of the test vaccine is **reasonable**. The AE is **more likely explained** by the test vaccine than by another cause.	**4 = Probably** related to test vaccine.
There is **evidence of exposure** to the test vaccine. The temporal sequence of the AE onset **relative** to **administration** of the test vaccine is **reasonable**. The AE is **more likely explained** by the test vaccine than by another cause. Rechallenge (if feasible) is **positive**. The AE shows a **pattern consistent** with **previous knowledge** of the test vaccine **or** test vaccine class.	**5 = Definitely** related to test vaccine.

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

SAEv

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

SERIOUS ADVERSE EXPERIENCE

34977

USE THIS FORM If the AE ....

- resulted in death
- was immediately life threatening
- resulted in persistent or significant disability/incapacity
- resulted in inpatient hospitalization or the prolongation of an existing inpatient hospitalization
- is a congenital anomaly/birth defect
- is an other important medical event
- is a cancer
- is an overdose (whether accidental or intentional)

NOTE: All Serious AEs must be reported to Merck within 24 hours.

THIS PAGE IS TO BE REVIEWED/COMPLETED AT EACH VISIT.

Were there any **serious AEs** since last visit? **None** ☐ *or complete form below*

Type of SAE	Systemic ☐ Injection site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection site ☐ Laboratory ☐ Other ☐
SAE term		
Check if **worsening of pre-existing condition**	☐	☐
Onset date *(Lab date if lab SAE)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Stop date *(Not applicable for lab or other)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Duration (if less than 24 hours) *(Not applicable for lab or other)*	Hour ☐ Minute ☐ Second ☐	Hour ☐ Minute ☐ Second ☐
Intensity *(Not applicable for lab or other)*	Mild ☐ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Maximum size *(1-8) (Injection site SAE only)*		
Injection site *(Injection site SAE only)*	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other *(specify):* _____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other *(specify):* _____
Did the SAE result in:		
Persistent or significant disability/incapacity?	No ☐ Yes ☐	No ☐ Yes ☐
Hospitalization or prolongation?	No ☐ Yes ☐	No ☐ Yes ☐
Death? *(Provide death date)*	No ☐ Yes ☐	No ☐ Yes ☐
Death date:	DD-Mon-YYYY:	DD-Mon-YYYY:
Is the SAE:		
Immediately life-threatening?	No ☐ Yes ☐	No ☐ Yes ☐
Cancer?	No ☐ Yes ☐	No ☐ Yes ☐
Due to overdose?	No ☐ Yes ☐	No ☐ Yes ☐
Congenital anomaly/birth defect?	No ☐ Yes ☐	No ☐ Yes ☐
Other important medical event?	No ☐ Yes ☐	No ☐ Yes ☐
Action taken on primary test vaccine due to SAE:	None ☐ No further test vaccinations given ☐ Discontinued from follow-up only ☐	None ☐ No further test vaccinations given ☐ Discontinued from follow-up only ☐
Did SAE reappear after restarting test product? *(Rechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did primary test vaccine cause SAE? *(Refer to Guidelines for Causality, then enter classification)*	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initials DD-Mon-YYYY	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initials DD-Mon-YYYY
Check if **SAE is associated with any Other Suspect Therapy** *(Refer to AEos form)*	☐	☐

Brief description of SAE (if necessary):

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording. →

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

AEOS

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

ADVERSE EXPERIENCE-OTHER SUSPECT THERAPY

34977

THIS PAGE IS TO BE REVIEWED/COMPLETED AT EACH VISIT.

If there is NO Other Suspect Therapy for an SAE, do NOT complete this form.

INSTRUCTIONS:

On the **Serious Adverse Experience (SAE)** worksheet, indicate in the comments section of that AE page which (if any) of the Adverse Events may have been caused by an other suspect therapy (according to the Investigator). On **THIS form,** transcribe the name/start date of the other suspected therapy from the Prior/Concomitant therapy, Prior/Concomitant vaccine or Other Study-Related Medication worksheet, then answer the following 4 questions below.

Drug name *(from Prior/Concomitant therapy, Prior/Concomitant vaccine or Other Study-Related Medication worksheet)*		
Start date *(from Prior/Concomitant therapy, Prior/Concomitant vaccine or Other Study-Related Medication worksheet)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Action taken on other suspect therapy due to the adverse event:	None ☐ Reduced ☐ Interrupted ☐ Increased ☐ Discontinued ☐	None ☐ Reduced ☐ Interrupted ☐ Increased ☐ Discontinued ☐
Did the adverse event diminish after stopping other suspect therapy? *(Dechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did the adverse event reappear after restarting other suspect therapy? *(Rechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did other suspect therapy cause the adverse event? *(Refer to Guidelines for Causality, then enter classification)*	Possibly ☐ Probably ☐ Definitely ☐ Inv. Initials DD-Mon-YYYY	Possibly ☐ Probably ☐ Definitely ☐ Inv. Initials DD-Mon-YYYY

Comments:

Investigator's name:

If this worksheet is **used as a source document** it must be **initialed** and **dated** by the individual making the observation/recording.

INSTRUCTIONS FOR REPORTING MEDICAL HISTORY

Day 1:

Report any acute or chronic medical conditions that occurred in the past year. If a chronic condition has not manifested signs or symptoms in the past year, but is suspected to be present, report the condition.

Month 2 through Month 18:

Report any medical history or procedures that have occurred since the last study visit.

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

MH

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

MEDICAL HISTORY

35001

Any **new** background or **concomitant conditions**, **drug allergies** and **surgeries/procedures**?

None ☐ *or complete form below*

NOTE: *List all new conditions since last history was taken in accordance with the protocol.*

MEDICAL HISTORY TERM	YEAR DIAGNOSED	ACTIVE? No	ACTIVE? Yes
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording.

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

CVX

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

CONCOMITANT NON-STUDY VACCINE

34996

Were any vaccinations other than study vaccine(s) received since the last visit (inactive and live-virus vaccines)?

No ☐ *If **yes**, complete form below.*

VACCINE NAME	ROUTE OF ADMINISTRATION	VACCINATION SITE *(specify)*	DATE OF VACCINATION (DD-Mon-YYYY)
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording.

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

MONTH 12

A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents

Was visit completed? **No** ☐ *If **yes**, complete form below.*

Date of visit: _____
DD-Mon-YYYY

WORKSHEETS COMPLETED AT THIS VISIT

Worksheet	Worksheet ID	*Indicate the Source Document below ONLY for those that differ from the Source Document Identification Log* Worksheet	VRC	Chart	Other, *specify*:
Telephone contact log	----	☐	☐	☐	_____
Subject telephone contact	STC	☐	☐	☐	_____
Serious adverse experience	SAEv/AEos	☐	☐	☐	_____
Medical history	MH	☐	☐	☐	_____
Concomitant non-study vaccine	CVX	☐	☐	☐	_____
Patient (or subject) status††	STATUS	☐	☐	☐	_____

†† *Complete **STATUS** when **patient** is **excluded, completed or discontinued. Found in STATUS section of patient (subject) binder.***

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording →

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

Source Document - Retain in Patient Binder - Do Not Send to the Sponsor

TELEPHONE CONTACT INSTRUCTIONS

Please use the log below to document all telephone attempts. The timing of the phone call will be twelve months after day one ± 3 weeks. **Information from this log will need to be transcribed onto the Telephone Contact worksheet for the Month 12 visit.**

The following question is asked to the parent/guardian of the subject to record any new/worsening medical conditions, hospitalizations, or additional vaccines received. If the parent/guardian of the subject during the phone call reports a serious adverse event, new medical history or additional vaccine(s) received, study personnel should indicate this new information on the appropriate worksheet (MH, SAEv or CVX).

- Complete SAEv and notify Merck Monitor within 24 hours if the subject has the following condition: death, vaccine related SAE (possible, probable and definite), congenital abnormalities (of the subject's offspring), or cancer.
- Enter information onto MH for all other conditions.
- Enter additional vaccine(s) received on the CVX worksheet.
- The Month 12 phone call should occur 12 months from Day 1 visit ± 3 weeks.

TELEPHONE CONTACT LOG

Since his/her last visit, has the subject:

seen a doctor for any new or worsening medical condition?

No ☐

Yes ☐ *If **yes**, please explain:* _____

been hospitalized?

No ☐

Yes ☐ *If **yes**, please explain:* _____

received any additional vaccines?

No ☐

Yes ☐ *If **yes**, please explain:* _____

Attempt 1: Date _____ DD-Mon-YYYY

Attempt 2: Date _____ DD-Mon-YYYY

Attempt 3: Date _____ DD-Mon-YYYY

Attempt 4: Date _____ DD-Mon-YYYY

Attempt 5: Date _____ DD-Mon-YYYY

REASON CONTACT NOT COMPLETED

Unable to contact after 5 attempts ☐

No attempts made ☐ *(specify reason)* _____

Other ☐ *(specify)* _____

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording. →

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

STC

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

SUBJECT TELEPHONE CONTACT

51040

Was telephone contact completed?

No ☐ *Complete **Reason Contact Not Completed** section at the bottom of the worksheet.*

Yes ☐ *Complete **Telephone Contact Completed** section .*

Prescribed time: _____ *Month 12* _____

TELEPHONE CONTACT COMPLETED

Date call completed: _____
DD-Mon-YYYY

Since his/her last visit, has the subject seen a doctor for any new or worsening medical condition?

No ☐

Yes ☐ ***If yes,** complete SAEv and/or MH worksheets.*

Refused to provide information ☐

Since his/her last visit, has the subject been hospitalized?

No ☐

Yes ☐ ***If yes,** complete SAEv and/or MH worksheets.*

Refused to provide information ☐

Since his/her last visit, has the subject received any additional vaccinations?

No ☐

Yes ☐ ***If yes,** complete CVX worksheet.*

Refused to provide information ☐

REASON CONTACT NOT COMPLETED

Unable to contact after 5 attempts ☐

No attempts made ☐ *(specify reason)* _____

Other *(specify)* ☐ _____

DO NOT RECORD ANY CLINICAL INFORMATION ON THIS FORM

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording.

GENERAL INSTRUCTIONS FOR COMPLETING
SERIOUS ADVERSE EXPERIENCE (**SAEv**) REPORT FORM

If the AE ....

- resulted in death
- was immediately life threatening
- resulted in persistent or significant disability/incapacity
- resulted in inpatient hospitalization or the prolongation of an existing inpatient hospitalization
- is a congenital anomaly/birth defect
- is an other important medical event
- is a cancer
- is an overdose (whether accidental or intentional)

Do NOT use THIS form, USE the SAE form.

BLOCK ON SAE FORM	INSTRUCTIONS
Visit # *(Cumulative worksheet ONLY)*	Record the visit number for the period when the SAE started.
Type of SAE	Systemic – any clinical SAE other than injection site SAE. Injection site = occurs at the injection site only. Laboratory = results from laboratory assessment of tissue or other specimen. Other = neither systemic, nor injection site, nor laboratory.
SAE term	List all SAE. If diagnosis is made, the diagnosis should be in lieu of listing the individual symptoms, signs or laboratory data. For laboratory SAE, use the term 'increased' or 'decreased'.
Check if worsening of pre-existing condition	Check if SAE is a worsening of a pre-existing condition. A pre-existing condition is a clinical condition which is diagnosed prior to use of a Merck product or protocol-specific intervention and which is documented as part of the patient's (subject's) medical history.
Onset date *(Lab date if lab SAE)*	Date when SAE began. If laboratory or other SAE enter the date of the laboratory exam or special safety exam on which the SAE was noted.
Stop date *(Not applicable for lab or other)*	Enter last date that SAE or symptoms were present.
Duration (If less than 24 hours) *(Not applicable for lab or other)*	If SAE resolved in less than 24 hours, specify the length of time it was present and check the appropriate unit.
Intensity: *(Not applicable for lab or other)*	
Mild	Aware of symptom, but easily tolerated.
Moderate	Definitely acting like something is wrong.
Severe	Extremely distressed or unable to do usual activities.
Maximum size (1-8) *(Injection site SAE only)*	Record quantitative evaluation provided on vaccination report card for applicable injection site SAE only (redness or swelling).
Injection site *(Injection site SAE only)*	Enter the site at which the injection was given for injection site SAE only.
Did the SAE result in:	
Persistent or significant disability/incapacity?	Substantial disruption of a person's ability to conduct normal life functions.
Hospitalization or prolongation?	New inpatient hospitalization or prolonged existing stay.
Death?	Record death date in the space provided.
Is the SAE:	
Immediately life-threatening?	Places the patient (subject) at **immediate** risk of death from the experience as it occurred.
Cancer?	Malignant process including basal-cell carcinoma.
Due to overdose?	Result of an overdose (whether accidental or intentional).
Congenital anomaly/birth defect?	In offspring of a patient (subject) who has taken the test vaccine regardless of time to diagnosis.
Other important medical event?	May not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the patient (subject) and may require medical or surgical intervention to prevent one of the outcomes listed previously.
Action taken on primary test vaccine due to SAE:	
None	No action was taken with test vaccine(s).
No further test vaccinations given *(Multi-dose studies only)*	Subsequent scheduled study vaccines were not administered due to SAE.
Discontinued from follow-up only	No action was taken with test vaccinations because no subsequent vaccinations were scheduled, but patient (subject) did not complete protocol specified clinical follow-up period.
Did SAE reappear after restarting test vaccine? *(Rechallenge)* *(Multi-dose studies only)*	If SAE reappeared or worsened after the test vaccine was restarted, check **Yes.** If SAE did not recur after the test vaccine was restarted or rechallenge was ambiguous, check **No.** If not applicable, check **NA.**
Did primary test vaccine cause SAE? *(Refer to Guidelines for Causality, then enter classification)*	Check classification as determined by the Investigator using GUIDELINES FOR CAUSALITY (see reverse side).
NCI common toxicity criteria *(Refer to protocol) (If applicable)*	Toxicity grade should be assigned using Common Toxicity Criteria. ***See the protocol for details***
Check if SAE is an Event of Clinical Interest (ECI)	Check the box if the event is a **Special Interest SAE** *(requires rapid communication to sponsor)* or a protocol defined **endpoint**.

GUIDELINES FOR CAUSALITY:

Assessing the Relationship of Adverse Experiences to Test Vaccine

The assessment of causality is reported according to the investigator's **best** clinical judgement. The confidence in a given **classification increases** as the number **and/or** intensity of its respective **criteria increase**.

NOTE: 1. If test vaccine was discontinued because of AE, the MRL Monitor ***MUST*** approve **all** rechallenges (multi-dose studies only).
2. Test vaccine can be defined as any clinical material, i.e., placebo, comparative agent etc. received in this study.

CRITERIA	CLASSIFICATION
The patient (subject) **did not receive** the test vaccine. **OR** The temporal sequence of the AE onset **relative** to **administration** of the test vaccine is **not reasonable**. **OR** There is **another obvious** cause of the AE.	**1 = Definitely not** related to test vaccine.
There is **evidence of exposure** to the test vaccine. There is **another more likely** cause of the AE. Rechallenge (if performed) is **negative or ambiguous.**	**2 = Probably not** related to test vaccine.
There is **evidence of exposure** to the test vaccine. The temporal sequence of the AE onset relative to **administration** of the test vaccine is reasonable. The AE could have been due to **another equally likely cause**.	**3 = Possibly** related to test vaccine.
There is **evidence of exposure** to the test vaccine. The temporal sequence of the AE onset **relative** to **administration** of the test vaccine is **reasonable**. The AE is **more likely explained** by the test vaccine than by another cause.	**4 = Probably** related to test vaccine.
There is **evidence of exposure** to the test vaccine. The temporal sequence of the AE onset **relative** to **administration** of the test vaccine is **reasonable**. The AE is **more likely explained** by the test vaccine than by another cause. Rechallenge (if feasible) is **positive**. The AE shows a **pattern consistent** with **previous knowledge** of the test vaccine **or** test vaccine class.	**5 = Definitely** related to test vaccine.

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

SAEv

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

SERIOUS ADVERSE EXPERIENCE

34977

USE THIS FORM If the AE ....

- resulted in death
- was immediately life threatening
- resulted in persistent or significant disability/incapacity
- resulted in inpatient hospitalization or the prolongation of an existing inpatient hospitalization
- is a congenital anomaly/birth defect
- is an other important medical event
- is a cancer
- is an overdose (whether accidental or intentional)

NOTE: All Serious AEs must be reported to Merck within 24 hours.

THIS PAGE IS TO BE REVIEWED/COMPLETED AT EACH VISIT.

Were there any **serious AEs** since last visit? **None** ☐ *or complete form below*

Type of SAE	Systemic ☐ Injection site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection site ☐ Laboratory ☐ Other ☐
SAE term		
Check if **worsening of pre-existing condition**	☐	☐
Onset date *(Lab date if lab SAE)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Stop date *(Not applicable for lab or other)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Duration (if less than 24 hours) *(Not applicable for lab or other)*	Hour ☐ Minute ☐ Second ☐	Hour ☐ Minute ☐ Second ☐
Intensity *(Not applicable for lab or other)*	Mild ☐ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Maximum size *(1-8) (Injection site SAE only)*		
Injection site *(Injection site SAE only)*	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other *(specify):* _____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other *(specify):* _____
Did the SAE result in:		
Persistent or significant disability/incapacity?	No ☐ Yes ☐	No ☐ Yes ☐
Hospitalization or prolongation?	No ☐ Yes ☐	No ☐ Yes ☐
Death? *(Provide death date)*	No ☐ Yes ☐	No ☐ Yes ☐
Death date:	DD-Mon-YYYY:	DD-Mon-YYYY:
Is the SAE:		
Immediately life-threatening?	No ☐ Yes ☐	No ☐ Yes ☐
Cancer?	No ☐ Yes ☐	No ☐ Yes ☐
Due to overdose?	No ☐ Yes ☐	No ☐ Yes ☐
Congenital anomaly/birth defect?	No ☐ Yes ☐	No ☐ Yes ☐
Other important medical event?	No ☐ Yes ☐	No ☐ Yes ☐
Action taken on primary test vaccine due to SAE:	None ☐ No further test vaccinations given ☐ Discontinued from follow-up only ☐	None ☐ No further test vaccinations given ☐ Discontinued from follow-up only ☐
Did SAE reappear after restarting test product? *(Rechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did primary test vaccine cause SAE? *(Refer to Guidelines for Causality, then enter classification)*	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initials DD-Mon-YYYY	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initials DD-Mon-YYYY
Check if **SAE is associated with any Other Suspect Therapy** *(Refer to AEos form)*	☐	☐

Brief description of SAE (if necessary):

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording. →

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

AEos

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

ADVERSE EXPERIENCE-OTHER SUSPECT THERAPY

34977

THIS PAGE IS TO BE REVIEWED/COMPLETED AT EACH VISIT.

If there is NO Other Suspect Therapy for an SAE, do NOT complete this form.

INSTRUCTIONS:

On the **Serious Adverse Experience (SAE)** worksheet, indicate in the comments section of that AE page which (if any) of the Adverse Events may have been caused by an other suspect therapy (according to the Investigator). On **THIS form,** transcribe the name/start date of the other suspected therapy from the Prior/Concomitant therapy, Prior/Concomitant vaccine or Other Study-Related Medication worksheet, then answer the following 4 questions below.

Drug name *(from Prior/Concomitant therapy, Prior/Concomitant vaccine or Other Study-Related Medication worksheet)*		
Start date *(from Prior/Concomitant therapy, Prior/Concomitant vaccine or Other Study-Related Medication worksheet)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Action taken on other suspect therapy due to the adverse event:	None ☐ Reduced ☐ Interrupted ☐ Increased ☐ Discontinued ☐	None ☐ Reduced ☐ Interrupted ☐ Increased ☐ Discontinued ☐
Did the adverse event diminish after stopping other suspect therapy? *(Dechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did the adverse event reappear after restarting other suspect therapy? *(Rechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did other suspect therapy cause the adverse event? *(Refer to Guidelines for Causality, then enter classification)*	Possibly ☐ Probably ☐ Definitely ☐ Inv. Initials DD-Mon-YYYY	Possibly ☐ Probably ☐ Definitely ☐ Inv. Initials DD-Mon-YYYY

Comments:

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording.

INSTRUCTIONS FOR REPORTING MEDICAL HISTORY

Day 1:

Report any acute or chronic medical conditions that occurred in the past year. If a chronic condition has not manifested signs or symptoms in the past year, but is suspected to be present, report the condition.

Month 2 through Month 18:

Report any medical history or procedures that have occurred since the last study visit.

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

MH

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

MEDICAL HISTORY

35001

Any **new** background or **concomitant conditions**, **drug allergies** and **surgeries/procedures**?

None ☐ *or complete form below*

NOTE: *List all new conditions since last history was taken in accordance with the protocol.*

MEDICAL HISTORY TERM	YEAR DIAGNOSED	ACTIVE? No	ACTIVE? Yes
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording.

HPV ADOLESCENT/PREADOLESCENT SAFETY STUDY

Month 12

CVX

Compound	Protocol	Study Site	IIN	VISIT	Allocation Number
V501	018-00			7	

CONCOMITANT NON-STUDY VACCINE

34996

Were any vaccinations other than study vaccine(s) received since the last visit (inactive and live-virus vaccines)?

No ☐ *If **yes**, complete form below.*

VACCINE NAME	ROUTE OF ADMINISTRATION	VACCINATION SITE *(specify)*	DATE OF VACCINATION (DD-Mon-YYYY)
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	
	Injection ☐ Oral ☐ Other ☐ *(specify)*_____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other ☐ *(specify)*_____	

Investigator's name:

If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording. →

Phase III - Addendum

Subject: Pregnancy Reporting and Follow-up HPV Vaccine Clinical Program	Dept.: Rev.: Effective Date:	976 00 26-Jul-2004

I. INTRODUCTION

Females of childbearing potential are being enrolled in the HPV vaccine program. Subjects are excluded from enrollment in the clinical studies if they are pregnant. Pregnancy tests are performed prior to each vaccination. In the Phase III clinical studies, women who become pregnant are not discontinued from participation in the studies. If a woman becomes pregnant during the vaccination period, vaccination is stopped. Subjects are followed for specimen collection only; or vaccination is deferred until pregnancy outcome (see individual protocols for study-specific details). All pregnancies throughout the duration of the study are reported and followed for outcome.

Whether or not associated with an adverse event, all reports of use of a Merck product during pregnancy are reportable to Worldwide Product Safety & Epidemiology (WPS&E). Since studies within the HPV vaccine program include enrollment of women of childbearing potential, the following paragraph, or similar language, is included in the protocols:

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient (spontaneously reported to them) which occurs during the safety follow-up period (Day 1 through Month 7, inclusive, of the study). All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page.

II. PURPOSE

The purpose of this *addendum* is (1) to describe the procedures for the reporting of all pregnancies for the Phase III studies, (2) to describe the procedures for following all reported pregnancies for outcome (completion/termination), and (3) to describe the appropriate forms needed in order to fulfill reporting requirements.

This document will be sent to each Phase III HPV vaccine investigative site for incorporation into the standard study-related procedures at the site (administrative binder).

III. DEFINITIONS

MPREG – Maternal Pregnancy Worksheet

PPREG – Previous Pregnancy Worksheet

OPREG – Outcome Pregnancy Worksheet

SAEv – Serious Adverse Event Worksheet (Subject)

SAE-INFv – Serious Adverse Event Worksheet (Infant)

WPS&E – Worldwide Product Safety & Epidemiology; Department within Merck & Co., Inc. responsible for collection of all adverse experience information and reporting to regulatory agency(ies) as required

FOLLOW-UP PERIOD (for pregnancy) - For Phase III studies, all pregnancies will be reported on the worksheets. In addition to reporting on worksheets, pregnancies (and their outcomes) occurring from Day 1 through Month 7 will be reported to WPS&E.

Please refer to Pregnancy Reporting and Follow-up Guideline (Rev. 02, 22-Feb-00) for additional definitions.

IV. PROCEDURES

RESPONSIBILITY OF THE INVESTIGATOR/DESIGNEE

1. Any pregnancy in a subject (either detected by a study pregnancy test or spontaneously reported to study site personnel) which occurs throughout the duration of the study must be reported to the SPONSOR.

A. Pregnancy Reporting after Consent and Prior to Day 1 Vaccination

1. Any subject who has signed consent and found to be pregnant prior to vaccination at Day 1 requires completion of an Adverse Event Report Form.

2. This subject does not need to be followed for outcome and CTS worksheets do not need to be completed.

B. Pregnancy Reporting Occurring From Day 1 through Month 7

(Adverse Event Report - Initial)

1. For pregnancies that occur after Day 1 (following receipt of the first dose of clinical material) through Month 7, the pregnancy must be reported to one of the individuals listed on the SPONSOR Contact Information page (Clinical Monitor or Medical Program Clinical Specialist [MPCS] or Subsidiary Representative). The

information should be submitted on an Adverse Event Report Form (Attachment 1). The following initial report information is required:

Patient Information

a) Allocation Number – Provide the allocation number of the subject.
b) Age – Provide the subject's age at the onset of the pregnancy and/or subject's date of birth.
c) Sex – Female
d) Weight – Provide the weight with the appropriate units (LB or KG).
e) Weeks Gestation– Provide the weeks of gestation at the time of reporting and/or provide date of LMP.
f) Onset date - Date of first diagnostic test that reveals pregnancy (i.e., serum/urine βhCG, ultrasound).

Study Title

g) Complete study title (including protocol number).

Recent/Concomitant Therapy

h) Provide any recent/concomitant therapy given within 14 days prior to onset of the pregnancy to include:
   - *Therapy/Drug Name*: Be careful to spell drug names correctly. Do not provide therapies that were prescribed following the onset of pregnancy unless the therapy resulted in AEs. Therapies used to treat AEs can be mentioned in the narrative.
   - *Daily dose*: Provide the total daily dose of the drug.
   - *Start date*: Provide the date the subject received the first dose of the medication temporally associated with pregnancy onset. Do not give the start date of the study unless that is when they actually started the drug.
   - *Stop date*: Provide the date that the subject discontinued therapy. Do not give the stop date of the study unless they also stopped the therapy on that date. Provide "CONT" if the subject continued therapy. Please do not list a dash (-).
   - *Indication*: Provide the reason that the subject was taking the concomitant therapy. Be sure to include the indication as a concurrent condition if appropriate.

   Receipt of HPV vaccine/placebo should also be listed in this section. Indicate date(s) any dose(s) of vaccine/placebo received.

Concurrent Conditions

i) List any concurrent conditions that developed prior to the vaccination and were still present at the time of the pregnancy (e.g., diabetes mellitus, carcinoma).

Phase III - Addendum

Other Medical History

j) Include all pertinent medical events that occurred prior to the pregnancy onset date but which would not necessarily be considered a concurrent condition.

Laboratory Results/Diagnostic Tests

k) Provide any laboratory test or diagnostic test results which would add meaningful information regarding the pregnancy. Include normal as well as abnormal test results if they are pertinent. Provide the date of testing, if available, in chronologic sequence.

Narrative and Comments

l) A description of the event (narrative) and any comments (which may include the action taken, i.e., discontinued, and information concerning follow-up activity). This section should also include, subject's final outcome or current status, the investigator's statement about causality, and information concerning follow-up activity (i.e., additional information is expected; or not further information was provided).

Administrative Section

m) Name of primary investigator and, if not reported by the PI, the name and address of study personnel reporting the pregnancy.

2. All pregnancies reported through (and including) the Month 7 study visit should be reported to the SPONSOR within 5 business days of learning of the pregnancy. The investigator/designee should then complete an Adverse Event Report form (blank copy can be found in the administrative binder for the study or can be sent upon request) with the information listed above. When complete, the Adverse Event Report form should be faxed to the appropriate contact person at the SPONSOR.

   NOTE: As per the protocol, pregnancy is not considered an adverse experience. Therefore, the questions on the adverse event report form asking "Did the AE result in: Death, Hospitalization (or prolong existing hospitalization), Persistent or significant disability, Life threatening, Cancer, Due to overdose, Congenital anomaly, Other important medical event" do not need to be addressed by the investigator/designee.

3. Any subject who reports being pregnant between Month 6 and Month 12 should be questioned as to the estimated date of conception. If the date of conception was prior to the Month 7 visit, the pregnancy must be reported to one of the individuals listed on the SPONSOR Contact Information page as outlined previously. If the date of conception was after the Month 7 visit, see section C below.

4. Pregnancy is reportable in discontinued subjects if it is spontaneously reported and conception occurred within one month of vaccination. If the pregnancy

occurred greater than one month following the last dose of study vaccine/placebo, the pregnancy does not need to be reported on an Adverse Event Report form but should be captured on CTS worksheets (MPREG, PPREG, OPREG).

Follow-up

5. For all subjects who become pregnant from Day 1 through Month 7 (whether continuing or discontinued), information regarding the progress of the pregnancy will be required each trimester (at week 12, week 24, and at term). This information will be captured on the Pregnancy Update Worksheets (Attachment 2). The Pregnancy Update worksheet form should be faxed to the MPCS assigned to your study site so that information collected can be forwarded to WPS&E. A copy of the Pregnancy Update worksheet should be retained at the study site. The original Pregnancy Update worksheet should be sent to the SPONSOR.

6. If a subject discontinues participation in the trial due to her pregnancy, she should be informed of the need and importance of maintaining contact with the study site personnel in order to report the progress and outcome of the pregnancy. With the subject's permission, the Investigator should obtain contact information so that additional information regarding her pregnancy may be recorded.

7. Adverse experiences that occur during pregnancy should be documented in the narrative section of the AER form. All adverse experiences shall be assessed by the Investigator for seriousness, and relationship to study vaccine. All Adverse experiences that meet the serious criteria will be reported to the SPONSOR within 24 hours.

8. Subjects who are excluded from the study due to a positive pregnancy at Day 1 do not require follow-up as per Section IV.A.1-2.

Outcome

9. Outcome (completion/termination) of the pregnancy must be reported to the SPONSOR using the Pregnancy Outcome Questionnaire (Attachment 3). The final outcome of the pregnancy should be reported as close to the estimated delivery date as possible (not to exceed 1 year after the initial pregnancy report).

10. If the outcome of the pregnancy is associated with a serious adverse event (e.g., congenital anomaly, unplanned C-section), an Adverse Event Report Form should be completed. All serious adverse events must be reported to the SPONSOR within 24 hours. Information regarding serious adverse events may be obtained from the subject. Additional information may be obtained from the subject's physician and/or pediatrician, if appropriate and agreed to by the

subject. If possible, a discharge summary should accompany the Adverse Event Report.

NOTE: Any fetal outcome that is reported on a CTS OPREG worksheet should not be recorded again on an SAE/SAE-INFv worksheet (i.e., spontaneous abortion, late fetal death, elective termination).

NOTE: For any pregnancy which occurs during the course of the study, the site must ascertain whether the subject's infant experienced any congenital anomalies that were undetected at the time of the initial pregnancy outcome reporting. The subject should be queried for such information at any scheduled visit and unscheduled visit for one year post-partum. After one year of post partum follow up, congenital abnormalities will be captured through spontaneous reporting by the subject. This assessment must be captured in the source document. If a congenital anomaly is detected, the site will capture this information on the SAEv and SAE-INFv worksheets.

11. If the subject can not be reached to report the outcome of the pregnancy, this information should be documented and reported to the SPONSOR.

B. *Pregnancy Reporting Occurring From Day 1 through Month 7*

(CTS Worksheets)

1. In addition to the Adverse Event Report form and Pregnancy Update Worksheet, the following worksheets must be completed for each pregnancy (Attachment 4):

   MPREG
   OPREG
   PPREG (if applicable)
   SAEv (if applicable)
   SAE-INFv (if applicable)

2. Complete all worksheets as required according to the protocol specific Data Handling Guidelines.

3. These worksheets should be submitted to the SPONSOR along with worksheets from regularly scheduled study visits as per the standard procedures. These worksheets do not need to be faxed to the SPONSOR.

C. *Reporting of Pregnancy Occurring Post-Month 7*

1. Pregnancies occurring post-Month 7 do not need to be reported on an Adverse Event Report form. The Pregnancy Outcome Questionnaire does not need to be submitted for pregnancies occurring post-Month 7. The Pregnancy Update worksheet should be completed for pregnancies occurring post-Month 7 since this information is used to complete the OPREG

worksheet.

2. The following worksheets must be completed for each pregnancy:

   MPREG
   OPREG
   PPREG (if applicable)
   SAEv (if applicable)
   SAE-INFv (if applicable)

D. Summary

1. The following table provides a summary of the report forms and worksheets needed to fulfill reporting requirements for pregnancy.

Summary Table of Required Forms

Case	Required Forms							
	AER form	Outcome Questionnaire	Trimester Update	MPREG	PPREG†	OPREG	SAEv*	SAE-INFv*
Pregnancy (for subjects excluded due to pregnancy at Day 1)	X							
Pregnancy (Day 1 to MO 7)	X	X	X	X	X	X	X	X
Pregnancy spontaneously reported in discontinued subject (subject pregnant within 1 month of last study dose)	X	X	X	X	X	X	X	X
Pregnancy (post-Month 7)			X	X	X	X	X	X

† PPREG only applicable if subject had history of previous pregnancy.
* If applicable

Phase III - Addendum

RESPONSIBILITY OF THE CLINICAL TEAM

E. Reporting of Pregnancy to WPS&E (those occurring Day 1 through MO 7 only)

1. Once a pregnancy is reported (occurring from Day 1 through Month 7) to the SPONSOR from a clinical study site, the event must be reported to WPS&E via an Adverse Event Report Form (within 2 working days if associated with a serious outcome and within 10 working days if no known serious outcome, or the outcome is as yet unknown). The report will include all the previously mentioned information.

2. Information from the NWAES report will be tracked according to individual protocol requirements. The information may include protocol number, study site number, allocation number, estimated date of delivery, outcome and date of outcome.
   Note: If EDD is not given, it will be estimated to be ~36 weeks from the date of the initial report.

3. The tracking database/spreadsheet will then be checked monthly to ensure outcome information is being received. A follow-up notification will be sent to sites/subsidiaries where outcome information is still outstanding.

4. Any new information, regarding the pregnancy, reported from the clinical study sites will be reported to WPS&E in a follow-up report (via an AER Form). This information will be based on data submitted on the Pregnancy Update worksheet.

5. Once the outcome of a pregnancy is reported to the clinical team, a final report will be sent to WPS&E using the information recorded on the Pregnancy Outcome Questionnaire (via an AER Form). If a subject can not be reached in order to report the outcome of the pregnancy (i.e., lost to follow-up), a report should be filed with WPS&E indicating this fact.

6. The clinical team will ensure that copies of all reports are sent to the appropriate personnel (i.e., original to RIBL, electronic copy to WPS&E, copy to site, study file, MRA).

7. The final outcome of the pregnancy should be reported as close to the estimated delivery date as possible (not to exceed 1 year after filing of the initial pregnancy report).

Phase III - Addendum

8. For pregnancies occurring Post-Month 7, reporting to WPS&E by clinical research is not required. Information regarding pregnancies occurring Post-Month 7 will come in-house on the appropriate worksheets, per standard procedures.

Phase III - Addendum

ATTACHMENTS

Attachment 1 – Adverse Event Report Form
Attachment 2 – Pregnancy Worksheet - Trimester Update
Attachment 3 – Pregnancy Outcome Questionnaire
Attachment 4 – CTS Pregnancy Worksheets (MPREG, PRPREG, OPREG)
Attachment 5 – SAEv, SAE-INFv
Attachment 6 – Sample Reminder Letter

Attachment 1

MERCK RESEARCH LABORATORIES

ADVERSE EVENT REPORT

PATIENT INFORMATION — FIRST NAME OR INITIALS _____ LAST _____ ALLOCATION NO. _____ AGE _____ SEX _____ WEIGHT _____ KG _____ LB PREGNANT _____ WKS. GEST. _____

COMPLETE STUDY TITLE:

ADVERSE EVENT(S)	IS AE IN LABELING (Y / N)	ONSET DATE	CAUSALITY[a] Y OR N	OUTCOME[b]	DID AE RESULT IN: DEATH*	HOSPITALIZATION OR PROLONG EXISTING HOSPITALIZATION	PERSISTENT OR SIGNIFICANT DISABILITY	WAS AE LIFE THREATENING	IS AE CANCER	IS AE DUE TO	IS AE OVERDOSE	IS AE CONGENITAL	IS AE ANOMALY	IS AE OTHER MED EVENT
					ENTER Y FOR YES OR N FOR NO FOR EACH AE									

*If patient died, record death as an adverse event, specify date, complete item (a) above, and record probable cause(s) of death here.

PROBABLE CAUSE(S) OF DEATH
1. _____
2. _____
3. _____

PRIMARY SUSPECT DRUG	FORMULATION (e.g. Tablet)	ROUTE	INDICATION FOR USE	STRENGTH (mg or specify units)	FREQUENCY	TOTAL DAILY DOSE AT TIME OF AE (mg or specify units)	START DATE	STOP DATE	ACTION TAKEN[c]
SECONDARY SUSPECT DRUG AND OTHER MERCK THERAPY									

DID ADVERSE EVENT (AE) DIMINISH AFTER STOPPING SUSPECT DRUG? ___ YES ___ NO ___ NOT APPLICABLE (Suspect drug not stopped) If 'YES' specify AE(s) _____

DID ADVERSE EVENT REAPPEAR AFTER RESTARTING SUSPECT DRUG? ___ YES ___ NO ___ NOT APPLICABLE (Suspect drug not restarted) If 'YES' specify AE(s) _____

RECENT / CONCOMITANT THERAPY (WITHIN 14 DAYS OF ONSET OF AE)	DAILY DOSAGE (mg or specify units)	START DATE	STOP DATE	INDICATION FOR USE

a) CAUSALITY
Was there a reasonable possibility that the adverse experience may have been caused by the suspect drug?

b) OUTCOME
1 = Recovered
2 = Not Recovered

c) ACTION TAKEN REGARDING SUSPECT DRUG
1 = None
2 = Discontinued
3 = Dosage Reduced
4 = Dosage Interrupted

NOTE: COMPLETE PAGE 2

cc:

WAES-USA

ALLOCATION NO. _____

MEDICAL HISTORY (RELEVANT TO AE)	
CONCURRENT CONDITIONS (ONSET PRIOR TO SUSPECT THERAPY)	OTHER MEDICAL HISTORY

LABORATORY RESULTS / DIAGNOSTIC TESTS (RELEVANT TO AE)	DATE	VALUE	UNITS	COMMENTS (NORMAL / ABNORMAL)

NARRATIVE AND COMMENTS

FULL NAME OF PRIMARY INVESTIGATOR _____

NAME AND ADDRESS OF REPORTING PHYSICIAN _____

STUDY NO. _____ COMPASSIONATE USE _____ MK/V# _____ MISC CRF

EXTENSION NO. _____ AMENDMENT NO. _____

IND NO. _____ IIN NO. _____ INITIAL REPORT ___ OR FOLLOW-UP ___

DATE MERCK RECEIVED DATA RECORDED ON THIS REPORT _____

PERSON REPORTING: NAME _____

PHONE NUMBER: _____

SIGNATURE _____ DATE: _____

Attachment 2

Pregnancy Worksheet - Trimester Update

CIN 2/3 EFFICACY TRIAL IN WOMEN

Unscheduled

Compound	Protocol	Study Site	IIN	VISIT	Baseline Number	Allocation Number
V501	015-00			U		

PREGNANCY WORKSHEET - Monthly Update

Date information obtained: _____ (DD-Mon-YYYY) Gestational Week (At time of report): _____

Medications

NOTE: *List all medications/dosage taken since last report (only include those not already listed in PRX/CRX/PCRXc worksheets).*

DRUG NAME	TOTAL DAILY DOSAGE		START DATE (DD-Mon-YYYY)	STOP DATE (or check if continuing) (DD-Mon-YYYY)	MEDICAL CONDITION BEING TREATED
	Dose	Units			
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	
				☐ Continuing	

Pregnancy Complications

NOTE: *Update on maternal health (i.e., gestational diabetes, infections, etc.) since last report.*

COMPLICATION	START DATE (DD-Mon-YYYY)	STOP DATE (DD-Mon-YYYY)

Procedures During Pregnancy

NOTE: *List any procedures performed since last report (i.e., ultrasound, amniocentesis, etc.).*

PROCEDURE	PROCEDURE DATE (DD-Mon-YYYY)	MEDICAL CONDITION BEING TREATED	RESULT

Comments:

Investigator's name:

If this worksheet is used as a source document, it must be **initialed** and **dated** by the individual making the observation/recording →

Attachment 3

MERCK Research Laboratories

Pregnancy Outcome Questionnaire-HPV Vaccine

Merck & Co., Inc. is committed to the CONFIDENTIAL collection of patient information. In order to allow for the collection of pregnancy outcome data, minimize duplicate reporting, and prevent loss to follow-up, please COMPLETE ALL SECTIONS below. Please correct any inaccurate pre-filled information.

Subject ID (initials and allocation number): _____

Pregnancy Outcome (**If multiple birth**, please photocopy and complete a form for each infant)

↳❑ Liveborn infant: Birthdate ___/___/___ Sex _____ Weight _____ Weeks from LMP ____
Was the infant normal? ❑yes ❑no
Were there congenital anomalies? If so, describe _____
Were there other complications or abnormalities? If so, describe _____
_____

↳❑ Elective termination ❑ Spontaneous abortion (<20 weeks) ❑ Fetal death/stillbirth (≥20 weeks)
Date ____/____/____ Weeks from LMP _____
Were the products of conception examined? ❑yes ❑no ❑unknown
Was the fetus normal? ❑yes ❑no ❑unknown
If no, describe _____

Obstetric Information

❑no ❑yes Complication during pregnancy, specify _____
❑no ❑yes Complication during labor/delivery, specify _____
❑no ❑yes Diagnostic test during pregnancy. If yes, dates and test results:_____
❑no ❑yes Infections or illnesses during pregnancy, specify _____
❑no ❑yes Concurrent medical conditions, specify _____
_____

Other Medication Used During This Pregnancy

Name of medication	Date(s) of use	Strength (eg. 5 mg)	Number of doses taken	Reason for Use

Infant Adverse Event

❑no ❑yes If yes, describe
_____
_____
_____

Questionnaire was completed by:_____ **Date:** _____

Merck Use Only	WAES Number _____

Attachment 4
CTS Pregnancy Worksheets
(MPREG, PPREG, OPREG)

SHORT PROTOCOL TITLE

Unscheduled

MPREG

Compound	Protocol	Visit
XXXXXXX	XXX-XX	U

Baseline No. *(Site - Sequence No.)*	Allocation Number
__ __ __ __ - __ __ __ __	

MATERNAL INFORMATION

35003

Date completed: _____ DD-Mon-YYYY

Date of Last Menstrual Period: _____ DD-Mon-YYYY Date of Estimated Delivery: _____ DD-Mon-YYYY

PREGNANCY HISTORY *(Indicate "0" if not applicable)*:

Number of Previous Pregnancies: _____

Indicate the number for each category below (Indicate "0" if not applicable):

LIVE BIRTHS		ABORTIONS	
Number of Full Term Births		Number of Spontaneous Abortions (< 20 Weeks)	
Number of Premature Births (< 37 Weeks)		Number of Late Fetal Deaths (≥ 20 Weeks)	
		Number of Elective Abortions	

MATERNAL PREGNANCY HISTORY

35001

Maternal pregnancy history?

None ☐ *or complete below*

NOTE: • *Record any **maternal** medical conditions from previous pregnancies (i.e., gestational diabetes, hypertension, ectopic pregnancy).*

• *Use the **Previous Pregnancy Outcome** (**PPREG**) worksheet to record information on the fetus/infant from previous pregnancies.*

MEDICAL HISTORY TERM	YEAR DIAGNOSED	ACTIVE? No	Yes
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

Comments:

If this worksheet is used as a **source document**, it must be **initialed** and **dated** by the individual making the observation/recording.

Initials | DD-Mon-YYYY

SHORT PROTOCOL TITLE

Unscheduled

PPREG

Compound	Protocol	Visit
XXXXXXX	XXX-XX	U

Baseline No. *(Site - Sequence No.)*	Allocation Number
___ ___ ___ ___-___ ___ ___ ___	

PREVIOUS PREGNANCY OUTCOME

35004

Please complete ONE page for each fetus/infant.

Date completed: _____ DD-Mon-YYYY

FETUS/INFANT Number: _____ Date of Delivery/Termination: _____ DD-Mon-YYYY

The information on this worksheet refers to a: Live Birth ☐ *(complete sections 1 and 3)*

Fetal Loss ☐ *(complete sections 2 and 3)*

1. LIVE BIRTH *(Must complete section 3)*:

Live Birth Method: C-section ☐ Vaginal ☐

Reason for C-section:

- Repeat or Elective Section No ☐ Yes ☐
- Fetal Distress No ☐ Yes ☐
- Failure to Progress or Dystocia No ☐ Yes ☐
- Cephalopelvic Disproportion No ☐ Yes ☐
- Breech, Malpresentation, or Transverse Lie No ☐ Yes ☐
- Cord Prolapse, Placenta Previa No ☐ Yes ☐
- Premature Delivery; Multiple Gestation No ☐ Yes ☐
- Other No ☐ Yes ☐ *(Specify):* _____

Gender: Female ☐ Male ☐

Birth Weight: ____ gm ☐ lbs ☐

Gestational Age: _____ (weeks from LMP)

2. FETAL LOSS *(Must complete section 3)*:

Gestational age: _____ weeks from LMP

Type of Fetal Loss *(Check only one)*:

- Spontaneous Abortion (< 20 wks from LMP) ☐
- Late Fetal Death (≥ 20 wks from LMP) ☐
- Elective Abortion ☐ *(Provide reason)*

_____

Reason for elective abortion:

Fetal Abnormality *(describe in section 3)*

No ☐ Yes ☐

Maternal Condition or Disease No ☐ Yes ☐

Personal Decision No ☐ Yes ☐

3. WAS FETUS/INFANT NORMAL?

Yes ☐ No ☐ Unknown ☐

*If **NO**, select reason below:*

Congenital Anomaly No ☐ Yes ☐

Other Abnormality No ☐ Yes ☐ *(If **yes**, describe below:)*

_____

NOTE: *Describe any additional information that might help in interpreting the outcome of this pregnancy (including exposure to X-rays, teratogens, alcohol, tobacco, etc.). Additionally, provide any relevant information on the pregnancy, labor, delivery, or termination.*

Comments:

If this worksheet is used as a **source document**, it must be **initialed** and **dated** by the individual making the observation/recording.	Initials	DD-Mon-YYYY

SHORT PROTOCOL TITLE

Unscheduled

OPREG

Compound	Protocol	Visit
XXXXXXX	XXX-XX	U

Baseline No. *(Site - Sequence No.)*	Allocation Number
___ ___ ___ ___ - ___ ___ ___ ___	

OUTCOME OF PREGNANCY

35004

Please complete ONE page for each fetus/infant.

Date completed: _____ DD-Mon-YYYY

FETUS/INFANT Number: _____ Date of Delivery/Termination: _____ DD-Mon-YYYY

The information on this worksheet refers to a: Live Birth ☐ *(complete sections 1 and 3)*

Fetal Loss ☐ *(complete sections 2 and 3)*

1. LIVE BIRTH *(Must complete section 3)*:

Live Birth Method: C-section ☐ Vaginal ☐

Reason for C-section:

- Repeat or Elective Section No ☐ Yes ☐
- Fetal Distress No ☐ Yes ☐
- Failure to Progress or Dystocia No ☐ Yes ☐
- Cephalopelvic Disproportion No ☐ Yes ☐
- Breech, Malpresentation, or Transverse Lie No ☐ Yes
- Cord Prolapse, Placenta Previa No ☐ Yes ☐
- Premature Delivery; Multiple Gestation No ☐ Yes ☐
- Other No ☐ Yes ☐ *(Specify):* _____

Gender: Female ☐ Male ☐

Birth Weight: _____ gm ☐ lbs ☐

Gestational Age: _____ (weeks from LMP)

2. FETAL LOSS *(Must complete section 3)*:

Gestational age: _____ weeks from LMP

Type of Fetal Loss *(Check only one)*:

- Spontaneous Abortion (< 20 wks from LMP) ☐
- Late Fetal Death (≥ 20 wks from LMP) ☐
- Elective Abortion ☐ *(Provide reason)*

Reason for elective abortion:

- Fetal Abnormality *(describe in section 3)* No ☐ Yes ☐
- Maternal Condition or Disease No ☐ Yes ☐
- Personal Decision No ☐ Yes ☐

3. WAS FETUS/INFANT NORMAL?

Yes ☐ No ☐ Unknown ☐

*If **NO**, select reason below:*

- Congenital Anomaly No ☐ Yes ☐ *(If **yes**, complete SAE worksheet)*
- Other Abnormality No ☐ Yes ☐ *(If **yes**, describe below:)*

_____

_____

NOTE: *Describe any additional information that might help in interpreting the outcome of this pregnancy (including exposure to X-rays, teratogens, alcohol, tobacco, etc.). Additionally, provide any relevant information on the pregnancy, labor, delivery, or termination.*

Comments:

If this worksheet is used as a **source document**, it must be **initialed** and **dated** by the individual making the observation/recording.	Initials	DD-Mon-YYYY

Attachment 5
SAEv, SAE-INFv

SHORT PROTOCOL TITLE

Time Frame (Day, Week, Month) SAEv

Compound	Protocol	Visit	Baseline No. *(Site - Sequence No.)*	Allocation Number
V501	000-00		_____ - _____	

SERIOUS ADVERSE EXPERIENCE

34977

USE THIS FORM If the AE ....

- resulted in death
- was immediately life threatening
- resulted in persistent or significant disability/incapacity
- resulted in inpatient hospitalization or the prolongation of an existing inpatient hospitalization
- is a congenital anomaly/birth defect
- is an other important medical event
- is a cancer
- is an overdose (whether accidental or intentional)

NOTE: All Serious AEs must be reported to Merck within 24 hours.

THIS PAGE IS TO BE REVIEWED/COMPLETED AT EACH VISIT.

Did any **serious AEs** occur during the protocol specified clinical follow-up period? **None** ☐ *or complete form below*

Type of SAE	Systemic ☐ Systemic-lactation ☐ Systemic-pregnancy ☐ Injection site ☐ Laboratory ☐ Laboratory-lactation ☐ Laboratory-pregnancy ☐ Other ☐	Systemic ☐ Systemic-lactation ☐ Systemic-pregnancy ☐ Injection site ☐ Laboratory ☐ Laboratory-lactation ☐ Laboratory-pregnancy ☐ Other ☐
SAE term		
Check if **worsening of pre-existing condition**	☐	☐
Onset date *(Lab date if lab SAE)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Stop date *(Not applicable for lab or other)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Duration (if less than 24 hours) *(Not applicable for lab or other)*	Hour ☐ Minute ☐ Second ☐	Hour ☐ Minute ☐ Second ☐
Intensity *(Not applicable for lab or other)*	Mild ☐ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Maximum size *(1-8) (Injection site SAE only)*		
Injection site *(Injection site SAE only)*	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other *(specify)*: _____	Right arm ☐ Left arm ☐ Right thigh ☐ Left thigh ☐ Other *(specify)*: _____
Did the SAE result in:		
Persistent or significant disability/incapacity?	No ☐ Yes ☐	No ☐ Yes ☐
Hospitalization or prolongation?	No ☐ Yes ☐	No ☐ Yes ☐
Death? *(Provide death date)*	No ☐ Yes ☐	No ☐ Yes ☐
Death date:	DD-Mon-YYYY:	DD-Mon-YYYY:
Is the SAE:		
Immediately life-threatening?	No ☐ Yes ☐	No ☐ Yes ☐
Cancer?	No ☐ Yes ☐	No ☐ Yes ☐
Due to overdose?	No ☐ Yes ☐	No ☐ Yes ☐
Congenital anomaly/birth defect?	No ☐ Yes ☐	No ☐ Yes ☐
Other important medical event?	No ☐ Yes ☐	No ☐ Yes ☐
Action taken on primary test vaccine due to SAE:	None ☐ No further test vaccinations given ☐ Discontinued from follow-up only ☐	None ☐ No further test vaccinations given ☐ Discontinued from follow-up only ☐
Did SAE reappear after restarting test product? *(Rechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did primary test vaccine cause SAE? *(Refer to Guidelines for Causality, then enter classification)*	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initials DD-Mon-YYYY	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initials DD-Mon-YYYY
Check if **SAE is associated with any Other Suspect Therapy** *(Refer to AEos form)*	☐	☐
Brief description of SAE (if necessary):		

If this worksheet is used as a **source document**, it must be **initialed** and **dated** by the individual making the observation/recording. | Initials | DD-Mon-YYYY

SHORT PROTOCOL TITLE

Time Frame (Day, Week, Month)

SAE-INFv

Compound	Protocol	Visit	Baseline No. *(Site - Sequence No.)*	Allocation Number
V501	000-00		___ ___ ___ - ___ ___ ___	

SERIOUS ADVERSE EXPERIENCE *(Infant)*

XXXXX

USE THIS FORM If the AE ....

- resulted in death
- was immediately life threatening
- resulted in persistent or significant disability/incapacity
- resulted in inpatient hospitalization or the prolongation of an existing inpatient hospitalization
- is a congenital anomaly/birth defect
- is an other important medical event
- is a cancer
- is an overdose (whether accidental or intentional)

NOTE: All Serious AEs must be reported to Merck within 24 hours.

INFANT DATE OF BIRTH DD-Mon-YYYY:	**TIME OF BIRTH** *(For multiple births only)* : 24 hr. clock	
Type of SAE	Systemic-neonatal ☐ Systemic-lactation ☐ Systemic-other ☐ Other ☐	Systemic-neonatal ☐ Systemic-lactation ☐ Systemic-other ☐ Other ☐
SAE term		
Check if **worsening of pre-existing condition**	☐	☐
Onset date	DD-Mon-YYYY:	DD-Mon-YYYY:
Stop date *(Not applicable for other)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Duration (if less than 24 hours) *(Not applicable for other)*	Hour ☐ Minute ☐ Second ☐	Hour ☐ Minute ☐ Second ☐
Intensity *(Not applicable for other)*	Mild ☐ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Did the SAE result in:		
Persistent or significant disability/incapacity?	No ☐ Yes ☐	No ☐ Yes ☐
Hospitalization or prolongation?	No ☐ Yes ☐	No ☐ Yes ☐
Death? *(Provide death date)*	No ☐ Yes ☐	No ☐ Yes ☐
Death date:	DD-Mon-YYYY:	DD-Mon-YYYY:
Is the SAE:		
Immediately life-threatening?	No ☐ Yes ☐	No ☐ Yes ☐
Cancer?	No ☐ Yes ☐	No ☐ Yes ☐
Due to overdose?	No ☐ Yes ☐	No ☐ Yes ☐
Congenital anomaly/birth defect?	No ☐ Yes ☐	No ☐ Yes ☐
Other important medical event?	No ☐ Yes ☐	No ☐ Yes ☐
Did primary test vaccine cause SAE? *(Refer to Guidelines for Causality, then enter classification)*	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initials DD-Mon-YYYY	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initials DD-Mon-YYYY

Brief description of SAE (if necessary):

If this worksheet is used as a **source document**, it must be **initialed** and **dated** by the individual making the observation/recording.	Initials	DD-Mon-YYYY

Attachment 6
Sample Reminder Letter

Date

Name
Address
Address
Address

Subject: Merck & Co., Inc. HPV Vaccine Protocol _____
Study _____-_____
Pregnancy Outcome (initials/allocation number)

Dear Dr. _____,

The purpose of this letter is to remind you that a report documenting the outcome of the reported pregnancy for subject (initials/allocation number) is now due. Please complete the Pregnancy Outcome Questionnaire and return, via fax, to the Medical Monitor/MPCS/Subsidiary Representative assigned to your study site.

Very truly yours,

Medical Monitor/MPCS/Subsidiary Representative

WAES ADVERSE EXPERIENCE REPORT

WAESNUM: **0404GBR00229 v 9**

human papillomavirus vaccine

Initial Report Date : 27-Apr-2004

Protocol # 018 Extension # 0 Amendment # 0 Site # 0017 Allocation # 70888

Action Taken: None

AE/Lowest Level Term/Reported	Onset	Ser	Assn	Died	Hos	Dis	LT	CA	Cong	OD	OM	CC	End	Outcome
Appendicitis	23-Apr-2004	Y	N	N	Y	N	N	N	N	N	N	N	N	I

Appendicitis

appendicitis

Cause of Death:

Primary Therapy	Lot No.	Total Daily Dose / Rte	Start	Stop	Duration
human papillomavirus vaccine		IM	14-Feb-2004		
human papillomavirus vaccine		IM	22-Apr-2004		

Secondary Therapy	Lot No.	Total Daily Dose / Rte	Start	Stop	Duration

Concomitant	Lot No.	Total Daily Dose / Rte	Start	Stop	Duration

	CONCURRENT CONDITIONS
AGE 14 year	Tonsillitis
SEX : F	
RACE :	

Literature Citation:

Narrative :

Information has been received from an investigator concerning a 14 year old female with tonsillitis (2004) who entered a study, title as stated above. On 14-FEB-2004 the patient was vaccinated with the first dose of human papilloma virus (HPV) vaccine or placebo for HPV prophylaxis. On 22-APR-2004 the patient received the second dose of study vaccine. There was no concomitant medication. On 23-APR-2004 the patient experienced abdominal pain and was treated with actaminophen and ibuprofen (NUROFEN) (doses not reported). On 24-APR-2004 the patient was seen by her doctor who diagnosed the patient with appendicitis of severe intensity. On 27-APR-2004 the patient was hospitalised for an appendix removal and was considered recovered from the appendicitis. On 28-APR-2004 the patient was discharged from hospital. The reporting investigator felt that appendicitis was probably not related to study therapy.

The record for this patient was unblinded on 14-MAR-2005. The patient was treated with HPV (6 , 11, 16, 18) VLP vaccine.

Additional information is not expected.

LAB DATA	DATE	RESULT	COMMENT

DIAGNOSTIC TEST	DATE	RESULT

Table 6-1
Subject Disposition by Vaccination Group

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine		Non-Alum Placebo		Total	
	n	(%)	n	(%)	n	(%)
SCREENING FAILURES					20	
RANDOMIZED	1184		597		1781	
VACCINATED AT:						
Dose 1	1179	(99.6)	596	(99.8)	1775	(99.7)
Dose 2	1149	(97.0)	573	(96.0)	1722	(96.7)
Dose 3	1123	(94.8)	562	(94.1)	1685	(94.6)
VACCINATION PERIOD (Day 1 Through Month 7)						
ENTERED	1179		596		1775	
COMPLETED[†]	1120	(95.0)	560	(94.0)	1680	(94.6)
CONTINUING[‡]	1	(0.1)	0	(0.0)	1	(0.1)
DISCONTINUED	58	(4.9)	36	(6.0)	94	(5.3)
WITH LONG-TERM FOLLOW-UP[§]	7	(0.6)	4	(0.7)	11	(0.6)
Clinical adverse experience	2	(0.2)	0	(0.0)	2	(0.1)
Other reasons	5	(0.4)	4	(0.7)	9	(0.5)
WITHOUT LONG-TERM FOLLOW-UP[‖]	51	(4.3)	32	(5.4)	83	(4.7)
Clinical adverse experience	1	(0.1)	0	(0.0)	1	(0.1)
Lost to follow-up	17	(1.4)	7	(1.2)	24	(1.4)
Moved	4	(0.3)	1	(0.2)	5	(0.3)
Other reasons	1	(0.1)	2	(0.3)	3	(0.2)
Parent withdrew consent	9	(0.8)	8	(1.3)	17	(1.0)
Withdrew consent	19	(1.6)	14	(2.3)	33	(1.9)

[†] Subjects completed 3 doses of vaccinations and entered the long-term follow-up period.

[‡] Subject did not meet the cutoff date for Month 7 visit completion and did not withdraw from the study.

[§] Subjects received fewer than 3 doses of vaccinations and entered the long-term follow-up period.

[‖] Subjects discontinued on or before Month 7 and did not enter the long-term follow-up period.

Status percentages are calculated based on the number of subjects who entered the respective time period.

n = Number of subjects with the indicated characteristic.

HPV = Human papillomavirus; VLP = Virus-like particles.

Table 11-8
Number (%) of Subjects With Specific Concomitant Vaccination (Incidence >0% in One or More Vaccination Groups)
(Vaccination Period, Day 1 Through Month 7) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Subjects in analysis population	1179		596	
Subjects with one or more concomitant vaccinations	70	(5.9)	33	(5.5)
Subjects with no concomitant vaccinations	1109	(94.1)	563	(94.5)
Concomitant vaccinations				
BCG vaccine	8	(0.7)	1	(0.2)
diphtheria toxoid	3	(0.3)	0	(0.0)
diphtheria toxoid (+) pertussis vaccine (unspecified) (+) tetanus toxoid	1	(0.1)	0	(0.0)
diphtheria toxoid (+) tetanus toxoid	10	(0.8)	4	(0.7)
hepatitis A virus vaccine (unspecified)	1	(0.1)	0	(0.0)
hepatitis A virus vaccine (unspecified) (+) hepatitis B virus vaccine (unspecified)	0	(0.0)	1	(0.2)
hepatitis A virus vaccine inactivated	1	(0.1)	0	(0.0)
hepatitis A virus vaccine inactivated (+) hepatitis B virus vaccine rHBsAg (yeast)	2	(0.2)	0	(0.0)
hepatitis B virus vaccine (unspecified)	4	(0.3)	3	(0.5)
influenza virus 3v reassortant vaccine live intranasal (cold adapted Ann Arbor master strain)	0	(0.0)	1	(0.2)
influenza virus sAg 3v vaccine inactivated	1	(0.1)	1	(0.2)
influenza virus split virion 3v vaccine inactivated	3	(0.3)	1	(0.2)
influenza virus vaccine (unspecified)	3	(0.3)	0	(0.0)
measles virus vaccine live (Moraten) (+) mumps virus vaccine live (Jeryl Lynn) (+) rubella virus vaccine live (HPV-77)	3	(0.3)	2	(0.3)
measles virus vaccine live (Moraten) (+) mumps virus vaccine live (Jeryl Lynn) (+) rubella virus vaccine live (Wistar RA 27/3) (+) varicella virus vaccine live (Oka/Merck original process)	5	(0.4)	6	(1.0)
measles virus vaccine live (unspecified)	12	(1.0)	7	(1.2)
measles virus vaccine live (unspecified) (+) mumps virus vaccine live (unspecified) (+) rubella virus vaccine live (unspecified)	1	(0.1)	1	(0.2)

Table 11-8 (Cont.)
Number (%) of Subjects With Specific Concomitant Vaccination (Incidence >0% in One or More Vaccination Groups)
(Vaccination Period, Day 1 Through Month 7) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
measles virus vaccine live (unspecified) (+) rubella virus vaccine live (unspecified)	1	(0.1)	1	(0.2)
meningococcal vaccine (unspecified)	1	(0.1)	0	(0.0)
poliovirus vaccine inactivated (unspecified)	2	(0.2)	4	(0.7)
poliovirus vaccine live oral	0	(0.0)	1	(0.2)
rabies virus vaccine (chick embryo)	0	(0.0)	2	(0.3)
tetanus toxoid	11	(0.9)	8	(1.3)
tick-borne encephalitis virus vaccine	1	(0.1)	0	(0.0)
varicella virus vaccine live (Oka/Merck)	1	(0.1)	0	(0.0)
yellow fever virus vaccine	6	(0.5)	0	(0.0)

Percentages are calculated as the number of subjects with the specific concomitant vaccination divided by the number of subjects in the analysis population for the vaccination group.
Although a subject may have had two or more concomitant vaccinations, the subject is counted only once for a given concomitant vaccination.
n = Number of subjects with the indicated characteristic.
N = Number of subjects randomized in the vaccination group.

Table 11-9

Number (%) of Subjects With Specific Aluminum-Contatining Concomitant Vaccination (Incidence >0% in One or More Vaccination Groups)

(Vaccination Period, Day 1 Though Month 7) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Subjects in analysis population	1179		596	
Subjects with one or more concomitant vaccinations	30	(2.5)	16	(2.7)
Subjects with no concomitant vaccinations	1149	(97.5)	580	(97.3)
Concomitant vaccinations				
diphtheria toxoid	3	(0.3)	0	(0.0)
diphtheria toxoid (+) pertussis vaccine (unspecified) (+) tetanus toxoid	1	(0.1)	0	(0.0)
diphtheria toxoid (+) tetanus toxoid	10	(0.8)	4	(0.7)
hepatitis A virus vaccine (unspecified)	1	(0.1)	0	(0.0)
hepatitis A virus vaccine (unspecified) (+) hepatitis B virus vaccine (unspecified)	0	(0.0)	1	(0.2)
hepatitis A virus vaccine inactivated	1	(0.1)	0	(0.0)
hepatitis A virus vaccine inactivated (+) hepatitis B virus vaccine rHBsAg (yeast)	2	(0.2)	0	(0.0)
hepatitis B virus vaccine (unspecified)	4	(0.3)	3	(0.5)
tetanus toxoid	11	(0.9)	8	(1.3)
tick-borne encephalitis virus vaccine	1	(0.1)	0	(0.0)

Percentages are calculated as the number of subjects with the specific concomitant vaccination divided by the number of subjects in the analysis population for the vaccination group.

Although a subject may have had two or more concomitant vaccinations, the subject is counted only once for a given concomitant vaccination.

n = Number of subjects with the indicated characteristic.

N = Number of subjects randomized in the vaccination group.

Table 6-12
Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Subjects in analysis population	1179		596	
Subjects with one or more medical condition	805	(68.3)	416	(69.8)
Subjects with no medical condition	374	(31.7)	180	(30.2)
Blood And Lymphatic System Disorders	**12**	**(1.0)**	**6**	**(1.0)**
Congenital, Familial And Genetic Disorders	**22**	**(1.9)**	**17**	**(2.9)**
Ear And Labyrinth Disorders	**32**	**(2.7)**	**19**	**(3.2)**
Ear Pain	10	(0.8)	8	(1.3)
Eye Disorders	**60**	**(5.1)**	**32**	**(5.4)**
Astigmatism	9	(0.8)	6	(1.0)
Conjunctivitis	21	(1.8)	11	(1.8)
Myopia	21	(1.8)	13	(2.2)
Gastrointestinal Disorders	**91**	**(7.7)**	**49**	**(8.2)**
Abdominal Pain	18	(1.5)	11	(1.8)
Constipation	17	(1.4)	8	(1.3)
Gastrooesophageal Reflux Disease	10	(0.8)	6	(1.0)
General Disorders And Administration Site Conditions	**29**	**(2.5)**	**13**	**(2.2)**

Table 6-12 (Cont.)
Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Immune System Disorders	**233**	**(19.8)**	**108**	**(18.1)**
Drug Hypersensitivity	58	(4.9)	36	(6.0)
Hypersensitivity	32	(2.7)	17	(2.9)
Seasonal Allergy	141	(12.0)	56	(9.4)
Infections And Infestations	**429**	**(36.4)**	**234**	**(39.3)**
Bronchitis	21	(1.8)	14	(2.3)
Cellulitis	3	(0.3)	8	(1.3)
Impetigo	12	(1.0)	5	(0.8)
Influenza	27	(2.3)	12	(2.0)
Nasopharyngitis	13	(1.1)	8	(1.3)
Otitis Externa	12	(1.0)	9	(1.5)
Otitis Media	61	(5.2)	41	(6.9)
Otitis Media Chronic	7	(0.6)	9	(1.5)
Pharyngitis	78	(6.6)	45	(7.6)
Pharyngitis Streptococcal	44	(3.7)	28	(4.7)
Pneumonia	21	(1.8)	9	(1.5)
Rhinitis	12	(1.0)	10	(1.7)
Sinusitis	53	(4.5)	20	(3.4)
Tonsillitis	13	(1.1)	13	(2.2)
Upper Respiratory Tract Infection	82	(7.0)	48	(8.1)
Urinary Tract Infection	14	(1.2)	6	(1.0)
Varicella	28	(2.4)	17	(2.9)
Viral Infection	24	(2.0)	19	(3.2)
Viral Pharyngitis	14	(1.2)	8	(1.3)

Table 6-12 (Cont.)
Number (%) of Subjects With Specific Medical Conditio ns (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Injury, Poisoning And Procedural Complications	**128**	**(10.9)**	**61**	**(10.2)**
Contusion	15	(1.3)	10	(1.7)
Joint Injury	12	(1.0)	3	(0.5)
Joint Sprain	15	(1.3)	9	(1.5)
Limb Injury	11	(0.9)	8	(1.3)
Skin Laceration	7	(0.6)	6	(1.0)
Investigations	**24**	**(2.0)**	**11**	**(1.8)**
Metabolism And Nutrition Disorders	**36**	**(3.1)**	**20**	**(3.4)**
Obesity	18	(1.5)	13	(2.2)
Musculoskeletal And Connective Tissue Disorders	**103**	**(8.7)**	**54**	**(9.1)**
Arthralgia	20	(1.7)	14	(2.3)
Back Pain	19	(1.6)	7	(1.2)
Scoliosis	12	(1.0)	6	(1.0)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**42**	**(3.6)**	**24**	**(4.0)**
Skin Papilloma	37	(3.1)	22	(3.7)
Nervous System Disorders	**139**	**(11.8)**	**83**	**(13.9)**
Headache	99	(8.4)	56	(9.4)
Migraine	25	(2.1)	17	(2.9)

Table 6-12 (Cont.)

Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Psychiatric Disorders	**104**	**(8.8)**	**43**	**(7.2)**
Abnormal Behaviour	13	(1.1)	0	(0.0)
Attention Deficit/Hyperactivity Disorder	78	(6.6)	35	(5.9)
Renal And Urinary Disorders	**26**	**(2.2)**	**9**	**(1.5)**
Reproductive System And Breast Disorders	**73**	**(6.2)**	**36**	**(6.0)**
Dysmenorrhoea	51	(4.3)	22	(3.7)
Respiratory, Thoracic And Mediastinal Disorders	**252**	**(21.4)**	**148**	**(24.8)**
Asthma	114	(9.7)	69	(11.6)
Asthma Exercise Induced	6	(0.5)	6	(1.0)
Bronchospasm	18	(1.5)	13	(2.2)
Cough	28	(2.4)	14	(2.3)
Epistaxis	8	(0.7)	6	(1.0)
Pharyngolaryngeal Pain	10	(0.8)	11	(1.8)
Rhinitis Allergic	77	(6.5)	41	(6.9)
Skin And Subcutaneous Tissue Disorders	**173**	**(14.7)**	**81**	**(13.6)**
Acne	58	(4.9)	27	(4.5)
Dermatitis Atopic	12	(1.0)	9	(1.5)
Dermatitis Contact	15	(1.3)	6	(1.0)
Eczema	34	(2.9)	22	(3.7)

Table 6-12 (Cont.)
Number (%) of Subjects With Specific Medical Conditions (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Prior to Vaccination 1) All Vaccinated Subjects

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1184)		Non-Alum Placebo (N=597)	
	n	(%)	n	(%)
Surgical And Me dical Procedures	**95**	**(8.1)**	**55**	**(9.2)**
Adenoidectomy	18	(1.5)	6	(1.0)
Ear Tube Insertion	19	(1.6)	10	(1.7)
Tonsillectomy	18	(1.5)	15	(2.5)

Although a subject may have had 2 or more medical conditions, the subject is counted only once within a category. The same subject may appear in different categories.

Terms for medical conditions are from MedDRA Version 7.1.

n = Number of subjects with the indicated characteristic.

N = Number of subjects randomized into each vaccination group; HPV = Human papillomavirus; VLP = Virus-like particles.

Table 8-25
Number (%) of Subjects With New Medical Conditions
(Incidence =1% in One or More Vaccination Groups) by System Organ Class
(Vaccination Period, Day 1 Through Month 7)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1179)		Non-Alum Placebo (N= 594)	
	n	(%)	n	(%)
Subjects in analysis population	1179		594	
Subjects with one or more new medical conditions	520	(44.1)	280	(47.1)
Subjects with no new medical conditions	659	(55.9)	314	(52.9)
Ear And Labyrinth Disorders	**13**	**(1.1)**	**10**	**(1.7)**
Eye Disorders	**23**	**(2.0)**	**7**	**(1.2)**
Gastrointestinal Disorders	**43**	**(3.6)**	**30**	**(5.1)**
Abdominal Pain	8	(0.7)	8	(1.3)
General Disorders And Administration Site Conditions	**17**	**(1.4)**	**5**	**(0.8)**
Immune System Disorders	**21**	**(1.8)**	**9**	**(1.5)**
Seasonal Allergy	12	(1.0)	5	(0.8)
Infections And Infestations	**265**	**(22.5)**	**150**	**(25.3)**
Bacterial Infection	7	(0.6)	6	(1.0)
Gastroenteritis Viral	7	(0.6)	7	(1.2)
Influenza	20	(1.7)	13	(2.2)

Table 8-25 (Cont.)
Number (%) of Subjects With New Medical Conditions
(Incidence =1% in One or More Vaccination Groups) by System Organ Class
(Vaccination Period, Day 1 Through Month 7)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1179)		Non-Alum Placebo (N= 594)	
	n	(%)	n	(%)
Nasopharyngitis	26	(2.2)	21	(3.5)
Otitis Media	10	(0.8)	12	(2.0)
Pharyngitis	30	(2.5)	13	(2.2)
Pharyngitis Streptococcal	19	(1.6)	11	(1.9)
Sinusitis	12	(1.0)	9	(1.5)
Tinea Pedis	15	(1.3)	7	(1.2)
Tonsillitis	12	(1.0)	10	(1.7)
Upper Respiratory Tract Infection	41	(3.5)	15	(2.5)
Viral Infection	9	(0.8)	6	(1.0)
Injury, Poisoning And Procedural Complications	**90**	**(7.6)**	**45**	**(7.6)**
Musculoskeletal And Connective Tissue Disorders	**53**	**(4.5)**	**27**	**(4.5)**
Arthralgia	15	(1.3)	7	(1.2)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	**11**	**(0.9)**	**7**	**(1.2)**
Nervous System Disorders	**66**	**(5.6)**	**36**	**(6.1)**
Headache	58	(4.9)	30	(5.1)
Psychiatric Disorders	**16**	**(1.4)**	**10**	**(1.7)**

Table 8-25 (Cont.)
Number (%) of Subjects With New Medical Conditions
(Incidence =1% in One or More Vaccination Groups) by System Organ Class
(Vaccination Period, Day 1 Through Month 7)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N= 1179)		Non-Alum Placebo (N= 594)	
	n	(%)	n	(%)
Reproductive System And Breast Disorders	**24**	**(2.0)**	**7**	**(1.2)**
Respiratory, Thoracic And Mediastinal Disorders	**55**	**(4.7)**	**32**	**(5.4)**
Cough	12	(1.0)	10	(1.7)
Pharyngolaryngeal Pain	16	(1.4)	7	(1.2)
Skin And Subcutaneous Tissue Disorders	**46**	**(3.9)**	**28**	**(4.7)**
Acne	11	(0.9)	8	(1.3)
Surgical And Medical Procedures	**36**	**(3.1)**	**17**	**(2.9)**

Percentages are calculated based on the number of subjects in analysis population.
Although a subject may have had two or more new secondary diagnoses, the subject is counted only once within a category. The same subject may appear in different categories.
Terms for medical conditions are from MedDRA Version 7.1.
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Table 8-1
Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)		Protocol Non-Compliant Vaccination Regimen† (M=2)			
					Following Injection of HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		Following Injection of Non-Alum Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1179		594		2		2	
Subjects without follow-up	14		10		0		0	
Subjects with follow-up	1165		584		2		2	
Number (%) of subjects:								
with no adverse experience	202	(17.3)	192	(32.9)	0	(0.0)	0	(0.0)
with one or more adverse experiences	963	(82.7)	392	(67.1)	2	(100)	2	(100)
injection-site adverse experiences	877	(75.3)	292	(50.0)	2	(100)	1	(50)
systemic adverse experiences	541	(46.4)	260	(44.5)	1	(50)	2	(100)
with vaccine-related‡ adverse experiences	913	(78.4)	339	(58.0)	2	(100)	1	(50)
injection-site adverse experiences	877	(75.3)	292	(50.0)	2	(100)	1	(50)
systemic adverse experiences	274	(23.5)	134	(22.9)	0	(0.0)	0	(0.0)
with serious adverse experiences	5	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued§ due to an adverse experience	3	(0.3)	0	(0.0)	0			
discontinued due to a vaccine-related adverse experience	2	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)

Table 8-1 (Cont.)
Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)		Protocol Non-Compliant Vaccination Regimen[†] (M=2)			
					Following Injection of HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		Following Injection of Non-Alum Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.

[†] Subjects who were cross-treated with quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine and placebo.

[‡] Determined by the Investigator to be possibly, probably or definitely related to the vaccine.

[§] Discontinued = Subject discontinued from therapy.

n = Number of subjects with the indicated characteristic.

N = Number of subjects who received only the clinical material in the given column.

M = The number of subjects who were non-compliant with the protocol vaccination regimen. There were 2 subjects randomized to the placebo group who received quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine at 1 or more visits and placebo at 1 or more visits.

Table 8-4
Number (%) of Subjects With Injection-Site Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups)
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	1179				594			
Subjects without follow-up	14				10			
Subjects with follow-up	1165				584			
Number (%) of subjects with one or more injection-site adverse experiences	877	(75.3)			289	(49.5)		
Injection Site Erythema	237	(20.3)	237	(20.3)	77	(13.2)	77	(13.2)
Injection Site Haemorrhage	27	(2.3)	27	(2.3)	15	(2.6)	15	(2.6)
Injection Site Pain	853	(73.2)	853	(73.2)	265	(45.4)	265	(45.4)
Injection Site Paraesthesia	17	(1.5)	17	(1.5)	10	(1.7)	10	(1.7)
Injection Site Pruritus	13	(1.1)	13	(1.1)	5	(0.9)	5	(0.9)
Injection Site Reaction	13	(1.1)	13	(1.1)	4	(0.7)	4	(0.7)
Injection Site Swelling	241	(20.7)	241	(20.7)	45	(7.7)	45	(7.7)

Percentages are calculated based on the number of subjects with follow-up.

Although a subject may have had 2 or more adverse experiences, the subject is counted only once in the overall total.

Adverse experience terms are from MedDRA Version 7.1.

n = Number of subjects with the indicated characteristic.

N = Number of subjects who received only the clinical material in the given column.

VR = Vaccine related. Entries in this column refer to the number (%) of subjects with injection-site adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to the vaccine.

HPV = Human papillomavirus; VLP = Virus-like particles.

Table 8-11

Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1179				594			
Subjects without follow-up	14				10			
Subjects with follow-up	1165				584			
Number (%) of Subjects with one or more systemic adverse experiences	541	(46.4)			260	(44.5)		
Number (%) of Subjects with no systemic adverse experience	624	(53.6)			324	(55.5)		
Ear And Labyrinth Disorders	**19**	**(1.6)**	**8**	**(0.7)**	**7**	**(1.2)**	**3**	**(0.5)**
Gastrointestinal Disorders	**150**	**(12.9)**	**51**	**(4.4)**	**91**	**(15.6)**	**30**	**(5.1)**
Abdominal pain	19	(1.6)	7	(0.6)	12	(2.1)	7	(1.2)
Abdominal pain upper	38	(3.3)	12	(1.0)	17	(2.9)	3	(0.5)
Diarrhoea	43	(3.7)	11	(0.9)	21	(3.6)	3	(0.5)
Nausea	38	(3.3)	18	(1.5)	22	(3.8)	13	(2.2)
Vomiting	26	(2.2)	10	(0.9)	18	(3.1)	6	(1.0)
General Disorders And Administration Site Conditions	**149**	**(12.8)**	**102**	**(8.8)**	**60**	**(10.3)**	**42**	**(7.2)**
Fatigue	18	(1.5)	11	(0.9)	7	(1.2)	4	(0.7)
Pyrexia	100	(8.6)	74	(6.4)	45	(7.7)	32	(5.5)

Table 8-11 (Cont.)
Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections And Infestations	**117**	**(10.0)**	**15**	**(1.3)**	**71**	**(12.2)**	**7**	**(1.2)**
Influenza	10	(0.9)	5	(0.4)	12	(2.1)	3	(0.5)
Nasopharyngitis	34	(2.9)	5	(0.4)	22	(3.8)	1	(0.2)
Upper respiratory tract infection	8	(0.7)	1	(0.1)	9	(1.5)		
Injury, Poisoning And Procedural Complications	**31**	**(2.7)**			**15**	**(2.6)**		
Musculoskeletal And Connective Tissue Disorders	**80**	**(6.9)**	**35**	**(3.0)**	**36**	**(6.2)**	**15**	**(2.6)**
Arthralgia	21	(1.8)	10	(0.9)	9	(1.5)	5	(0.9)
Myalgia	31	(2.7)	19	(1.6)	10	(1.7)	6	(1.0)
Pain in extremity	19	(1.6)	10	(0.9)	14	(2.4)	7	(1.2)
Nervous System Disorders	**241**	**(20.7)**	**146**	**(12.5)**	**120**	**(20.5)**	**83**	**(14.2)**
Dizziness	25	(2.1)	19	(1.6)	9	(1.5)	7	(1.2)
Headache	221	(19.0)	133	(11.4)	110	(18.8)	76	(13.0)

Table 8-11 (Cont.)

Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Reproductive System And Breast Disorders	**14**	**(1.2)**			**8**	**(1.4)**		
Dysmenorrhoea	9	(0.8)			7	(1.2)		
Respiratory, Thoracic And Mediastinal Disorders	**85**	**(7.3)**	**10**	**(0.9)**	**51**	**(8.7)**	**7**	**(1.2)**
Cough	14	(1.2)	3	(0.3)	14	(2.4)	3	(0.5)
Nasal congestion	12	(1.0)			9	(1.5)	1	(0.2)
Pharyngolaryngeal pain	52	(4.5)	6	(0.5)	24	(4.1)	2	(0.3)
Rhinorrhoea	6	(0.5)	1	(0.1)	8	(1.4)	2	(0.3)
Skin And Subcutaneous Tissue Disorders	**25**	**(2.1)**	**6**	**(0.5)**	**20**	**(3.4)**	**4**	**(0.7)**
Rash	7	(0.6)	3	(0.3)	8	(1.4)	1	(0.2)

Percentages are calculated based on the number of subjects with follow-up.

Although a subject may have had 2 or more systemic adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Adverse experience terms are from MedDRA Version 7.1.

n = Number of subjects with the indicated characteristic.

N = Number of subjects who received only the clinical material in the given column.

VR = Vaccine related. Entries in this column refer to the number (%) of subjects with systemic adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to the vaccine.

HPV = Human papillomavirus; VLP = Virus-like particles.