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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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 S 47F 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 †	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

† 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. s 47F , a -year-old female, reported to the study site on s 47F 2005 that she was pregnant. The pregnancy was confirmed at the study site by a serum pregnancy test performed on s 47F 2005. The subject's last vaccination occurred on s 47F 2004 and she completed the Month 7 visit on s 47F 2004. The pregnancy s 47F on s 47F 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 s 47F 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													
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	6	1	6	Renal failure acute	16 day	mod	prob not	no further test vaccines	recovered
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] yr	70	2	2	Appendicitis	5 day	severe	prob not	none	recovered
[redacted]	[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
[redacted]	[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
[redacted]	[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.

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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.**

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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.**

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HPV Adolescent/Preadolescent Safety Study

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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.

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

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
[redacted], M.D., Ph.D.
Merck Research Laboratories, UN-C141
Sumneytown Pike
West Point, PA 19486-0004
Telephone: [redacted]

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
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, 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.

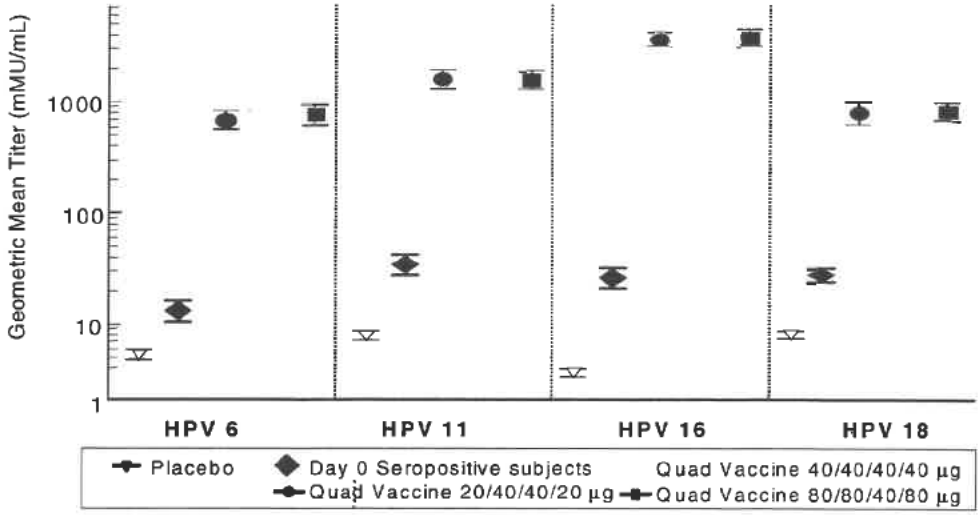
Further information can be obtained in the "Quadrivalent HPV Vaccine Confidential Investigator Brochure."

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