Statistical Data Analysis Plan

A Study to Evaluate the Efficacy of Quadrivalent HPV (Types 6, 11, 16, and 18) L1 Virus-Like Particle (VLP) Vaccine in Reducing the Incidence of HPV 6/11-, 16-, and 18-Related CIN, and HPV 16- and 18-Related AIS and Cervical Cancer, and HPV 6/11-, 16-, and 18-Related External Genital Warts, VIN and VaIN, and HPV 16- and 18-Related Vulvar and Vaginal Cancer in 16- to 23-Year-Old Women– the F.U.T.U.R.E. I Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease)

(Study 013)

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Data Analysis Plan

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EXECUTIVE SUMMARY

Background

The vaccine under study in Protocol 013 is a quadrivalent vaccine consisting of recombinant human papillomavirus (HPV) L1 virus-like particles (VLPs) for HPV types 6, 11, 16, and 18 expressed in the yeast *Saccharomyces cerevisiae*. HPV infection can result in dysplasia that may result in 2 related anogenital diseases: cancer and genital warts.

Every year, 471,000 cases of cervical cancer are diagnosed worldwide [1]. The 5-year survival for this disease is 50 to 70% [2]. In the developed world, routine Papanicolaou (Pap) screening has reduced the incidence of cervical cancer by 75% [3]. 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 worldwide [1; 2; 4; 5].

Genital warts cause significant morbidity [6; 7; 8]. 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 [9].

Over 90 HPV types have been identified [10]. 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, while HPV 6 and 11 cause >90% of genital warts [11]. In addition, HPV 6, 11, 16, or 18 are present in ~50% of low-grade cervical dysplasia (CIN 1) cases [11]. Therefore, it is expected that a prophylactic vaccine that reduces infection with these 4 HPV types will greatly reduce the burden of HPV disease.

This study is designed to evaluate the efficacy of the quadrivalent HPV vaccine in reducing the incidence of: (1) HPV 6/11/16/18-related external genital warts, Vulvar Intraepithelial Neoplasia (VIN) and Vaginal Intraepithelial Neoplasia (VaIN), and HPV 16/18-related vulvar and vaginal cancer; and (2) HPV 6/11/16/18-related Cervical Intraepithelial Neoplasia (CIN), and HPV 16/18-related Adenocarcinoma In Situ (AIS) and cervical cancer. The epithelial architecture and environment of the cervix differs significantly from the architecture of the vagina and vulva. In particular, the cervix consists of non-keratinized epithelium, and the cervical epithelium is bathed in a thin layer of transudate that contains antibodies. The vaginal and vulvar mucosa, on the other

hand, consist of keratinized tissue, and the vulvar epithelium is dry (i.e., it is not bathed by transudate fluid containing antibodies). Given the differences between the cervical mucosa and vaginal/vulvar mucosa, the efficacy of the vaccine in preventing HPV disease due to HPV vaccine types may be different in these anatomic sites. Such differential efficacy may occur because the protection offered by the vaccine is dependent on localized antibody levels at the site of infection, which could differ between internal and external genital surfaces. Based on the potential for differential vaccine efficacy with regards to vaccine HPV type infections of the cervix and the vagina/vulva, this protocol has 2 independent, co-primary efficacy hypotheses; that is, the success or failure of 1 hypothesis does not impact the success or failure of the other.

Study Objectives and Hypotheses

The primary objectives of this study are to demonstrate that: (1) the quadrivalent HPV vaccine is generally well tolerated; (2) the quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 6/11/16/18-related external genital warts, VIN or VaIN, or HPV 16- and 18-related vulvar or vaginal cancer compared with placebo; and (3) the quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 6/11-, 16-, and 18-related cervical dysplasia (any grade CIN) or HPV 16- and 18-related AIS or cervical cancer compared with placebo. The primary hypotheses of this study state that: (1) the quadrivalent HPV vaccine is generally well tolerated in 16- to 23-year-old females; (2) administration of a 3-dose regimen of quadrivalent HPV vaccine reduces the combined incidence of HPV 6/11/16/18-related external genital warts, VIN or VaIN, or HPV 16- and 18-related vulvar or vaginal cancer compared with placebo; and (3) administration of a 3-dose regimen of quadrivalent HPV vaccine reduces the combined incidence of HPV 6/11-, 16-, and 18-related cervical dysplasia (any grade CIN) or HPV 16- and 18-related AIS or cervical cancer compared with placebo. The study will be considered a success if the safety hypothesis ([1] above) is successful and either of the efficacy hypotheses ([2] and [3] above) is successful.

Study Design

Protocol 013 is a randomized, double-blind (operating under in-house blinding procedures), placebo-controlled, multicenter efficacy study. Protocol 013 has 2 treatment groups: a quadrivalent HPV vaccine group (n=2700) and a placebo group (n=2700). Protocol 013 will be conducted by randomizing subjects into each treatment group in the context of 2 separate immunogenicity substudies: a concomitant administration with hepatitis B vaccine (Recombinant) substudy (Protocol 011) and a monovalent HPV 16 bridging substudy (Protocol 012). A total of 5700 subjects will be randomized in the 2 substudies. Overall, 5400 of these subjects will participate in Protocol 013, which is designed to assess the quadrivalent HPV vaccine's impact on HPV 6/11/16/18-related clinical disease. The remaining 300 subjects will participate in Protocol 012 only. In both substudies, vaccines will be administered at Day 1, Month 2, and Month 6. The 2 substudies are replicative with respect to all protocol procedures related to the evaluation of the efficacy of the quadrivalent HPV vaccine. Each of the 2 immunogenicity substudies will have its own Data Analysis Plan (DAP). This DAP

focuses on the evaluation of the efficacy of the quadrivalent HPV vaccine in the overall protocol (Protocol 013).

Critical design features for Protocol 013 include regular visits to the study sites for Pap screening and collection of cervicovaginal swab specimens at Day 1, Months 3, 7, 12, 18, 24, 30, 36, and 48 (a Pap test will not be performed at Month 3), mandatory guidelines for ascertainment of external genital warts/lesions and the evaluation of Pap abnormalities, and mandatory guidelines for the treatment of confirmed cervical and external genital wart/lesion pathology.

Genital wart/lesion biopsies are to be performed when suspect lesions are identified. Cervical biopsies and/or Endocervical Curettages (ECCs) are to be performed per protocol-mandated Pap test triage guidelines. A subject with an external genital lesion that is histologically-confirmed to be HPV-related (e.g., VIN, VaIN, and genital warts) by the SPONSOR central laboratory is to be referred to colposcopy. If biopsies are performed, slides of biopsy specimens will be prepared at a central laboratory selected by the SPONSOR and reviewed by a pathologist there for the purpose of patient management. The slides of biopsy tissue will subsequently be reviewed by an independent Pathology Panel, consisting of up to 5 independent pathologists, for the purpose of providing the official diagnosis for the primary analysis of vaccine efficacy. All biopsy specimens will also be sent to the SPONSOR or a designee for HPV analysis.

The data from Protocol 013 and its substudies (Protocols 011 and 012) will be analyzed and reported in 3 distinct stages.

1. Since Month 7 is the primary time point for the immunogenicity and safety analyses for each of the 2 substudies, these analyses will be conducted when all subjects in the substudies have completed the Month 7 visit.

2. The CIN/Wart Efficacy Study (Protocol 013) employs a fixed event design, whereby the primary analysis of efficacy will be conducted at the time that specific target numbers of cases of the primary endpoints are observed. Given the event rates assumed in the protocol, the target numbers of cases are expected to be reached around the time that all subjects have completed their Month 36 visits (i.e., 3 years of follow-up).

3. The efficacy data from Protocol 013 will be combined with data from 3 other Phase IIb/III studies to evaluate the efficacy of the vaccine with respect to: (1) CIN 2/3 and cervical cancer related to HPV 16 and 18 and (2) CIN 2/3 and cervical cancer related to all HPV types. The analysis of the combined studies with respect to these efficacy endpoints is also endpoint driven. To accrue an adequate number of cases for the combined efficacy evaluation, the subjects in Protocol 013 will probably need to be followed for ~4 years. The time period between the occurrence of the primary efficacy analysis of Protocol 013 and the final analysis of the combined studies will be considered an extension phase. With respect to the objectives of this protocol, at the end of the extension phase, the vaccine efficacy with respect to the primary and

secondary endpoints will be re-estimated in order to refine the precision of the estimates.

To keep the primary efficacy data for Protocol 013 blinded while preparing the study reports for the immunogenicity and safety data for Protocols 011 and 012, a restricted clinical, statistical, and data management team will be formed to analyze the data from the immunogenicity substudies. All other personnel involved with the HPV vaccine program at the SPONSOR will remain blinded to the individual treatment assignments of the subjects in the 2 substudies. Only these blinded personnel will participate in the review and cleaning of efficacy data. Once the required numbers of cases of the primary endpoints are observed for Protocol 013, the data will be unblinded in order to perform the primary efficacy analyses along with the secondary and exploratory analyses. The extension phase of the study will be conducted in an unblinded manner from the perspective of the clinical, data management, and statistical personnel at the SPONSOR (for details please refer to Section VI.C.). However, for the purpose of endpoint collection for the primary efficacy phase *and* the extension phase of the study, laboratory personnel, the endpoint pathology panel, the investigators, site personnel, and subjects will remain blinded to whether subjects received the quadrivalent HPV vaccine or the quadrivalent HPV vaccine-matched placebo throughout the entire study period (4 years). Thus, all individuals who are responsible for the ascertainment and confirmation of efficacy endpoints will be blinded for the duration of the entire study.

Endpoints: Safety, Efficacy, and Immunogenicity

Safety

All reported clinical adverse experiences on the day of each vaccination and for 14 days after each vaccination (Day 1 through Day 15) will be summarized by treatment group to address safety and tolerability. The safety summaries and analyses will appear in the Clinical Study Reports (CSRs) for the substudies (Protocols 011 and 012) and not in the CSR for Protocol 013. The important variables of interest for safety/tolerability in the substudies are the occurrence of severe injection-site reactions and the incidence of any vaccine-related serious adverse experiences.

Although not considered to be an adverse experience, the incidence and outcomes of pregnancies that occur during the vaccination period (Day 1 to Month 7) will be monitored and evaluated by treatment group. These events will be summarized in the Protocol 013 CSR.

Efficacy/Immunogenicity

The primary endpoints of interest for efficacy are:

A. The number of subjects with ≥1 of the following: external genital warts, Vulvar Intraepithelial Neoplasia (VIN) or Vaginal Intraepithelial Neoplasia (VaIN) related to HPV 6, 11, 16, or 18, and/or vulvar or vaginal cancer related to HPV 16 or 18. This

endpoint will occur if, on a single biopsy or excised tissue specimen, the following occur:

- Pathology panel consensus diagnosis of genital wart, VIN 1, VIN 2, VIN 3, VaIN 1, VaIN 2, VaIN 3, vulvar cancer, or vaginal cancer

  AND

- HPV 6, 11, 16, or 18 detected by Thinsection Polymerase Chain Reaction (PCR) in an adjacent section from the same tissue block

B. The number of subjects with ≥1 of the following: Cervical Intraepithelial Neoplasia (CIN) related to HPV 6, 11, 16, or 18, and/or Adenocarcinoma In Situ (AIS) or cervical cancer related to HPV 16 or 18. This endpoint will occur if on a single cervical biopsy, Endocervical Curettage (ECC), Loop Electrosurgical Excision Procedure (LEEP) or Conization (cold knife/laser) specimen, the following occur:

- Pathology panel consensus diagnosis of CIN 1, CIN 2, CIN 3, AIS, or cervical cancer

  AND

- HPV 6, 11, 16, or 18 detected by Thinsection PCR in an adjacent section from the same tissue block

The secondary endpoints of interest for efficacy are: (1) the combined incidence of HPV 16- and 18-related cervical dysplasia (any grade CIN), or HPV 16- and 18-related AIS, or cervical cancer; and (2) the combined incidence of external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer due to any cause.

Additional exploratory efficacy and immunogenicity endpoints will be summarized. These endpoints are described in the main body of the Data Analysis Plan in Section III.A.

Data Analysis and Decision Criterion for Success of the Study

This study employs a fixed event design, whereby the analyses of the primary efficacy hypotheses are scheduled to be conducted at the time that specific target numbers of cases of the primary endpoints have been observed. Although the study will continue for 4 years, the study conclusions regarding the vaccine efficacy with respect to the primary endpoints will be based on the analyses conducted when at least 62 cases of HPV 6/11/16/18-related external genital warts *and* at least 38 cases of HPV 6/11/16/18-related CIN are observed. This is expected to occur when all subjects have completed 3 years in the study. The purpose of the study extension is to obtain more precise estimates of the vaccine efficacy with respect to the CIN endpoints, particularly CIN 2/3 and cervical carcinoma.

The first primary efficacy null hypothesis states that the vaccine efficacy against HPV 6/11/16/18-related external genital warts/VIN/VaIN is 20% or less while the alternative hypothesis states that the vaccine efficacy against this endpoint is >20%. The second primary efficacy null hypothesis states that the vaccine efficacy against HPV 6/11/16/18-related CIN is 20% or less while the alternative hypothesis states that the vaccine efficacy against this endpoint is >20%. Each of the 2 primary hypotheses will be tested by constructing a two-sided exact 97.5% confidence interval for vaccine efficacy. A lower bound of the 97.5% confidence interval >20% will lead to rejection of the null hypothesis. Success in the study will be achieved if *either* of the primary hypothesis tests is successful. Therefore, each primary efficacy hypothesis will be tested at the 0.025 level (two-sided) to control the overall type I error rate at the 0.05 level (two-sided).

I. INTRODUCTION

A. Objective of the Data Analysis Plan

This Data Analysis Plan (DAP) is intended to be a comprehensive and detailed description of the strategy, rationale, and statistical techniques that will be used to address the efficacy of the Quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine versus placebo against the following 2 endpoints: (1) HPV 6/11/16/18-related external genital warts, VIN, and VaIN and HPV 16/18-related vulvar and vaginal cancer; and (2) HPV 6/11/16/18-related CIN and HPV 16/18-related AIS and cervical cancer in 16- to 23-year-old women. Protocol 013 and Amendments 013-01 and 013-02 are covered by this DAP. The protocol is entitled, "A Study to Evaluate the Efficacy of Quadrivalent HPV (Types 6, 11, 16, and 18) L1 Virus-Like Particle (VLP) Vaccine in Reducing the Incidence of HPV 6/11-, 16-, and 18-Related CIN, and HPV 16- and 18-Related AIS and Cervical Cancer, and HPV 6/11-, 16-, and 18-Related External Genital Warts, VIN and VaIN, and HPV 16- and 18-Related Vulvar and Vaginal Cancer in 16- to 23-Year-Old Women–The F.U.T.U.R.E. I Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease)." There are 2 immunogenicity substudies within Protocol 013, Protocols 011 and 012. Each of the 2 substudies will be covered by its own DAP.

B. Description of the Study and Objectives/Hypotheses

1. Study Design

Protocol 013 is a randomized, double-blind (operating under in-house blinding procedures), placebo-controlled, multicenter efficacy study. Protocol 013 has 2 treatment groups: a quadrivalent HPV vaccine group (n=2700) and a placebo group (n=2700). Protocol 013 will be conducted by randomizing subjects into each treatment group in the context of 2 separate immunogenicity substudies: a concomitant administration substudy, which includes the administration of hepatitis B vaccine (Recombinant) (Protocol 011) and a monovalent HPV 16 bridging substudy (Protocol 012). A total of 5700 subjects will be randomized in the 2 substudies: Protocols 011 and 012. Overall, 5400 of these subjects will participate in Protocol 013, which is designed to assess the quadrivalent HPV vaccine's impact on HPV 6/11/16/18-related clinical disease. The remaining 300 subjects will participate in Protocol 012 only. These 2 substudies are replicative with respect to all protocol procedures related to the evaluation of the efficacy of the quadrivalent HPV vaccine.

B. Description of the Study and Objectives/Hypotheses (Cont.)

In Protocol 011, 1800 subjects will be randomized in a 1:1:1:1 ratio to receive quadrivalent HPV vaccine + hepatitis B vaccine (Recombinant), quadrivalent HPV vaccine + hepatitis B vaccine (Recombinant)-matched alum-placebo, quadrivalent HPV vaccine-matched alum-placebo + hepatitis B vaccine (Recombinant), or quadrivalent HPV vaccine-matched alum-placebo + hepatitis B vaccine (Recombinant)-matched alum-placebo. The number of subjects in each treatment group in the concomitant administration substudy is shown in Table 1.

Table 1

Protocol 011 (Concomitant Hepatitis B Vaccine Administration Substudy)
Treatment Regimens

Group	Treatment Regimen		N
	Quadrivalent HPV Vaccine	Hepatitis B Vaccine (Recombinant)	
A	Active	Placebo	450
B	Active	Active	450
C	Placebo	Active	450
D	Placebo	Placebo	450
Total			1800

This randomization maintains a 1:1 ratio of subjects in the quadrivalent HPV vaccine and placebo groups at the study centers participating in the concomitant administration substudy for the CIN/Wart Efficacy Study (Protocol 013).

In Protocol 012, 3900 subjects will be randomized in a 6:1:6 ratio to receive Final Manufacturing Process (FMP) quadrivalent HPV vaccine, Pilot Manufacturing Material (PMM) HPV 16 vaccine, or alum-placebo. The number of subjects in each treatment group in the monovalent HPV 16 bridging substudy is shown in Table 2.

B. Description of the Study and Objectives/Hypotheses (Cont.)

Table 2

Protocol 012 (Monovalent HPV 16 Bridging Substudy) Treatment Regimens

Group	Treatment Regimen	Studies in Which Group Will Participate	N
A	FMP Quadrivalent HPV Vaccine 0, 2, 6 months	Monovalent HPV 16 Bridging Substudy, CIN/Warts Efficacy Study	1800
B	PMM Monovalent HPV 16 Vaccine 0, 2, 6 months	Monovalent HPV 16 Bridging Substudy	300
C	Placebo 0, 2, 6 months	CIN/Warts Efficacy Study	1800
Total			3900

This randomization maintains a 1:1 ratio of subjects in the quadrivalent HPV vaccine and placebo groups at the study centers participating in the monovalent HPV 16 bridging substudy for the CIN/Wart Efficacy Study (Protocol 013). The 300 subjects randomized to receive PMM HPV 16 vaccine will participate in the monovalent HPV 16 bridging substudy only and will not participate in the CIN/Wart efficacy study.

Vaccine(s) will be administered at Day 1, Month 2, and Month 6 in both substudies. The participants in the 2 substudies will combine to comprise the quadrivalent HPV vaccine group and placebo group for the CIN/Wart efficacy study (Protocol 013) as described in Table 3.

Table 3

Protocol 013 (CIN/Wart Efficacy Study) Treatment Regimens

Efficacy Study Treatment Group	Treatment Regimens From Substudies Combining to Create Treatment Group	N
Quadrivalent HPV Vaccine	FMP Quadrivalent HPV (1800 subjects) FMP Quadrivalent HPV + Placebo (450 subjects) FMP Quadrivalent HPV + Hepatitis B Vaccine (Recombinant) (450 subjects)	2700
Placebo	Placebo (1800 subjects) Placebo + Hepatitis B Vaccine (Recombinant) (450 subjects) Placebo + Placebo (450 subjects)	2700
Total		5400

B. Description of the Study and Objectives/Hypotheses (Cont.)

Critical design features for Protocol 013 include regular visits to the study sites for Pap screening and collection of cervicovaginal swab specimens, mandatory guidelines for ascertainment of external genital warts/lesions and the evaluation of Pap abnormalities, and mandatory guidelines for the treatment of confirmed cervical and external genital wart/lesion pathology. The study flow chart is in Table 4.

B. Description of the Study and Objectives/Hypotheses (Cont.)

Table 4

Study Flow Chart

Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Event/Test Month:	Pre-Study	Day 1	Month 2	Month 3	Month 6	Month 7	Month 12	Month 18	Month 19	Month 24	Month 30	Month 36	Month 48
Obtain informed consent	+												
Gynecologic/medical history	+	+				+	+	+	+	+	+	+	+
Gynecological/ physical examination		+				+	+			+		+	+
Specimen collection/laboratory measurements (in serial order):													
Pregnancy test[†]		+	+		+			+	+	+			
Urine for gonorrhea PCR or LCR or SDA		+				+	+			+		+	+
Urine for chlamydia PCR or LCR or SDA		+				+	+			+		+	+
Serum for antibody measurements[‡]													
HPV RIA (Types 6, 11, 16, 18)		+				+	+			+		+	+
Neutralization (HPV Types 6, 11,16, 18)		+				+							
Retention serum, stored frozen at site		+				+	+			+		+	+
Serum for HEP B Markers (Protocol 011 only)													
Anti-HBs (Quantitative)[††]		+				+							
Anti-HBs (Qualitative)[‡‡]	+												
Anti-HBc (Qualitative)[‡‡]	+												
(b)(4) swabs		+		+		+	(+)	(+)		(+)	(+)	(+)	(+)
Swab for HSV culture (optional)[§§]		+				+	+	+		+	+	+	+
pH of vaginal fluid (optional)[§§]		+				+	+	+		+	+	+	+
Wet mount/trichomonas and BV (optional)		+				+	+	+		+	+	+	+
Whiff test for BV (optional)[§§]		+				+	+	+		+	+	+	+
KOH for yeast (optional)[§§]		+				+	+	+		+	+	+	+
(b)(4) swab		+		+		+	(+)	(+)		(+)	(+)	(+)	(+)
Pap test (ThinPrep™) for cytology[#]		+				+	+	+		+	+	+	+
Genital Wart Inspection		+		+		+	+	+		+	+	+	+
Vaccination[3,‖]		+	+		+			+	+	+			
Clinical follow-up for safety Vaccination[¶]		+	+	+	+	+							
Clinical follow-up for safety for SAEs only (Protocol 011 only)								+	+	+			

B. Description of the Study and Objectives/Hypotheses (Cont.)

Table 4 (Cont.)

Study Flow Chart

Note: Any test may be repeated if medically indicated.

(+) Specimen must be obtained for optional test to be done by the SPONSOR. In the event that the SPONSOR performs this assay, all samples will be analyzed.

The Month 2 visit can be performed within ±3 weeks. The Month 6 visit and all scheduled visits from Months 12 through 48 can be performed within ±4 weeks. The interval between the Month 2 and Month 3 visits and the Month 6 and Month 7 visits should be a minimum of 3 weeks and a maximum of 7 weeks from the previous vaccination. Any visit for pelvic specimen collection should be performed at least 2 days after menses is completed. An attempt should be made not to collect pelvic specimens within 2 days prior to menses, if possible. If, despite the above, visible blood is noted in the vagina, the specimen may be collected. The presence of visible blood in the vagina should be noted on the Specimen Collection Case Report Form.

† By a serum or urine test performed day of vaccination. The urine pregnancy test must be sensitive to 25 IU HCG and be negative for vaccination.

‡ Serum for antibody measurements may be collected after the pelvic exam, but before vaccination. Assay testing to be performed at Merck Research Laboratories.

§ Temperature and weight will be measured prior to each injection.

‖ Vaccinations for Months 18, 19, and 24 are for the hepatitis B vaccine placebo recipients to receive optional hepatitis B vaccine (RECOMBIVAX™) (Protocol 011 only).

¶ Each participant will record on a Vaccination Report Card (VRC) her oral temperature 4 hours after each injection and 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, 3, and 7, the study personnel together with the participant will review the VRC. At Months 2, 3, 6, and 7, subjects will be solicited for any gynecologic health concerns and any serious AEs that they may have encountered.

Pap test to be performed by central laboratory selected by SPONSOR.

†† Test to be performed by Merck Research Laboratory.

‡‡ Test to be performed by a local laboratory and if negative, meets inclusionary criteria.

§§ May be performed if indicated at the investigator's discretion.

B. Description of the Study and Objectives/Hypotheses (Cont.)

Genital wart/lesion biopsies are to be performed when suspect lesions are identified. Cervical biopsies and/or Endocervical Curettages (ECCs) are to be performed per protocol-mandated Pap test triage guidelines. A subject with an external genital lesion that is histologically-confirmed to be HPV-related (e.g., VIN, VaIN and genital warts) by the SPONSOR central laboratory is to be referred to colposcopy.

If biopsies are performed, slides of biopsy specimens will be prepared at a central laboratory selected by the SPONSOR and reviewed by a pathologist for the purpose of patient management. Uniform fixation, processing, and sectioning methods will be used and will be under the control of the single central laboratory for standardization of the reading of cytology and histopathology.

The slides of biopsy tissue will subsequently be reviewed by an independent Pathology Panel, consisting of up to 5 independent pathologists, for the purpose of providing the official diagnosis for the primary analysis of vaccine efficacy. All biopsy specimens will also be sent to the SPONSOR or a designee for HPV analysis. For each biopsy specimen, the pathology panel will be blinded to the treatment group assignment of the subject from whom the biopsy was collected as well as to the results of the HPV analysis of the biopsy and of swabs obtained from that subject during the routine visits.

In this study, HPV analysis includes: (1) type-specific PCR assays to identify subjects who are infected with HPV types at enrollment and, potentially, to detect the onset of new HPV infection during the study follow-up period; (2) serologic assays to measure HPV type-specific and VLP-specific antibody responses following vaccination or after natural infection with vaccine HPV types; and (3) HPV type-specific localizing assays to determine the causal HPV type within a clinical lesion (such as a genital wart or a CIN lesion) for efficacy assessments.

2. Study Reporting

The data from Protocol 013 and its substudies (Protocols 011 and 012) will be analyzed and reported in 3 distinct stages.

a. Since Month 7 is the primary time point for the immunogenicity and safety analyses for each of the 2 substudies, these analyses will be conducted when all subjects in the substudies have completed the Month 7 visit.

B. Description of the Study and Objectives/Hypotheses (Cont.)

b. The CIN/Wart Efficacy Study (Protocol 013) employs a fixed event design, whereby the primary analysis of efficacy will be conducted at the time that specific target numbers of cases of the primary endpoints are observed. Given the event rates assumed in the protocol, the target numbers of cases are expected to be reached around the time that all subjects have completed their Month 36 visits (i.e., 3 years of follow-up).

c. The efficacy data collected from Protocol 013 will be combined in a prespecified analysis with efficacy data from Protocols 005, 007, and 015 to evaluate the vaccine efficacy with respect to: (1) vaccine-type HPV-related CIN 2/3 and cervical carcinoma and (2) CIN 2/3 and cervical cancer related to all HPV types. The final analysis of the combined studies with respect to these efficacy endpoints is also endpoint driven. To accrue an adequate number of cases for the combined efficacy evaluation, the subjects in Protocol 013 will need to be followed for ~4 years. The time period between the occurrence of the primary efficacy analysis of Protocol 013 and the final analysis of the combined studies for each subject in Protocol 013 will be considered an extension phase. With respect to the objectives of this protocol, at the end of the extension phase, the vaccine efficacy with respect to the primary and secondary endpoints will be re-estimated in order to refine the precision of the estimates. The plan for the combined analysis will appear in a separate DAP and the results will appear in a separate report.

The details of maintaining the study blinding are discussed in Section VI.C.

3. Primary Objectives

a. Safety

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

b. Efficacy

1) To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the incidence of the composite endpoint of HPV 6/11/16/18-related external genital warts, VIN or VaIN, or HPV 16- and 18-related vulvar or vaginal cancer compared with placebo.

B. Description of the Study and Objectives/Hypotheses (Cont.)

2) To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the incidence of the composite endpoint of HPV 6/11-, 16-, and 18-related cervical dysplasia (any grade CIN) or HPV 16- and 18-related Adenocarcinoma In Situ (AIS) or cervical cancer, compared with placebo.

4. Secondary Objectives

a. To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the incidence of the composite endpoint of HPV 16- and HPV 18-related cervical dysplasia (any grade CIN) or HPV 16- and 18-related Adenocarcinoma In Situ (AIS) or cervical cancer, compared with placebo.

b. To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the incidence of the composite endpoint of external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer compared with placebo.

5. Exploratory Objectives

a. To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the incidence of cervical dysplasia (any grade CIN), compared with placebo.

b. To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the incidence of definitive therapy (e.g., LEEP and cold-knife conization, or definitive wart therapy), compared with placebo.

c. To evaluate the relationship between the antibody response to the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine and the disease endpoints.

d. To evaluate persistence of the antibody response to the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine.

e. To evaluate the efficacy of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine with respect to disease endpoints that occur following the second dose of the vaccine.

B. Description of the Study and Objectives/Hypotheses (Cont.)

f. To demonstrate that intramuscular administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the incidence of clinically-diagnosed external genital HPV-related lesions (e.g., genital warts), compared with placebo.

6. Primary Hypotheses

a. Safety

The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in 16- to 23-year-old females. *(No vaccine-related serious adverse events (SAEs) are expected. If no vaccine-related SAE is observed among the 2700 subjects administered the quadrivalent vaccine, there is a 97.5% probability that the true rate is <0.13%.)*

b. Efficacy

1) Administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the combined incidence of HPV 6/11/16/18-related external genital warts, VIN or VaIN, or HPV 16- and 18-related vulvar or vaginal cancer compared with placebo. *(It is anticipated that the quadrivalent HPV vaccine will reduce the combined incidence of HPV 6/11/16/18-related external genital warts, VIN or VaIN, or HPV 16/18-related vulvar or vaginal cancer by 80% compared with placebo. The statistical criterion for success requires that the lower bound of the confidence interval for the vaccine efficacy exclude 20% or less.)*

OR

2) Administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the combined incidence of HPV 6/11-, 16- and 18-related cervical dysplasia (any grade CIN) or HPV 16- and 18-related AIS or cervical cancer compared with placebo. *(It is anticipated that the quadrivalent HPV vaccine will reduce the combined incidence of HPV 6/11/16/18-related CIN or HPV 16/18-related AIS or cervical cancer by 80% compared with placebo. The statistical criterion for success requires that the lower bound of the confidence interval for the vaccine efficacy exclude 20% or less.)*

B. Description of the Study and Objectives/Hypotheses (Cont.)

7. Secondary Hypotheses

a. Administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the combined incidence of HPV 16- and 18-related cervical dysplasia (any grade CIN) or HPV 16- and 18-related AIS or cervical cancer compared with placebo. *(It is anticipated that the quadrivalent HPV vaccine will reduce the combined incidence of HPV 16/18-related CIN or HPV 16/18-related AIS or cervical cancer by 80% compared with placebo. The statistical criterion for success requires that the lower bound of the confidence interval for the vaccine efficacy exclude 0%.)*

b. Administration of a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine reduces the combined incidence of external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer compared with placebo. *(It is anticipated that the quadrivalent HPV vaccine will reduce the combined incidence of external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer by 70% compared with placebo. The statistical criterion for success requires that the lower bound of the confidence interval for the vaccine efficacy exclude 0%.)*

II. STUDY PARTICIPANTS CHARACTERISTICS

Subject characteristics of age, gender, race/ethnicity, number of lifetime sexual partners (male and female), tobacco use, pregnancy history, age at first sexual intercourse, lifetime gynecologic medical history, history of sexually transmitted diseases, and contraceptive use will be summarized by treatment group and overall for all subjects who entered the study. In addition, serostatus for HPV 6, 11, 16, and 18 at Day 1 and PCR status for HPV 6, 11, 16, and 18 at Day 1, Month 3, and Month 7 will be presented by treatment group and overall. Finally, since the study is being conducted in 4 distinct geographical regions, the above subject characteristics and the serostatus and PCR status for the 4 HPV types will also be summarized by geographical region (United States, Latin America, Europe and Asia-Pacific). Balance between treatment groups and geographical regions with respect to subject characteristics will be determined by observation. Subject characteristics will also be summarized in the per-protocol population, which is described later in Section III.B.

The number and percentage of subjects with specific medications prior to the first vaccination and specific concomitant medications will be summarized by treatment group in the CSRs for the 2 substudies, Protocols 011 and 012.

III. IMMUNOGENICITY ANALYSES

A. Efficacy/Immunogenicity Endpoints

The primary endpoints of interest for efficacy are:

1. The number of subjects with ≥1 of the following: external genital warts, Vulvar Intraepithelial Neoplasia (VIN) or Vaginal Intraepithelial Neoplasia (VaIN) related to HPV 6, 11, 16, or 18, or vulvar or vaginal cancer related to HPV 16 or 18. This endpoint will occur if on a single biopsy or excised tissue specimen, the following occur:

   - Pathology panel consensus diagnosis of genital wart, VIN 1, VIN 2, VIN 3, VaIN 1, VaIN 2, VaIN 3, vulvar cancer, or vaginal cancer

     AND

   - HPV 6, 11, 16, or 18 detected by Thinsection PCR in an adjacent section from the same tissue block

2. The number of subjects with ≥1 of the following: Cervical Intraepithelial Neoplasia (CIN) related to HPV 6, 11, 16, or 18, or Adenocarcinoma In Situ (AIS) or cervical cancer related to HPV 16 or 18. This endpoint will occur if on a single cervical biopsy, ECC, LEEP, or Conization (cold knife/laser) specimen, the following occur:

   - Pathology panel consensus diagnosis of CIN 1, CIN 2, CIN 3, AIS or cervical cancer

     AND

   - HPV 6, 11, 16, or 18 detected by Thinsection PCR in an adjacent section from the same tissue block

The secondary endpoints of interest for efficacy are: (1) the combined incidence of HPV 16- and 18-related cervical dysplasia (any grade CIN) or HPV 16- and 18-related AIS or cervical cancer; and (2) the combined incidence of external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer due to any cause.

The key exploratory endpoints of interest for efficacy are: (1) the incidence of cervical dysplasia (any grade CIN) due to any cause, (2) the incidence of definitive therapy (e.g., LEEP and definitive wart therapy), and (3) the incidence of clinically-diagnosed external genital HPV-related lesions (e.g., genital warts). The incidence of specific grades of CIN and the incidence of CIN related to subgroups of the vaccine HPV types are also of

A. Efficacy/Immunogenicity Endpoints (Cont.)

interest, as well as the incidence of other gynecologic procedures. The vaccine efficacy in preventing Pap abnormalities will be summarized and, data permitting, the vaccine efficacy in preventing infection with vaccine HPV types will be explored. In addition, the vaccine efficacy with respect to the primary endpoints of the study will be summarized by vaccine HPV type, lesion type, and anatomic location.

Some exploratory immunogenicity endpoints will also be analyzed, including the antibody responses in vaccine recipients who have breakthrough cases of HPV 6/11/16/18-related external genital warts, VIN, or VaIN or HPV 6-, 11-, 16-, or 18-related CIN or worse and the persistence of antibody over time.

Data permitting, the potential therapeutic effects of administering the quadrivalent vaccine to subjects who are already infected at baseline with a vaccine HPV type, but who have not yet mounted an immune response to the HPV infection on their own, will be assessed. Specifically, exploratory analyses will be performed to assess the vaccine's impact in reducing the duration of infection, in increasing the incidence of clearance of infection and in reducing the incidence of CIN or worse in subjects who are seronegative and PCR positive at Day 1.

B. Study Participant Populations

Five (5) patient populations will be considered for the efficacy analysis: 1 per-protocol population and 4 modified intention-to-treat (MITT) populations. The efficacy analysis using the per-protocol population will be the primary analysis. Supplemental analyses of the primary and secondary efficacy endpoints will be provided using the 4 MITT populations. The populations that will be considered for the exploratory efficacy endpoints are described in their respective sections. The per-protocol and MITT populations differ with regard to the inclusion/exclusion of protocol violators who are described below.

Per-Protocol Population

To be included in the per-protocol analyses, subjects must:

1) receive all 3 injections with the correct dose of the correct clinical material,

2) be seronegative by RIA to the appropriate HPV types before the first injection and PCR-negative to the appropriate HPV types through Month 7,

B. Study Participant Populations (Cont.)

3) not receive any nonstudy inactivated vaccine 14 days before or after a study vaccine or any nonstudy live virus vaccine 21 days before or 14 days after a study vaccine,

4) not receive immune globulin (including RhoGAM™) or blood-derived products at any time through Month 7 of the study,

5) not receive immunosuppressives or have an immune disorder considered by the Clinical Monitor to potentially interfere with the subject's response to the vaccine,

6) not concurrently participate in any other clinical studies of investigational agents or clinical studies involving collection of cervical specimens, which, in the opinion of the Clinical Monitor, may potentially interfere with the subject's response to the vaccine,

7) have a Month 7 visit within a day range considered acceptable for defining the subject's Month 7 PCR status.

To be included in the primary efficacy analysis for the HPV 6- and HPV 11-related endpoints, subjects must be seronegative by RIA to HPV 6 and 11 at Day 1 and PCR-negative to HPV 6 and 11 from Day 1 through Month 7 (on swabs and biopsies). To be included in the primary and secondary efficacy analyses for the HPV 16- and HPV 18-related endpoints, subjects are only required to be seronegative by RIA at Day 1 and PCR-negative from Day 1 through Month 7 (on swabs and biopsies) for the component being analyzed.

For the secondary efficacy analysis regarding external genital warts, VIN, VaIN, vulvar cancer, and vaginal cancer due to any cause and the exploratory efficacy analysis regarding any grade CIN due to any cause, again only subjects who are HPV 6 and 11 seronegative by RIA at Day 1 and HPV 6 and 11 PCR-negative from Day 1 through Month 7 (on swabs and biopsies) will be eligible to be counted as cases of HPV 6- or 11-related disease. Only subjects who are HPV 16 seronegative by RIA at Day 1 and HPV 16 PCR-negative from Day 1 through Month 7 (on swabs and biopsies) will be eligible to be counted as cases of HPV 16-related disease. Similarly, only subjects who are HPV 18 seronegative by RIA at Day 1 and HPV 18 PCR-negative from Day 1 through Month 7 (on swabs and biopsies) will be eligible to be counted as cases of HPV 18-related disease. For each of HPV types 31, 33, 35, 45, 51, 52, 55, 56, 58, 59, and 68, only subjects who are PCR-negative from Day 1 through Month 7 for the given HPV type (on swabs and biopsies) will be eligible to be counted as cases of disease related to that type. No

B. Study Participant Populations (Cont.)

baseline serology testing will be performed for these 11 high-risk HPV types. Therefore, all subjects who are PCR-negative from Day 1 through Month 7 for one of the types, even though they may be baseline seropositive for that type, will be eligible to be counted as cases of disease related to that type. (This approach is conservative, since subjects who have baseline positive serology for a given HPV type have already mounted an immune response to that type.) With respect to disease endpoints related to HPV types that are not among the 15 listed above, subjects who meet criteria (1) and (3) through (7) above and have normal Pap results from Day 1 through Month 7 will be eligible to meet the case criteria. A sensitivity analysis will be performed in which all subjects who meet criteria (1) and (3) through (7) above (regardless of Pap test results from Day 1 through Month 7) will be eligible to meet the case criteria.

For immunogenicity, the per-protocol population will be further restricted. Subjects who violate the vaccination regimen by failing to receive vaccinations within acceptable day ranges and subjects who have postvaccination blood samplings outside of acceptable day ranges will be excluded from the immunogenicity analyses.

If infection endpoints are analyzed, the per-protocol population for this analysis will be the same as for the efficacy endpoints with one additional exclusion. Subjects who have engaged in sexual intercourse within 48 hours prior to Day 1, Month 3, or Month 7 will be excluded from the analysis. Also, if a subject has engaged in sexual intercourse within 48 hours prior to any visit after Month 7, that visit will be considered missing. The sexual intercourse restriction is imposed for the infection analyses because deposition of HPV by a sexual partner could result in a positive finding on the PCR assay that does not represent the subject's infection.

Modified Intention-to-Treat Populations

The first MITT analysis will include all subjects who are seronegative at Day 1 and PCR negative from Day 1 through Month 7 (on swabs and biopsies) to the appropriate vaccine HPV type(s), who receive all 3 vaccinations, and who have any follow-up visit following Month 7. The primary difference between this population and the per-protocol population is the inclusion of general protocol violators.

B. Study Participant Populations (Cont.)

The second MITT analysis will include all subjects who are seronegative at Day 1 and PCR negative from Day 1 through Month 3 (on swabs and biopsies) to the appropriate vaccine HPV type(s), who receive at least the first 2 vaccinations, and who have any follow-up visit following Month 3. Cases will be counted starting after Month 3 instead of starting after Month 7 for this analysis. This population will be used for evaluating the vaccine efficacy starting after the second dose of the vaccine (an exploratory objective of the study). It is important to acknowledge that most subjects who receive 2 doses will go on to receive their third vaccination, so it will be difficult to assess the vaccine efficacy Postdose 2. It will be mostly confounded with the vaccine efficacy Postdose 3. On the other hand, if many subjects develop disease endpoints between their second and third vaccinations, then it may be possible to assess the efficacy of the vaccine in that interval.

The third MITT analysis will include all subjects who are seronegative and PCR negative (on swabs and biopsies) to the appropriate vaccine HPV type(s) at Day 1, who receive at least 1 vaccination, and who have any follow-up visit after 1 month following the first injection. Cases will be counted starting after Day 1 for this analysis.

The fourth MITT analysis will include all subjects who receive at least 1 vaccination and who have any follow-up visit after 1 month following the first injection, regardless of initial serology and PCR status. Cases will be counted starting after Day 1 for this analysis.

The MITT populations include incorrectly randomized subjects and subjects who received the incorrect clinical material in the analysis according to the treatment group to which they were randomized by the study allocation schedule.

C. Approaches to Efficacy and Immunogenicity Analysis

At the time when at least 62 cases of HPV 6/11-, 16-, and 18-related external genital warts *and* at least 38 cases of HPV 6/11-, 16-, and 18-related CIN have been observed, the study will be unblinded and the primary efficacy analysis will be conducted, along with all of the secondary and exploratory analyses. The unblinding is expected to occur around the time that all subjects have completed their Month 36 visits. The study conclusions regarding the vaccine efficacy and all other endpoints will be made based on these analyses.

C. Approaches to Efficacy and Immunogenicity Analysis (Cont.)

In determining when the primary analysis will be performed, only cases of external genital warts will be counted for the external genital warts/VIN/VaIN endpoint to ensure that genital warts have adequate representation in the analysis of this endpoint. The VIN and VaIN cases will be included in the actual analysis of the endpoint. In addition, only CIN cases that were a consequence of a colposcopy due to a Pap test abnormality at a scheduled visit will be counted in determining when the primary analysis will be performed. CIN cases that were a consequence of a colposcopy due to a diagnosis of an external genital lesion but with no Pap test abnormality will not be counted. These CIN cases will also not be included in the per-protocol primary, secondary, and exploratory efficacy analyses because they may lead to an ascertainment bias, which is explained in detail in Section VI.D.5. They will be included in a sensitivity analysis.

1. Primary Hypotheses

The first primary efficacy null hypothesis states that the vaccine efficacy against HPV 6/11/16/18-related external genital warts/VIN/VaIN or HPV 16/18-related vulvar or vaginal cancer is 20% or less. The alternative hypothesis states that the vaccine efficacy against this endpoint is >20%. The second primary efficacy null hypothesis states that the vaccine efficacy against HPV 6/11/16/18-related CIN or HPV 16/18-related cervical cancer is 20% or less. The alternative hypothesis states that the vaccine efficacy against this endpoint is >20%. A point estimate of the vaccine efficacy will be provided for each endpoint. Each of the 2 primary hypotheses will be tested by constructing a two-sided exact 97.5% confidence interval for vaccine efficacy. A lower bound of the 97.5% confidence interval >20% will lead to rejection of the null hypothesis. Success in the study will be achieved if either of the primary hypothesis tests is successful. Therefore, each primary efficacy hypothesis will be tested at the 0.025 level (two-sided) to control the overall type I error rate at the 0.05 level (two-sided). The primary analyses will be exact and will not adjust for extraneous factors such as age and number of lifetime sexual partners.

The estimate of the vaccine efficacy will account for the follow-up (i.e., person-time at risk) in the vaccine and placebo groups. Since the endpoints for the primary analyses are composite endpoints, any subject who is eligible to have met an endpoint criterion according to the HPV 6/11-related disease definition, the HPV 16-related disease definition, or the HPV 18-related disease definition will be included in the population at risk for the primary analyses. Almost all subjects will be included in the population at risk for the secondary and exploratory analyses, since almost

C. **Approaches to Efficacy and Immunogenicity Analysis (Cont.)**

all subjects should be eligible to have met an endpoint criterion with respect to at least 1 of the 15 HPV types for which subjects are being tested. The method that will be used to compute the follow-up time for each subject in the population at risk is described in Section VI.D.4.

2. Secondary Hypotheses

The first secondary efficacy null hypothesis states that the vaccine efficacy against HPV 16/18-related CIN, AIS, and cervical cancer is 0%. The alternative hypothesis states that the vaccine efficacy against this endpoint is >0%. The second secondary efficacy null hypothesis states that the vaccine efficacy against external genital warts, VIN, VaIN, vulvar cancer, and vaginal cancer is 0%. The alternative hypothesis states that the vaccine efficacy against this endpoint is >0%. A point estimate of the vaccine efficacy and a two-sided exact 95% confidence interval for vaccine efficacy will be provided for each endpoint. If the lower bound of the 95% confidence interval is >0%, the corresponding null hypothesis will be rejected.

3. Exploratory Analyses

For the analysis of some of the exploratory efficacy endpoints, efficacy estimates and 95% confidence intervals will be provided for descriptive purposes only. Therefore, no multiplicity adjustment will be made. Study conclusions will be solely based on the primary and secondary hypothesis tests. If the total number of cases observed for any of the endpoints is <15, only the efficacy estimate will be provided and the confidence interval will not be provided. Incidence rates will be provided for the remainder of the exploratory efficacy endpoints. These incidence rates will account for the follow-up (i.e., person-time at risk) in the vaccine and placebo groups.

a. Supplementary Summaries of the Primary Endpoints

The vaccine efficacy with respect to the primary endpoints will be summarized by HPV type (i.e., all HPV 6-related endpoints, all HPV 11-related endpoints). For each vaccine HPV type, a point estimate of the vaccine efficacy will be provided along with a 95% confidence interval using the methodology described above for the primary analyses. In addition, the primary endpoints will be summarized by lesion type (i.e., all vaccine-related low-grade lesions and all vaccine-related high-grade lesions), and by anatomic location (i.e., all vaccine-related external genital warts, all vaccine-related vulvar lesions, all

C. Approaches to Efficacy and Immunogenicity Analysis (Cont.)

vaccine-related vaginal lesions and all vaccine-related cervical lesions). The summary by lesion type will also be provided using the central laboratory diagnosis as opposed to the pathology panel diagnosis. Efficacy estimates may be provided for these summaries. The above analyses and summaries will be provided for the per-protocol and the first MITT populations. They may be provided for the second, third, and fourth MITT populations if there are substantial differences among the populations.

b. CIN Endpoints

The vaccine efficacy with respect to the incidence of all CIN (any grade due to any cause) will be estimated. The vaccine efficacy will also be estimated with respect to the incidence of the following endpoints: (1) HPV 16- or 18-related CIN 2/3; (2) CIN 2/3 due to any cause; (3) HPV 6/11-, 16- or 18-related CIN 1; and (4) CIN 1 due to any cause. Point estimates and confidence intervals for the vaccine efficacy will be provided using the methodology described above for the primary analyses. The HPV 16- and 18-related CIN 2/3 endpoint and the HPV 6/11/16/18-related CIN 1 endpoint will be summarized in the per-protocol and all 4 MITT populations. To be included in all of the CIN summaries due to any cause (CIN due to any cause, CIN 2/3 due to any cause, and CIN 1 due to any cause), subjects will be required to be seronegative and PCR negative at Day 1 for relevant HPV types or have normal Pap test results at Day 1 (see Section III.B.).

c. Genital Warts

In order to evaluate the impact of the vaccine on clinically diagnosed external genital HPV-related lesions (regardless of whether they were histologically confirmed as being HPV-related or not), the vaccine efficacy with respect to the incidence of all clinically diagnosed external genital HPV-related lesions (e.g., genital warts) will be estimated. A point estimate and confidence interval for the vaccine efficacy will be provided using the methodology described above for the primary analyses. To be included in this evaluation, subjects will be required to be seronegative and PCR negative at Day 1 for all the HPV types for which subjects are tested.

C. **Approaches to Efficacy and Immunogenicity Analysis (Cont.)**

d. **Gynecologic Procedures**

To assess the vaccine's potential impact on definitive therapy, the vaccine efficacy will be summarized with respect to the incidence of definitive therapy for cervical lesions, warts, and external genital lesions. Incidence rates will be provided by treatment group for the following subcategories of the above endpoint: (1) definitive therapy for warts and external genital lesions, and (2) definitive therapy for cervical lesions. In order to evaluate the impact of the vaccine on other procedures, e.g., colposcopies and biopsies, the incidence rates will be provided by treatment group for the following: (1) wart and external genital lesion biopsy, and (2) colposcopy and cervical biopsy. In order to evaluate the impact of the vaccine on procedures for external genital lesions and warts, and cervical procedures, the incidence rates will be provided by treatment group for the following: (1) wart and external genital lesion biopsy and definitive therapy for warts and external genital lesions; and (2) colposcopy, cervical biopsy, and definitive therapy for cervical lesions. Finally, the impact of the vaccine on all gynecologic procedures will be evaluated by summarizing, by treatment group, the combined incidence of colposcopy, cervical biopsy, definitive therapy for cervical lesions, wart and external genital lesion biopsy, definitive therapy for warts and external genital lesions, and wart medical therapy. To be included in these summaries, subjects will be required to be seronegative and PCR negative at Day 1 to all the HPV types for which subjects are tested and have normal Pap test results at Day 1.

e. **Pap Abnormalities**

The incidences of the following Pap abnormalities will be summarized by treatment group: (1) HSIL or worse, (2) LSIL or worse, (3) ASC-US with positive HPV probe or worse (ASC-H, HSIL, LSIL, Atypical Glandular Cells), and (4) ASC-US or worse. To be included in these summaries, subjects will be required to be seronegative and PCR negative from Day 1 through Month 7 to all HPV types for which subjects are tested and have normal Pap test results from Day 1 through Month 7. The incidences of the above Pap abnormalities will also be summarized in subjects who are seronegative and PCR negative at Day 1 to all HPV types for which subjects are tested and have normal Pap test results at Day 1.

C. **Approaches to Efficacy and Immunogenicity Analysis (Cont.)**

f. **HPV Infection**

If type-specific HPV PCR assays for the vaccine HPV types are performed on the (b)(4) and (b)(4) swab and the (b)(4) swab collected at Months 12, 18, 24, 30, 36, and 48, then the vaccine efficacy in preventing sustained vaccine HPV type-related infection will be estimated. For these summaries, a subject will be considered to be a case of sustained HPV infection, if, following the Month 7 visit, she: (1) is subsequently detected as positive by the Merck PCR assay for at least 1 gene common for the same vaccine HPV type in 2 or more consecutive cervicovaginal or biopsy samples (if both/all samples are cervicovaginal swabs, then at least 2 samples must have been collected at least 4 months apart; if one of the samples is a biopsy sample showing evidence of disease, then the time interval between the biopsy sample and the previous or next positive sample can be <4 months); or (2) demonstrates vaccine HPV type PCR positivity at the last visit of record for the subject. The vaccine efficacy with respect to this endpoint will be summarized in the per-protocol population and the first, second, and third MITT populations.

g. **Potential Therapeutic Effect of the Vaccine**

Data permitting, an exploratory analysis to assess the potential therapeutic effects of administering the quadrivalent vaccine to subjects who are already infected at baseline with a vaccine HPV type, but who have not yet mounted an immune response to the HPV infection on their own, will be performed. Specifically, the vaccine's impact in reducing the duration of infection in subjects who are seronegative and PCR positive at Day 1 will be estimated as well as the vaccine's impact in increasing the incidence of clearance of infection in these subjects and in reducing the incidence of CIN or worse in these subjects.

The duration of infection from the Month 3 visit onwards in subjects who are seronegative and PCR positive at Day 1 to HPV 16, for example, will be compared between the vaccine and placebo groups by constructing product-limit (Kaplan-Meier type) plots. Infection is defined as in Section III.C.3.f. For HPV 16, the duration of infection is defined as the number of days between the visit date at which the HPV 16 infection is first detected (Month 3 visit or later) and the visit date of the last visit at which HPV 16 PCR positivity is detected (in either swabs or biopsies).

C. **Approaches to Efficacy and Immunogenicity Analysis (Cont.)**

The incidence of clearance of HPV 16 infection will be estimated by treatment group among the Day 1 HPV 16 seronegative and PCR positive subjects and the 95% confidence intervals for the incidences will be provided. Clearance is defined as no detection of HPV 16 infection by PCR on at least 2 cervicovaginal swabs obtained at consecutive scheduled visits starting at the Month 3 visit onwards and no occurrence thereafter of infection of the same HPV type as detected by PCR on 2 or more swabs obtained at consecutive scheduled visits. The time to clearance of infection in these subjects will be compared between the vaccine and placebo groups by constructing product-limit (Kaplan-Meier type) plots.

With regard to the incidence of CIN, among the Day 1 HPV 16 seronegative and PCR positive subjects, the incidence of HPV 16 related CIN will be estimated in each treatment group and the 95% confidence intervals for these rates will be provided. Cases of CIN that are diagnosed as a result of a colposcopy at the Month 3 visit or later will be included in this analysis.

Similar analyses will be performed for HPV types 6 and 18. For the HPV 18 analysis, subjects who are seronegative and PCR positive at Day 1 to HPV 18 will be included. For the HPV 6 analysis, subjects who are seronegative to both HPV 6 and 11 and PCR positive to HPV 6 at Day 1 will be included. For this analysis genital warts that occur after the Month 3 visit will also be included.

As a secondary approach, the above analyses will be performed for the HPV 6, 16, and 18 components in subjects who are: seropositive and PCR positive at Day 1 to the relevant component; and PCR positive at Day 1 to the relevant component, regardless of their serostatus.

h. Potential Protection Against Re-Infection

In order to assess whether the vaccine provides protection against re-infection in subjects who have already cleared their infection, the incidence of infection with vaccine HPV types will be summarized by treatment group in subjects who are seropositive and PCR negative at Day 1 to the relevant vaccine HPV type. Infection is defined as in Section III.C.3.f and cases will be counted starting at the Month 3 visit onwards. The 95% confidence intervals for the incidences will be provided. This will aid in evaluating whether the vaccine boosts immunity in these subjects so that they do not get re-infected.

C. **Approaches to Efficacy and Immunogenicity Analysis (Cont.)**

i. **Immunogenicity in Initially Negative Subjects**

The percentage of subjects with anti-HPV ≥200 milli-Merck units (mMU)/mL and the corresponding 95% confidence interval will be provided for each vaccine HPV type by treatment group and time point from Day 1 through Month 48, for subjects who are in the per-protocol immunogenicity population. The Geometric Mean Titers (GMTs) will also be summarized in the above groups of subjects for each vaccine HPV type by treatment group and time point from Day 1 through Month 48 and the corresponding 95% confidence intervals for the GMTs will be provided. Graphical displays of the GMTs over time may be created for each vaccine HPV type by treatment group to allow for an assessment of the persistence of antibody over time. The above summaries may also be provided in the subgroup of subjects who have a Month 48 visit.

j. **Immunogenicity in Initially Positive Subjects**

The percentage of subjects with anti-HPV ≥200 mMU/mL and the corresponding 95% confidence interval will be provided for each vaccine HPV type by treatment group and time point from Day 1 through Month 48, for subjects who are seropositive at Day 1 or PCR positive at any time point from Day 1 to Month 7 to the relevant vaccine HPV type(s). The GMTs will also be summarized in the above groups of subjects for each vaccine HPV type by treatment group and time point from Day 1 through Month 48 and the corresponding 95% confidence intervals for the GMTs will be provided. Graphical displays of the GMTs over time may be created for each vaccine HPV type by treatment group to allow for an assessment of the persistence of antibody over time. The above summaries may also be provided in the subgroup of subjects who have a Month 48 visit.

In order to supplement the evaluation of the potential therapeutic effect of the vaccine in Section III.C.3.g., for each vaccine HPV type, the GMTs and 95% confidence intervals in subjects who are seronegative and PCR positive at Day 1 to the relevant vaccine HPV type(s) will be provided by treatment group and time point and observationally compared with the GMTs in subjects who are seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant vaccine HPV type(s).

C. Approaches to Efficacy and Immunogenicity Analysis (Cont.)

In order to supplement the evaluation in Section III.C.3.h. of whether the vaccine provides protection against re-infection in subjects who have already cleared their infection, the GMTs and 95% confidence intervals will be provided for subjects who are seropositive and PCR negative at Day 1 by treatment group and time point for each vaccine HPV type. These GMTs will be observationally compared with those in subjects who are naïve to the relevant vaccine HPV type.

k. Correlates of Protection

An exploratory analysis of breakthrough HPV 6/11/16/18-related external genital warts/VIN/VaIN/vulvar or vaginal cancer and breakthrough HPV 6/11/16/18-related CIN/cervical cancer will be performed to try to establish the relationship between immune markers and protection from disease endpoints. Specifically, the immune responses in the non-breakthrough vaccinees will be compared with the immune responses in the breakthrough cases at all available time points (i.e., at Months 7, 12, 24, and 48). However, if there are few cases among the vaccine recipients, there may be insufficient information to establish an immune correlate of protection in this study.

4. Study Extension

Following the completion of the extension phase of the study, the vaccine efficacy with respect to the primary and secondary endpoints will be re-estimated in order to refine the precision of the estimates. In addition, the persistence of antibody response will be summarized for any extension time points that were not included in the report prepared at the time of the primary analysis.

D. Definition of Compliance Measure

Treatment compliance is defined in this study as receipt of all scheduled study vaccinations. To summarize treatment compliance, the numbers of subjects who receive each vaccination will be tabulated by treatment group. As stated in Section III.B., subjects who do not complete the full vaccination regimen will be excluded from the per-protocol primary analyses of efficacy but will be included in several MITT analyses.

D. Definition of Compliance Measure (Cont.)

Another important compliance measure in this study is the degree of subject compliance with follow-up visits following the completion of the vaccination series. Since colposcopy and wart examinations are required procedures for the identification of potential study endpoints, subjects who miss study follow-up visits or who visit their private gynecologists for examinations and/or treatment rather than the study investigators represent missed opportunities to observe endpoints. If these subjects develop vaccine HPV type-related warts or lesions during the time that they missed study visits or if they had vaccine HPV type-related warts or lesions identified and treated outside of the study, then these events would not be captured in the estimate of the vaccine efficacy in this study.

To partially protect against bias that may be introduced into the estimate of the vaccine efficacy by such situations, subjects are asked at every follow-up visit whether or not they have had colposcopy performed outside of the study. If a subject has had colposcopy performed outside of the study, information is solicited regarding whether or not a biopsy, wart or excised tissue specimen was collected during the colposcopy. If a tissue specimen was collected, every effort is made (with the subject's permission) to obtain the tissue specimen block from the subject's physician. If the block is obtained, sections of the block are sent for pathology panel review and PCR analysis. The pathology panel diagnosis and PCR results can then be used to assess whether or not the subject meets an endpoint definition. If the tissue block is not made available to Merck, the subject cannot qualify as an endpoint based on the tissue collected outside of the study.

To summarize compliance with respect to follow-up study visits, the numbers of subjects who complete each follow-up visit will be tabulated by treatment group. To provide measures of compliance with respect to follow-up study visits, the average interval between scheduled study visits will be computed for each subject and across subjects within a treatment group. The number of subjects with intervals longer than 9 months will be summarized by treatment group. In addition, the percentages of subjects in each group who had biopsies or excision procedures performed outside of the study will be summarized, and the percentages of subjects in each group who had biopsies or excision procedures performed outside of the study for whom the tissue samples were unavailable to Merck will be summarized. Differences in these measures between the treatment groups will be assessed observationally and the potential impact on the efficacy analyses will be noted.

IV. SAFETY ANALYSES

The primary safety hypothesis and all of the safety analyses through the Month 7 visit will be addressed in the clinical study reports for the 2 substudies (Protocols 011 and 012). For this study report (Protocol 013), listings of all subjects who received at least one injection *and* who experienced any of the following events after the Month 7 visit will be provided: death, a serious adverse experience (SAEs), a vaccine-related SAE, or a SAE due to procedures that are mandated by the study. Safety data from the 2 substudies will be combined with safety data from other Phase IIb/III studies for the Integrated Summary of Safety.

Although not considered to be an adverse experience, the incidence and outcomes of pregnancies that occur during the vaccination period (Day 1 to Month 7) will be monitored and evaluated by treatment group. The pregnancy summaries will appear in the Protocol 013 CSR.

Subjects who are incorrectly randomized will be included in the listings for safety according to the clinical material they received. If a subject received vaccine at any of the visits then the subject will be listed in the appropriate vaccine group. Subjects will be listed in the placebo group only if they received placebo at all visits.

V. INTERIM ANALYSES/DATA AND SAFETY MONITORING BOARDS

A. Efficacy

There are no interim efficacy analyses planned for Protocol 013 alone. As discussed earlier, the efficacy data collected from Protocol 013 will be combined in a prespecified analysis with efficacy data from Protocols 005, 007, and 015 to evaluate the vaccine efficacy with respect to: (1) vaccine-type HPV-related CIN 2/3 and cervical carcinoma and (2) CIN 2/3 and cervical cancer related to all HPV types. The final analysis of the combined studies with respect to these efficacy endpoints is also endpoint driven. An interim analysis of the *combined* data from Protocols 005, 007, 013, and 015 is planned to be conducted at the time that *at least* 33 cases of CIN 2/3 or cervical cancer related to HPV 16 or 18 have been observed across all 4 studies. The interim analysis of the combined data sets will be performed in conjunction with an interim analysis of Protocol 015's primary hypothesis (the CIN 2/3 efficacy study) and, therefore, will only be conducted when at least 19 cases of CIN 2/3 or cervical cancer related to HPV 16 or 18 have been observed in Protocol 015 *and* at least 33 cases have been observed across all 4 studies. If both these interim analyses meet the primary statistical criteria for success prespecified in their respective DAPs then the HPV project team will proceed with submission for regulatory review.

A. Efficacy (Cont.)

Since Protocol 013 is a pivotal Phase III efficacy study with primary endpoints that differ from the primary endpoint in the combined CIN 2/3 efficacy analysis, the integrity of the Protocol 013 primary endpoints must not be compromised by the unblinding of the Protocol 013 data for the submission. Therefore, the Protocol 013 data will not be completely screened, cleaned, and analyzed for the submission until the required numbers of the primary endpoints for the study have been observed (62 cases of vaccine-type HPV-related external genital warts and 38 cases of vaccine-type HPV-related CIN). It is expected that the required numbers of primary endpoints for Protocol 013 will be observed at approximately the same time as the required number of cases for the combined CIN 2/3 interim analysis. However, should the Protocol 013 primary endpoints take longer than expected to accrue, the submission will be delayed until the required numbers of endpoints are observed. Hence, the individual treatment group assignments of the subjects in Protocol 013 will not be revealed to the HPV project team until the required numbers of endpoints have been observed and the data are screened, cleaned, and unblinded for the primary analysis.

B. Safety

In order to ensure that no alarming, unusual, or unexpected safety problems are occurring with the vaccine, safety will be monitored during the study by the Data and Safety Monitoring Board (DSMB) that will determine if any actions should be taken based on the data. Periodically during the study (approximately every 6 months during the vaccination period and approximately every year thereafter), all available safety data from the study will be summarized by an unblinded Merck statistician who is not related to the HPV Vaccine program and sent to the DSMB. Summaries will also be provided in the event that there is a specific safety concern during the study.

In general, adverse experiences will be summarized descriptively as frequencies and percentages by treatment group and type of adverse experience (this will be done by vaccination visit and across all vaccination visits), and temperatures will be summarized. The DSMB manual specifies the details of the operating procedure for this process.

In particular, the DSMB will monitor the following parameters during the course of Protocol 013:

- the incidence and characteristics of serious adverse experiences (SAEs);
- the incidence and characteristics of nonserious adverse experiences - a general summary will be provided as well as summaries of specific injection-site and systemic adverse experiences;

B. Safety (Cont.)

- pregnancies and their outcomes;
- the incidence of breast-feeding during the vaccination period and the associated outcomes; and
- new medical conditions that arise during the study.

Serious adverse events will be reported to the DSMB at the same time Merck reports them to the FDA.

All summaries will be provided by treatment group and in total. However, in the by-treatment-group summaries, the treatment groups will be labeled as Group A and Group B unless the DSMB has a specific concern and requests that the groups be unblinded.

The interim summaries of safety will be performed on partially unscreened and unaudited data to ensure that the DSMB has the quickest access to the largest possible data set in any given summary. It is recognized that there may be minor changes in incidences and severity gradings of adverse experiences (AEs) based on the screening and auditing process. However, since DSMB decisions with regards to safety are likely to be based on large, unexpected differences in safety parameters between treatment groups, such inaccuracies are not likely to result in incorrect decisions.

VI. STATISTICAL TECHNICAL ISSUES

A. Planned Statistical Power and Sample Size

1. Primary Endpoints

In order to avoid problems with imprecise incidence and efficacy estimates, this study is powered based on a fixed event design. The power for a given number of observed primary endpoints was computed using the method of Chan and Bohidar [12]. The sample size was calculated such that the numbers of cases needed to yield ≥90% power for each primary hypothesis would be observed by ~Year 3 of the study (i.e., 2.5 years Postdose 3). The necessary sample size is 5400 subjects.

A. Planned Statistical Power and Sample Size (Cont.)

Assuming a true vaccine efficacy of 80%, a lower bound of the confidence interval for the true vaccine efficacy >20% under the alternative hypothesis, a two-sided α=0.025, and equal follow-up in the vaccine and placebo groups, 38 cases of each of the primary endpoints are required in order to have ≥90% power to declare the vaccine efficacious against each of these endpoints. For the purpose of calculating the sample size for this study, it is conservatively assumed that the study will continue until all of the disease cases have been observed in the placebo group.

The length of the primary phase of the study is 3 years and the Postdose 3 follow-up is ~2.5 years. The expected attrition rate through Year 3 of the study is 27%. With 2700 subjects randomized to the placebo group, it is expected that there will be ~1971 [2700 x 0.73] subjects in this group at the end of Year 3. It is assumed that the combined seropositivity rates at Day 1 and PCR positivity rates from Day 1 through Month 7 are 15%, 18%, and 18%, for HPV 6/11, 16, and 18, respectively. Therefore, with 1971 subjects in the placebo group after attrition, it is expected that 1675, 1616, and 1616 subjects will be evaluable for the per-protocol analyses of the HPV 6/11-, 16-, and 18-related endpoints, respectively.

For the second primary efficacy hypothesis, it is assumed that the HPV 6/11-related CIN incidence rate is 1.25%, the HPV 16-related CIN incidence rate is 1.0%, and the HPV 18-related CIN incidence rate is 0.25% over the first 2.5 years of Postdose 3 follow-up. Also, a subject who has reached a CIN endpoint related to 1 HPV vaccine type cannot be counted again if she develops CIN related to any of the other HPV vaccine types. Under these assumptions, 20 cases of HPV 6/11-related CIN, 15 cases of HPV 16-related CIN, and 3 cases of HPV 18-related CIN are expected to occur in the study by the Year 3 time point for a total of 38 CIN cases. If the primary analysis is performed when 38 cases of HPV 6/11-, 16- or 18-related CIN or worse are observed, then there is 91.1% power to declare the vaccine efficacious against this endpoint. With 38 cases of HPV 6/11/16/18-related CIN, assuming that there is equal follow-up in the vaccine and placebo groups, a 29/9 split (~69% observed efficacy) will be statistically significant. Figures 1, 2, and 3 display flowcharts with the calculations performed to obtain the expected numbers of HPV 6/11-, 16-, and 18-related CIN cases for the study, respectively.

A. Planned Statistical Power and Sample Size (Cont.)

For determining when the primary analysis will be performed, as previously discussed, only cases of HPV 6/11/16/18-related *external genital warts* will be counted to ensure that genital warts have adequate representation in the analysis of the genital warts/VIN/VaIN endpoint. Since HPV types 6 and 11 cause >90% of genital warts, only the 1675 evaluable HPV 6/11 naïve subjects have been considered as being at risk in the calculation of the expected number of genital wart cases. Assuming that the HPV 6/11-related external genital wart incidence rate is 3.75% over the first 2.5 years of Postdose 3 follow-up, 62 cases of external genital warts are expected in this study by the Year 3 time point. If the primary analysis is performed when 62 cases of HPV 6/11/16/18 related external genital warts are observed, then there is 99.5% power to declare the vaccine efficacious against this endpoint. With 62 cases of external genital warts, assuming that there is equal follow-up in the vaccine and placebo groups, a 44/18 split (~59% observed efficacy) will be statistically significant. Figure 4 displays a flowchart with the calculations performed to obtain the expected number of external genital wart cases for the study.

To ensure acceptable power for both primary hypotheses, the primary analysis will not be conducted until at least 62 cases of HPV 6/11-, 16-, and 18-related external genital warts AND at least 38 cases of HPV 6/11-, 16-, and 18-related CIN have occurred.

2. Secondary Endpoints

For the first secondary efficacy hypothesis regarding HPV 16- and 18-related CIN, the assumed true vaccine efficacy is 80%. Under all of the same assumptions as for the primary analysis, 15 cases of HPV 16-related CIN and 3 cases of HPV 18-related CIN are expected in the study by the time the primary analysis is performed. With 18 cases of HPV 16- or 18-related CIN or worse, there is 83.2% power to declare the vaccine efficacious against this endpoint with a two-sided α=0.05. Assuming that there is equal follow-up in the vaccine and placebo groups, a 14/4 split (~71% observed efficacy) will be statistically significant.

For the second secondary efficacy hypothesis, the assumed true vaccine efficacy is 70%. If the incidence rate of external genital warts related to any HPV type is 4.0% over the first 2.5 years of Postdose 3 follow-up and if all of the endpoints occur among the 1675 evaluable subjects in the placebo group, 67 cases of external genital warts/VIN/VaIN are expected in this study by the time the primary analysis is performed. With 67 cases of external genital warts/VIN/VaIN, there is 99.7% power to declare the

A. Planned Statistical Power and Sample Size (Cont.)

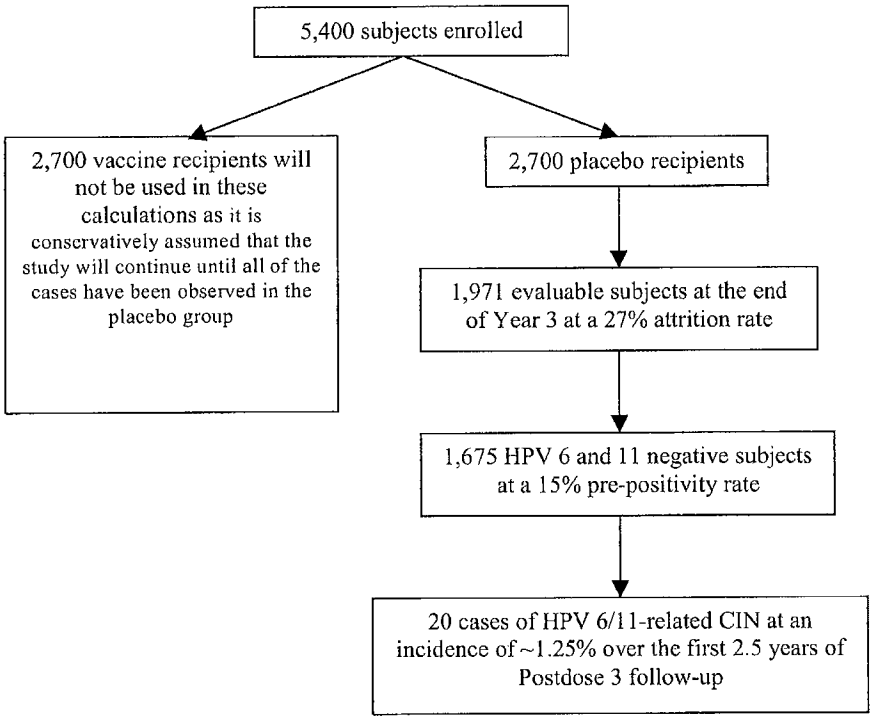
vaccine efficacious against this endpoint with a two-sided $^{n}_{J}$=0.05. Assuming that there is equal follow-up in the vaccine and placebo groups, a 42/25 split (~41% observed efficacy) will be statistically significant.

Note that since the efficacy analyses will be conducted when the required numbers of cases of the *primary* endpoints have been observed, the number of cases of HPV 16- and 18-related CIN or worse may differ from 18 at the time of analysis and/or the number of cases of external genital warts, VIN and VaIN may differ from 67 at the time of analysis. If this is the case, then the power estimates for these endpoints will be different from those estimates stated above.

A. Planned Statistical Power and Sample Size (Cont.)

Figure 1

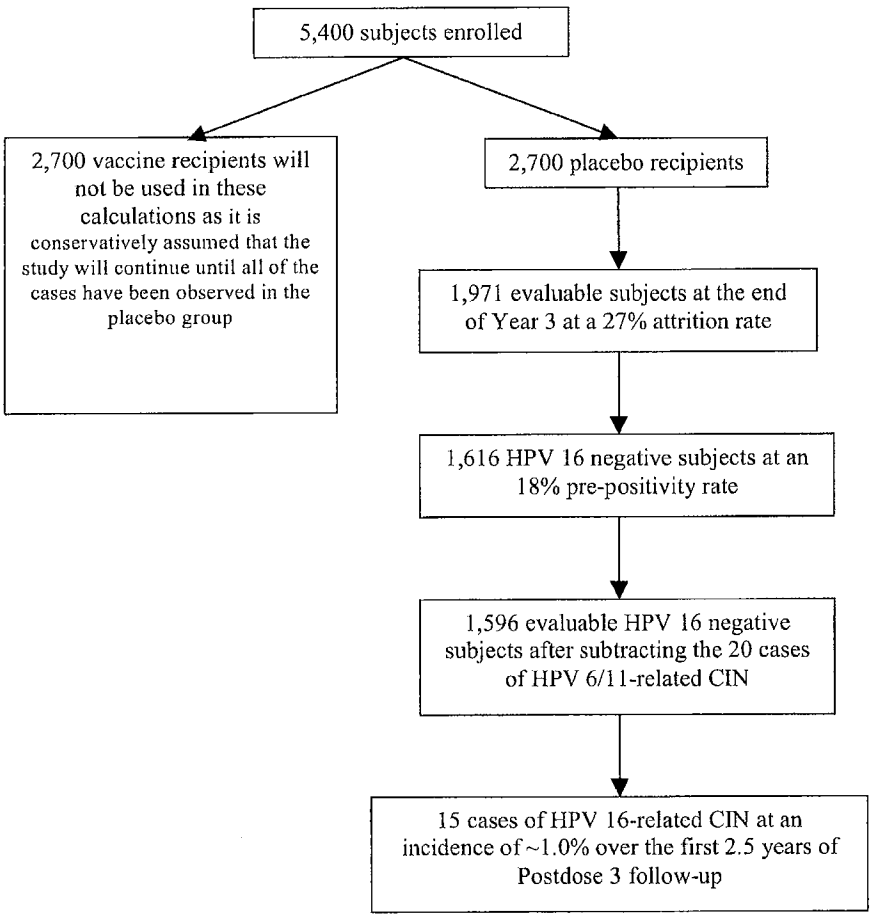
Determining the Expected Number of HPV 6/11-Related CIN Cases for the Study



A. Planned Statistical Power and Sample Size (Cont.)

Figure 2

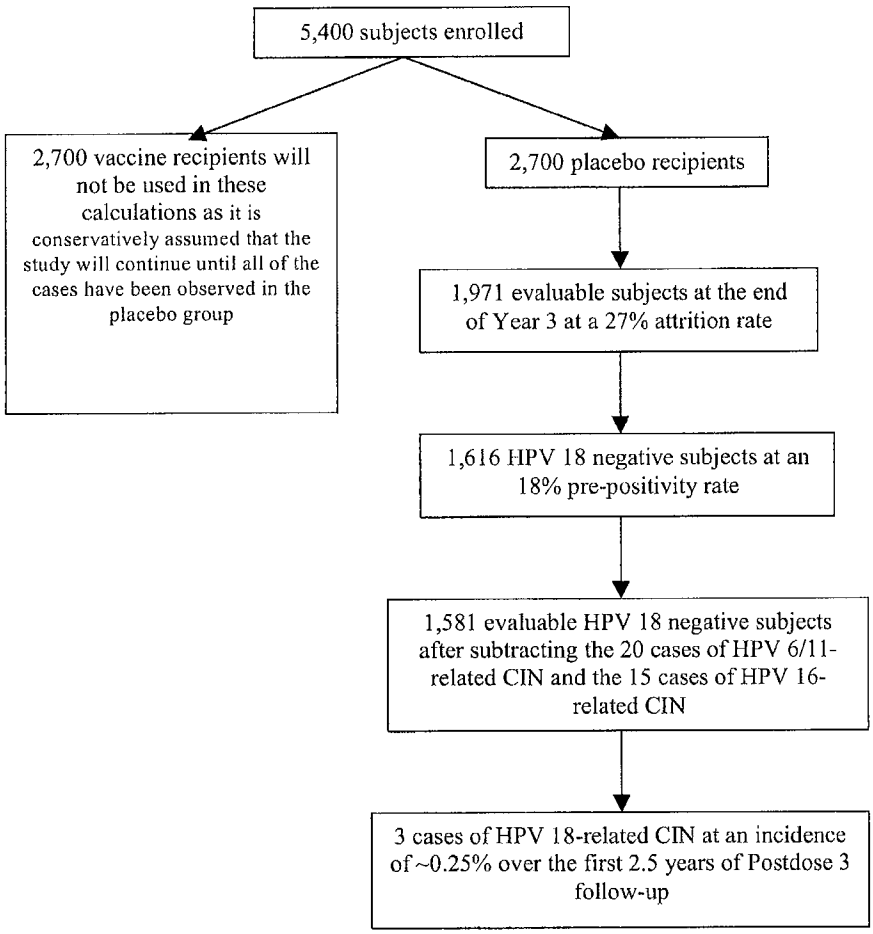
Determining the Expected Number of HPV 16-Related CIN Cases for the Study



A. Planned Statistical Power and Sample Size (Cont.)

Figure 3

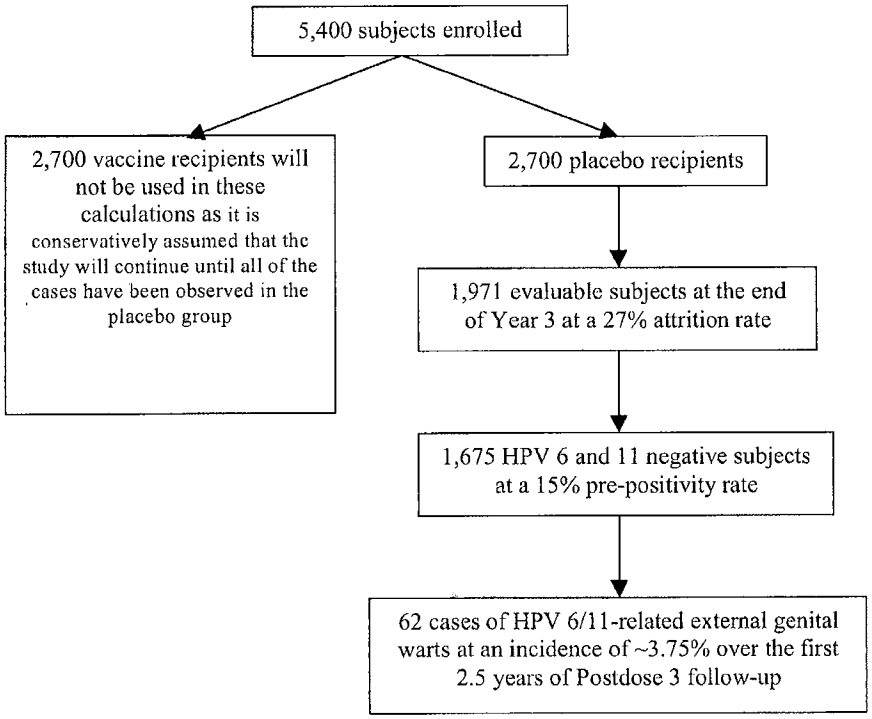
Determining the Expected Number of HPV 18-Related CIN Cases for the Study



A. Planned Statistical Power and Sample Size (Cont.)

Figure 4

Determining the Expected Number of
HPV 6/11-Related External Genital Wart Cases for the Study



B. Method of Assigning Study Participants to Treatment Groups

Participants in the study will be randomized in a 1:1 ratio to receive either vaccine or placebo within each investigative site. Case numbers will be assigned sequentially beginning with the lowest number available at the study site as subjects are enrolled in the study. Case numbers should not be reassigned for any reason.

C. Blinding/Unblinding

This is a double-blinded study (operating under in-house blinding procedures). Therefore, the subjects enrolled in the study, the investigators and study personnel, the laboratory personnel conducting the PCR, RIA, and neutralization assays on the clinical samples, and the Pathology Panel will be blinded to the treatment group assignments of the subjects for the duration of the entire study (4 years). The clinical, data management and statistical personnel involved with the protocol at the SPONSOR will be blinded to the treatment group assignments of the subjects through the primary efficacy evaluations (~3 years).

To ensure blinding of the subjects and the investigators and study personnel, the vaccine and placebo are supplied in identical vials labeled with a double-panel, blinded label. The vaccine and placebo are visually indistinguishable.

For this study, the duration of the primary efficacy phase will be ~3 years. However, the primary time point for the immunogenicity analyses for the concomitant administration (Protocol 011) and monovalent HPV 16 vaccine bridging (Protocol 012) substudies is Month 7 (one month following completion of the full vaccination regimen). The immunogenicity and safety analyses for the substudies may be conducted when all subjects in the substudies have completed the Month 7 follow-up. To keep the data for the efficacy evaluations blinded while preparing the study reports for the immunogenicity and safety data for Protocols 011 and 012, a restricted clinical, statistical, and data management team will be formed to analyze the data from the immunogenicity substudies. All clinical, statistical, and data management personnel can perform the screening and cleaning of data through Month 7, a process which includes data review and correction, and identification of protocol violators, in a blinded fashion. Once the data through Month 7 are cleaned and audited, a copy of the clean database will be made, and this copy will be unblinded for the restricted clinical, statistical, and data management team responsible for the immunogenicity and safety analyses. Only the team responsible for the immunogenicity and safety analyses will have access to the allocation schedules and the unblinded database. The primary database will remain blinded for the efficacy analysis. No member of the previously unblinded team (who participated in the

C. Blinding/Unblinding (Cont.)

immunogenicity analyses) will be responsible for screening and cleaning the data for the efficacy analysis. Therefore, the data for the efficacy analysis will be screened and cleaned in a blinded manner. The efficacy analysis will then be performed on the clean data set.

As previously discussed, Protocol 013 will continue into an in-house unblinded extension phase after the primary analysis. The purpose of the extension phase is to accrue additional data to address the objectives of a prespecified efficacy analysis of the combined data from Protocols 005, 007, 013, and 015. It is important to note that throughout the efficacy phase *and* the extension phase of this study, the laboratory personnel, the pathology panel, and the investigators, site personnel, and subjects will remain blinded to the individual treatment allocations of the subjects. Since the data collected, which impact ascertainment of the efficacy endpoints, are: the Pap tests, which are read by a central laboratory; the biopsy samples, which are read by the pathology panel; and the PCR test results, which are provided by a blinded laboratory, all investigators and technicians who have the entire responsibility for the ascertainment and confirmation of efficacy endpoints will be blinded for the duration of the entire study (4 years).

D. Statistical Methods

1. Efficacy

A one-sided test of H_0: $\vartheta_B \leq 0.2$ versus H_1: $\vartheta_B > 0.2$ will be conducted, for each of the primary efficacy hypotheses where $\vartheta_B = 1 - RR$, and RR is the relative risk of the vaccine compared with placebo. In addition, a 97.5% two-sided exact confidence interval for the vaccine efficacy will be provided. An exact conditional procedure will be used under the assumption that the number of cases in the vaccine group, C_v, and the number of cases in the placebo group, C_p, are independent Poisson random variables with means ε_v and ε_p [12]. (The relative risk of the vaccine is $\varepsilon_v/\varepsilon_p$.) The number of cases in the vaccine group C_v, given the total number of cases observed $C_v + C_p$, is binomially distributed with parameters, $C_v + C_p$, and $p = \varepsilon_v/(\varepsilon_v + \varepsilon_p)$, where p is the probability that a subject in the vaccine group is a case. The point estimate for p is $C_v/(C_v + C_p)$. The lower bound of the $100(1-\alpha)\%$ exact confidence interval for p can be calculated by searching for the p_L such that the probability of observing C_v or more vaccine cases out of C_v+C_p total cases is $\alpha/2$. The upper bound of the exact confidence interval for p can be calculated by searching for p_U such that the probability of observing C_v or fewer vaccine cases out of C_v+C_p total cases is $\alpha/2$. It follows that the exact confidence interval for vaccine efficacy will then have lower bound $VE_L = (1-2*p_U)/(1-p_U)$ and upper bound $VE_U = (1-2*p_L)/(1-p_L)$.

D. Statistical Methods (Cont.)

In the event that there is unequal follow-up between groups, the estimate of the vaccine efficacy must account for the follow-up in each group. Rather than $VE = 1 - C_v/C_p$, the point estimate for the vaccine efficacy will be $VE = 1 - (C_v/k_v)/(C_p/k_p)$, where k_v and k_p are the person-years of follow-up in the vaccine and placebo groups, respectively. The following formulas will be used for the endpoints of the confidence interval for the vaccine efficacy: lower bound $VE_L = (1-p_U/k)/(1-p_U)$ and upper bound $VE_U = (1-p_L/k)/(1-p_L)$, where $k = k_v/(k_v + k_p)$, Follow-Up in Vaccine Group/Total Follow-Up.

For each of the secondary efficacy hypotheses, a one-sided test of H_0: $\vartheta_s = 0$ versus H_1: $\vartheta_s > 0$ will be conducted. In addition, a 95% two-sided exact confidence interval for the vaccine efficacy will be provided.

For the estimates of vaccine efficacy with respect to the exploratory endpoints, point estimates and 95% confidence intervals for the vaccine efficacy will be computed using the method described above for the primary analysis.

2. Correlates of Protection

In addition to the methods described in Section III.C.3.j. for assessing the anti-HPV serum RIA responses as potential correlates of protection, the odds of developing breakthrough HPV 6/11/16/18-related external genital warts/VIN/VaIN and breakthrough HPV 6/11/16/18-related CIN will be modeled as a function of the corresponding Postdose 3 RIA titer using a logistic regression model. Length of postvaccination follow-up and study site will be included as additional model terms. Statistical significance of the coefficient for the RIA titer will be an indication that RIA titer is a predictor of breakthrough infection. The estimate of the coefficient will indicate the nature of the relationship. If there are few cases among the vaccine recipients, there may be insufficient information to establish an immune correlate of protection in this study.

3. Counting of Efficacy Endpoints

Cases will be counted periodically by an unblinded Merck Statistician who is not related to the HPV Vaccine program. For each of the primary endpoints, the number of subjects with events will be counted. In other words, each subject can be counted as a case only once for each of the primary endpoints. For example, if a subject develops HPV 6-related external genital warts, then HPV 6-related CIN 1, and then HPV 16-related CIN 1, she would count once as a case of HPV

D. Statistical Methods (Cont.)

6/11/16/18-related external genital warts/VIN/VaIN and once as a case of HPV 6/11/16/18-related CIN. Thus, if a subject becomes a case of one of the primary endpoints, she can still become a case of the other primary endpoint. Cases will be similarly counted for the secondary and exploratory efficacy endpoints. Specifically, each subject will be counted as a case *once* for each applicable endpoint.

4. Computation of Follow-Up Time

Follow-up for both the primary endpoints begins following the Month 7 visit. Therefore, each subject's follow-up time will be computed by calculating the number of days between her Month 7 visit date and her final visit date. This value will be converted to person-years by dividing by 365.25. For cases, the final visit date will be the visit date at which external genital warts, VIN, VaIN, CIN or cancer was detected. If a subject develops more than one case of disease that fits into a given endpoint classification, the final visit date will be the date at which the first endpoint in the given classification was detected. Each subject's follow-up time will be similarly computed for the secondary and exploratory efficacy endpoints.

Although the primary analyses are per-protocol and HPV type-specific, all subjects who are eligible for the per-protocol analyses of the HPV 6 and 11 endpoints, the HPV 16 endpoints or the HPV 18 endpoints will contribute follow-up time to the totals. For the secondary analysis of HPV 16- and 18-related disease, all subjects who are eligible for the per-protocol analysis of either the HPV 16 endpoints or the HPV 18 endpoints will contribute follow-up time to the totals. For the other secondary and exploratory analyses, all subjects who are eligible for the per-protocol analyses based on at least one of HPV 6 and 11, HPV 16, HPV 18, one of the 11 additional HPV types or the normal Day 1 and Month 7 Pap tests will contribute follow-up time to the totals.

5. Potential Biases

a. Ascertainment Bias

For the detection of cervical lesions, subjects in this study are triaged to colposcopy and biopsy based on the results of the Pap tests performed approximately every 6 months. However, subjects in the study also undergo an external genital wart/lesion examination approximately every 6 months, and colposcopy is frequently performed on subjects based solely on a discovery of genital warts as

D. Statistical Methods (Cont.)

well. This practice could introduce ascertainment bias if the vaccine is efficacious in preventing genital warts. If the vaccine is efficacious in preventing external genital warts/lesions, external genital warts/lesions will be found more often in the placebo recipients than in the vaccine recipients. Thus, the placebo recipients will be referred for colposcopy more often than the vaccine recipients, and, consequently, more CIN lesions will be detected in these subjects. This may cause the vaccine to appear more efficacious against CIN than it really is. To avoid this type of ascertainment bias, cases of CIN or worse that are detected during a colposcopy that was performed *solely* based on a finding of genital warts (i.e., without an accompanying abnormal Pap test result) will not be included in the primary or secondary analyses outlined in this DAP, nor will these CIN cases count toward the total number of cases needed to trigger the analyses. Sensitivity analyses will be performed in which all cases of CIN or worse are included regardless of the reason the colposcopy was performed. The Pap test result that will be considered in determining whether or not the colposcopy was performed based on a genital wart finding only will be the Pap test result from the most recent *scheduled* visit prior to the colposcopy date or on the colposcopy date. Pap test results from unscheduled visits at which colposcopies were performed will not be considered because they also represent data that could be influenced by the vaccine's impact on the genital wart endpoint.

A second source of potential ascertainment bias is the reflex HPV testing using the Hybrid Capture II assay. According to the mandatory triage strategy in this study, if a subject has a Pap result of ASC-US, she will undergo reflex HPV testing on residual ThinPrep™ material by Hybrid Capture II, DIGENE™. If at least 1 probe is positive, the subject will be referred for colposcopy. This is standard clinical practice among many practitioners in the United States. However, this practice may lead to a potential ascertainment bias if the vaccine is efficacious in preventing vaccine type HPV infection (as detected by Merck's HPV PCR assay). If the vaccine is efficacious in preventing vaccine type HPV infection, it will influence the outcome of the Hybrid Capture II test. Consequently, the placebo recipients will be referred for colposcopy more often than the vaccine recipients and therefore, more CIN lesions will be detected in the placebo recipients. This may cause the vaccine to appear more efficacious against CIN than it really is. It is important to note that since the Pap diagnoses of LSIL and HSIL are highly correlated with HPV positivity, if a subject has a Pap result of LSIL or HSIL, there is still a potential for ascertainment bias. However, it is also important to note that, like the

D. Statistical Methods (Cont.)

Pap diagnoses of LSIL and HSIL, the Hybrid Capture II assay is not specific for vaccine HPV types. It measures 11 High-Risk and 5 Low-Risk HPV types (including HPV 6, 11, 16, and 18), and this reduces the potential for ascertainment bias. To evaluate the ascertainment bias that may be introduce by the triage strategy, all biopsy specimens will be typed and the incidence of non-vaccine HPV types in the lesions will be compared between the vaccine and placebo groups using a confidence interval for the difference between incidence rates in the vaccine and placebo groups. If the incidence appears comparable, then it will be concluded that any ascertainment bias that exists is not serious. On the other hand, if substantial ascertainment bias is found to exist, then a sensitivity analysis to determine its effect on the efficacy estimates may be considered. It must also be noted that differences in these incidences may not necessarily be due to ascertainment bias but could be evidence of cross-protection between HPV types.

b. Censoring Due to Definitive Therapy

When a subject has a biopsy performed, the subject is referred for definitive therapy based on the central laboratory's diagnosis of the biopsy (not the consensus diagnosis of the pathology panel). A subject is typically referred for a central laboratory diagnosis of CIN 2 or worse. Once a subject is referred for definitive therapy, she is censored for the primary and secondary evaluations of vaccine efficacy. If she meets the case criteria for an endpoint based on any tissue samples collected up to the time of definitive therapy, or if the tissue sample collected at the time of definitive therapy qualifies her as having met an endpoint criterion, she will be counted as a case.

Since the pathology panel diagnosis is the diagnosis that determines the endpoint status of a subject and the central laboratory diagnosis determines whether or not the subject is referred for treatment, there is the potential for a subject to be censored for the analysis based on a central laboratory diagnosis of CIN 2 or worse, while the pathology panel diagnosis of the same lesion is less severe disease than CIN 2 or no disease. Though this situation is expected to occur infrequently, it could cause some of the subjects with the most potential for being classified as endpoints to be censored before meeting an endpoint criterion. Consequently, it could cause a slight bias in the estimate of vaccine efficacy. To assess the impact of this situation on the efficacy estimate, a sensitivity analysis will be performed in which the endpoint definition is based on the more severe of the central laboratory or pathology panel diagnosis of each biopsy.

D. Statistical Methods (Cont.)

6. Missing Data

Occasionally in the context of clinical studies, critical data are unavailable for analysis. This usually occurs because the data are not collected (e.g., the subject missed a visit or refused an examination) or because the samples from which the data are generated are mishandled (e.g., samples are lost or broken before reaching the laboratory) or are unsatisfactory (e.g., the slide cannot be read by the pathologist or the swab does not amplify in the PCR assay).

With respect to counting cases of vaccine-HPV-type-related external genital warts, VIN, VaIN, CIN and cancer, if a subject has a biopsy, excised tissue (for definitive wart therapy), ECC, LEEP, or conization specimen collected during the efficacy evaluation phase (post-Month 7), and the PCR result or pathology panel diagnosis is missing for the specimen, then the subject cannot be classified as a case based on that specimen.

When the missing data are needed to establish a subject's eligibility for analysis, the following rules will apply:

- With respect to missing serology results, subjects who are missing a baseline RIA result for a particular vaccine HPV type *will not* be eligible to be classified as cases of disease endpoints related to that HPV type.

- With respect to missing PCR results for cervicovaginal specimens, a subject's eligibility for analysis depends on the number of missing results. The PCR results for 2 cervicovaginal specimens collected at Day 1, 2 cervicovaginal specimens collected at Month 3, and 2 cervicovaginal specimens collected at Month 7 are used to determine each subject's eligibility for analysis. Since only 2 specimens are available at each time point to classify a subject as HPV positive or negative, subjects who are missing one or both of the PCR results for a given vaccine HPV type at Day 1, Month 3, or Month 7 *will not* be eligible to be classified as cases of disease endpoints related to that HPV type in the primary analysis. This rule was established because the 2 cervicovaginal specimens for PCR analysis are collected from different locations and 1 specimen may be insufficient to classify a subject as PCR negative for a given HPV type.

D. Statistical Methods (Cont.)

- If the PCR result from a biopsy sample taken between Day 1 and Month 7 (inclusive) is missing for a given vaccine HPV type, and the biopsy is diagnosed as abnormal, the subject *will not* be eligible to be classified as a case of a disease endpoint related to that type. If the PCR result is missing and the diagnosis is normal, the subject *will* be eligible. This rule was established because abnormal tissue is likely to be HPV PCR positive.

Similar rules for missing PCR results will be applied for the analyses of external genital warts/lesions and CIN related to non-vaccine HPV types.

Missing data that result from a subject dropping out of the study will be treated as missing (non-existent) in the primary analysis. However, a sensitivity analysis will be conducted in which the number of cases expected among subjects who are lost to follow-up will be projected assuming that these subjects are classified as cases with the same probability as those subjects who are not lost to follow-up. In this analysis, it will be assumed that subjects who are lost to follow-up prior to Month 7 (i.e., prior to completion of the vaccination series) will become classified as cases at the same rate as the placebo recipients in the primary analysis. That is, an assumption of "no vaccine efficacy" will be made in these subjects. The incidence rate that will be assumed for subjects who are lost to follow-up at Month 7 or following Month 7 (i.e., after completion of the vaccination series) will depend on each subject's treatment group. Vaccine recipients who complete the vaccination series and then drop out subsequently can be assumed to develop the endpoint of interest at the same rate as the vaccine recipients in the primary analysis who will all have also completed the vaccination series. Placebo recipients who complete the vaccination series and then drop out subsequently can be assumed to develop the endpoint of interest at the same rate as the placebo recipients in the primary analysis.

7. Interaction

Prior to conducting the formal statistical analyses described above, tests for study-site-by-treatment-group interaction will be performed. This section describes the general approach that will be taken for assessing the presence and nature of the interactions.

D. Statistical Methods (Cont.)

All interaction tests will be conducted at the $\alpha = 0.10$ level. If no statistically significant interaction is found, then the study sites will be pooled for the analysis. If a significant treatment-by-study-center interaction is found, the nature of the interaction will be examined and the relevance of the interaction in the context of the planned analysis will be evaluated. If the interaction cannot be disregarded, certain study sites may be analyzed separately.

To assess the impact of treatment-group-by-study-center interaction on the incidence rates of the various disease endpoints, logistic regression models will be used. The models will include terms for treatment group, study site, and treatment-group-by-study-site interaction. Due to the small numbers of cases of certain disease endpoints expected in this study, there will be low power to detect treatment-group-by-study-center interaction using the logistic regression models. Therefore, treatment-group-by-study-center interaction may need to be assessed observationally. If this is the case, any observed interaction will be described, but it may not be possible to analyze study sites separately and still maintain adequate power for the primary and secondary analyses.

E. Multiplicity

There are 2 primary efficacy hypotheses in this study. The study will be considered a success if either hypothesis test is successful. Therefore, each primary efficacy hypothesis will be tested at the 0.025 (two-sided) level to control the overall type I error rate at the 0.05 (two-sided) level.

F. Subgroup Analysis

Primary and secondary efficacy estimates and the GMTs at Day 1 and Months 7, 12, 24, and 48 will be provided by race, age (by year) and geographical region (United States, Latin America, Europe, and Asia-Pacific). Modeling techniques will be explored to assess the effects of various subgroups on the efficacy estimates in the Integrated Summary of Efficacy.

VII. GROUND RULES FOR ANALYSIS

A. Definition of Time Points

Each of the subjects will receive 3 doses of HPV vaccine or placebo. The vaccine or placebo will be administered at 0, 2, and 6 months. There will be no restrictions placed on the timing of the 3 vaccination visits for the per-protocol efficacy analysis. However, for the per-protocol immunogenicity analyses of the persistence of antibody titers, acceptable timing for the Month 2 vaccination visit will be 36 to 84 days (60 days ± 24 days), and acceptable timing for the Month 6 vaccination visit will be 148 to 218 days (183 days ± 35 days). These windows are a few days wider than the ones specified in the protocol in order to account for the differences in counting months at the study sites.

For the efficacy analyses, the postvaccination clinical samples collected at Month 7 will be considered as valid for identifying the PCR status of a subject if they are obtained 14 to 72 days (30 days - 16 days to 30 days + 42 days) following the Month 6 vaccination. No restrictions will be placed on the timing of the post Month 7 visits.

For the immunogenicity analysis of the persistence of antibody titers, only Month 7 serum samples that are collected 14 to 49 days (2 weeks to 7 weeks) following the Month 6 vaccination will be included. The protocol specified window for the Month 7 visit is 3 to 7 weeks following the Month 6 visit. One week has been added to the beginning of the window in order to be consistent with the windows in the Phase I protocols. The day range is more restrictive for the immunogenicity analysis than for the efficacy analysis because it is important to measure a Postdose 3 immune response that is as close to the peak response as possible. The acceptable day ranges relative to the first vaccination for the Month 12 to Month 48 visits are given in Table 5. The day ranges in Table 5 will only be imposed on the persistence serology samples for the purposes of summarizing immunogenicity data.

Table 5

Acceptable Day Ranges for Post Month 7 Visits

Visit	Day Range[†]	Midpoint of Range
Month 12	274 to 456	365
Month 24	639 to 821	730
Month 36	1004 to 1186	1095
Month 48	1369 to 1551	1460
[†]The day range is relative to the first vaccination.		

B. Definition of Which Value Within a Day Range Will be Used

For the efficacy analysis, with the exception of the Month 7 visit, multiple measurements within a day range are not possible, as no day ranges are imposed on the visits, scheduled or unscheduled. With respect to the Month 7 visit and the day ranges imposed on the Month 12, 24, 36, and 48 visits for the immunogenicity analysis, multiple visits within a day range are possible. However, since the visits in Protocol 013 are labeled, if multiple efficacy measurements are taken within the acceptable day range for a given visit, the values for the samples that are labeled with that visit by the study site will be the values that are used for the analysis. For example, if a subject comes to the clinic for a visit on Day 276 and again on Day 453, and the Day 276 visit is labeled Month 12 while the Day 453 visit is labeled Month 18, then the Day 276 visit will be used for the Month 12 visit, and the subject will be considered outside the day range for the Month 18 visit. As part of the routine screening process, the data will be screened prior to analysis to make sure that only one visit for each subject is labeled with each visit label.

C. Definition of Baseline Value

For the serum samples, the baseline values for a study participant are the assay results obtained from the sample that was collected from that subject on the day of the initial vaccination. The PCR results that will be used to establish that subjects are negative for HPV 6, 11, 16, and/or 18 at Day 1 and through Month 7 of the study are the HPV 6, 11, 16, and 18 results for the (b)(4) and (b)(4) swab and the (b)(4) swab at Day 1, Month 3 and Month 7, and the Thinsection PCR results from biopsies performed between Day 1 and Month 7 (inclusive).

D. Description of Data Handling Procedures Prior to Analysis

Once it has been determined that at least 62 cases of vaccine-HPV-type-related external genital warts and at least 38 cases of vaccine-HPV-type-related CIN have been observed, all data collected up until that time point will be screened and cleaned. This process will be completed before the data are unblinded. Subjects to be excluded from the per-protocol analyses will be identified prior to the unblinding of the database. All data handling guidelines and actions will also occur prior to unblinding according to Merck's Standard Operating Procedure (SOP) for "in-house blinded" studies, i.e., blinding for study participants, investigators, and internal Merck personnel. The in-house unblinded database will be "frozen" in order to ensure that analyses of data in response to regulatory queries will be performed on the same data as were used for that submission.

E. Description of Protocol Violations

1. Efficacy and Immunogenicity

The per-protocol analyses of efficacy and summaries of immunogenicity will exclude data according to the following rules:

a. Violations With Respect to the Vaccination Regimen or Sample Collection Regimen

1) Subjects who received any of their 3 vaccinations outside of the day ranges specified in Section VII.A. shall be excluded from the immunogenicity analyses only.

2) Subjects who received the incorrect clinical material or an incorrect dose of the correct clinical material at any of the 3 vaccination visits shall be excluded.

3) Incorrectly randomized subjects shall be excluded.

b. Inclusion/Exclusion Criteria Violations

1) Subjects who are younger than 16 or who are older than 23 years of age shall be included.

2) Subjects who have engaged in sexual intercourse within 48 hours prior to a scheduled visit which includes a pelvic exam shall be included in the efficacy and immunogenicity analyses. If an analysis of vaccine-HPV-type-related infection is performed, subjects who have engaged in sexual intercourse within 48 hours prior to a pelvic exam at Day 1, Month 3, or Month 7 will be excluded. If a subject has engaged in sexual intercourse within 48 hours prior to any visit after Month 7, the visit will be considered missing. The sexual intercourse restriction is imposed for the infection analyses because deposition of HPV by a sexual partner could result in a positive finding on the PCR assay that does not represent the subject's infection.

3) Subjects who become pregnant prior to Month 6 and subsequently choose to continue the pregnancy (i.e., not terminate the pregnancy) will be included in the efficacy analyses. These subjects will likely be excluded from the immunogenicity analyses as they most likely missed vaccinations due to the pregnancy.

4) Subjects who have a lifetime history of more than 4 male or female sexual partners shall be included.

E. Description of Protocol Violations (Cont.)

5) Subjects who are concurrently enrolled in clinical studies of investigational agents or studies involving collection of cervical specimens may or may not be included. These subjects will be judged on a case by case basis by the Clinical Monitor while the Clinical Monitor is still blinded to each subject's treatment assignment and case status.

6) Subjects with a history of any prior abnormal Pap test showing SIL, ASC-US, ASC-H, or biopsy showing CIN shall be included.

7) Subjects with a history of genital warts or treatment for genital warts shall be excluded.

8) Subjects with any known or suspected immune disorders may or may not be included. These subjects will be judged on a case by case basis by the Clinical Monitor while the Clinical Monitor is still blinded to each subject's treatment assignment and case status.

9) Subjects who are immunocompromised or have been diagnosed as having HIV infection shall be excluded.

c. Concomitant/Prior Therapy Violations

1) Subjects who have received any immune globulin (including RhoGAM™) or blood derived products at any time through Month 7 of the study shall be excluded.

2) Subjects receiving any immunosuppressives shall be excluded with the exception of subjects using topical or inhaled steroids.

3) Subjects who receive any nonstudy inactivated vaccine within 14 days before or after receipt of a study vaccine shall be excluded as well as subjects who receive any nonstudy live virus vaccine within 21 days before or 14 days after receipt of a study vaccine.

4) Subjects who have had prior vaccination with an HPV vaccine shall be excluded.

VIII. PRESENTATION AND FORMAT OF RESULTS

A. Outline of Results Section

The following is an outline of the anticipated sections that will appear in the "Results" portion of the clinical study report.

A. Outline of Results Section (Cont.)

Results

1. Subject Accounting
2. Subject Characteristics
3. Efficacy
4. Immunogenicity—Persistence of Antibody Responses
5. Safety

B. Format of Data Within Tables

1. Decimals

All means, standard errors, percentages, and confidence intervals will be reported to 1 decimal place.

2. Rounding

Means, standard errors, percentages, and confidence intervals will be rounded up to the next decimal place if the second decimal place is ≥5 and down to the next decimal place if <5.

C. Notation and Ordering of Treatment Groups

Group 1: Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	Group 2: Placebo

D. Reporting of Statistical Significance

All p-values will be rounded to the nearest thousandth (3 decimal places). All statistical tests with the exception of the interaction tests will be conducted at a one-sided α-level of 0.025. A p-value less than the prespecified α-level reflects statistical but not necessarily clinical significance.

IX. REFERENCES

1. Anonymous. Consensus statement: National Institutes of Health Consensus Development Conference statement on cervical cancer. Gynecol Oncol 1997;66:351-61.

2. Murakami M, Gurski KJ, Stellar MA. Human Papillomavirus vaccines for cervical cancer. J Immunother 1999;22(3):212-8.

3. Sigurdsson K. Effect of organized screening on the risk of cervical cancer: evaluation of screening activity in Iceland, 1964-1991. Int J Cancer 1993;54;563-70.

4. Cain JM, Howett MK. Preventing cervical cancer. Science 2000;288:1753-4.

5. Cox JT. Evaluation of abnormal cervical cytology. Clin Lab Med 2000;20(2):303-43.

6. Handsfield HH. Clinical presentation and natural course of anogenital warts. Am J Med 1997;102(5A):16-20.

7. Beutner KR, Reitano MV, Richwald GA, Wiley DJ, and the AMA Expert Panel on External Genital Warts. External genital warts: report of the American Medical Association consensus conference. Clin Infect Dis 1998;27:796-806.

8. Maw RD, Reitano M, Roy M. An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle. Int J STD AIDS 1998;9:571-8.

9. Green GE, Bauman NM, Smith RJH. Pathogenesis and treatment of juvenile onset recurrent respiratory papillomatosis. Otolaryngol Clin North Am 2000;33(1):187-207.

10. Alani RM, Munger K. Human papillomaviruses and associated malignancies. J Clin Oncol 1998;16:330-7.

11. Koutsky L. Epidemiology of genital human papillomavirus infection. Am J Med 1997;102(5A);3-8.

12. Chan ISF, Bohidar NR. Exact power and sample size for vaccine efficacy studies. Commun Stat – Theory Meth 1998:27:1305-22.

X. APPENDICES