Statistical Data Analysis Plan

Efficacy of Merck's HPV L1 VLP Vaccine in the Reduction of HPV 16- and 18-Related Cervical Intraepithelial Neoplasia Grades 2 and 3 (CIN 2/3) and HPV 16- and 18-Related Cervical Carcinoma in Young Women

(Studies 005, 007, 013, and 015)

Amendment 1

Prepared by

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SUMMARY OF DAP CHANGES:

Section	Change	Rationale for Change
Executive Summary - Study Objectives and Hypotheses; **Introduction** - Description of the Study and Objectives/ Hypothesis, Secondary Objective and Secondary Hypothesis	Revised the secondary objective and hypothesis to indicate that the secondary efficacy evaluation will be conducted in subjects who are naïve at baseline as opposed to subjects who are naïve from enrollment through Month 7.	PCR assay results are going to be available for non-vaccine HPV types only at baseline (rather than at baseline and Month 7).
Executive Summary – Efficacy Endpoints; **Efficacy Analyses** – Efficacy Endpoints, Primary Endpoint	Text was added/revised to clarify the definition of the primary endpoint for Protocols 005 and 007.	The additional text was necessary to clarify that for Protocols 005 and 007, disease cases in the combined analysis will be defined the same way as for the individual study analyses.
Executive Summary – Data Analysis and Decision Criterion; **Statistical Technical Issues** - Planned Statistical Power and Sample Size	Power for the interim analysis was revised.	The power in the original DAP was incorrect.
Introduction - Description of the Study and Objectives/ Hypothesis, Study Designs (text and Table 2); **Statistical Technical Issues** – Planned Statistical Power and Sample Size	Actual sample sizes have been included for Protocols 005 and 007.	Actual sample sizes are known now that these studies are completed and unblinded.
Introduction - Description of the Study and Objectives/ Hypothesis, Study Designs (Table 2)	An extended timeline for Protocols 013 and 015 has been provided.	These studies are currently scheduled to be completed in 2007.

Section	Change	Rationale for Change
Introduction - Description of the Study and Objectives/ Hypothesis, Study Designs (Table 2)	The monovalent vaccine has been included in the treatment arms of Protocol 013.	This was an omission in the original version of the DAP.
Introduction – Description of the Study and Objectives/ Hypothesis, Study Designs; **Efficacy Analyses** – Study Participant Populations; Approaches to Efficacy Analysis	The text was revised to indicate that the 5400 subjects randomized to receive quadrivalent HPV (Types 6, 11, 16, and 18) L1 HPV vaccine or placebo in Protocol 013 will contribute cases of HPV 16- and 18-related CIN 2/3 and cervical cancer to the primary analysis, while the HPV 16-related CIN 2/3 and cervical cancer cases among the 300 subjects randomized to receive monovalent HPV 16 vaccine will be summarized separately.	The original DAP specified that the HPV 16-related CIN 2/3 or worse cases among the 300 recipients of the monovalent HPV 16 vaccine were to be included in the primary efficacy analysis. However, due to the difficulty in interpretation in combining these with the HPV 16 AND 18-related cases from the quadrivalent HPV (Types 6, 11, 16, 18) L1 HPV vaccine recipients for comparison with placebo in Protocol 013, these cases will now be summarized separately.
Introduction – Description of the Study and Objectives/ Hypothesis, Study Designs (text and Table 2); **Efficacy Analyses** – Study Participant Populations; **Statistical Technical Issues** – Blinding/Unblinding; Statistical Methods, Missing Data	The serology assay has been changed from the competitive radioimmunoassay (cRIA) to the competitive Luminex immunoassay (cLIA) for Protocols 007, 013 and 015 in Table 2. In the text, the cLIA was specifically added or terminology was made more generic (i.e., changed from "cRIA" to "serology") to include the cLIA.	Use of the cRIA was discontinued during Protocol 007. The cLIA is being used for 007 and all subsequent studies.

Section	Change	Rationale for Change
Efficacy Analyses – Study Participant Populations	The section was restructured to propose new analysis populations for the secondary efficacy analysis.	Analysis populations for the secondary efficacy evaluation have been changed to incorporate the fact that the HPV assay results are only going to be available for non-vaccine HPV types only at baseline (rather than at baseline and Month 7).
Efficacy Analyses – Study Participant Populations	The MITT populations were re-ordered.	The re-ordering ensures consistency in the numbering of the MITTs in the study reports for the combined analysis and the individual studies.
Efficacy Analyses - Approaches to Efficacy Analyses; **Statistical Technical Issues** - Planned Statistical Power and Sample Size; Statistical Methods, Computation of Follow-up Time	The reference to a specific number of high risk HPV types for which assays will be available was removed.	The number of high risk HPV types for which assays will be available has changed.
Efficacy Analyses - Combining Studies for the Efficacy Assessment	Text was added to discuss the comparability of the cRIA and the cLIA.	Use of the cRIA was discontinued during Protocol 007. The cLIA is being used for 007 and all subsequent studies.
Interim Analyses/Data and Safety Monitoring Boards	Text was added to clarify that the secondary endpoint will be estimated only in the restricted MITT-2 and the MITT-3 populations.	Assay data for the non-vaccine HPV types will not be available at the interim analysis to allow for the type-specific estimation of the secondary endpoint.

Section	Change	Rationale for Change
Interim Analyses/Data and Safety Monitoring Boards; Statistical Technical Issues – Planned Statistical Power and Sample Size, Multiplicity	Text was added to introduce a test of the secondary hypothesis at the interim analysis.	This test was added to introduce a multiplicity adjustment to account for the early summary of the secondary endpoint.
Interim Analyses/Data and Safety Monitoring Boards; Statistical Technical Issues – Blinding/Unblinding	The language regarding sharing of interim results with a senior management committee in the event the interim data do not meet the statistical criteria for success has been removed.	The Sponsor has no intention of disseminating the data beyond the DSMB and unblinded statistician at this time should the interim data not meet the statistical criteria for success.

Data Analysis Plan

Efficacy of Merck's HPV L1 VLP Vaccine in the Reduction of HPV 16- and 18-Related Cervical Intraepithelial Neoplasia Grades 2 and 3 (CIN 2/3) and HPV 16- and 18-Related Cervical Carcinoma in Young Women

(Studies 005, 007, 013, and 015)

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EXECUTIVE SUMMARY

Background

Over 50% of sexually active adults will become infected with human papillomavirus (HPV) during their lifetime. HPV infection can result in genital warts and anogenital dysplasia that may result in cancer. These diseases are associated with substantial morbidity and mortality. Every year, 471,000 cases of cervical cancer are diagnosed worldwide. The 5-year survival for this disease is 70%. The impact of cervical cancer is accentuated by the fact that this disease generally affects women in their 30's to 50's, a time of peak productivity. In the developed world, routine Pap screening has reduced the incidence of cervical cancer by 75%. 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.

Over 90 HPV types have been identified. 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. Therefore, it is expected that a prophylactic quadrivalent HPV vaccine that reduces infection with these 2 HPV types will reduce the incidence of CIN 2/3 and cervical cancer.

The significant morbidity and mortality associated with HPV infection highlights the urgent need for effective preventive measures, particularly the need to consider approaches that will expedite access to a prophylactic HPV vaccine. However, 1 goal of a prophylactic vaccine's clinical development program is to provide an estimate of vaccine efficacy that has substantial precision, and since the precision of the estimate will be a function of sample size and the period of follow-up, a very large sample size and many years of follow-up will be required for substantial precision in the estimate of efficacy with respect to the incidence of CIN 2/3 and cervical cancer related to vaccine HPV types.

Merck is currently conducting 4 separate efficacy/immunogenicity trials of HPV vaccines (Protocol 005, 007, 013, and 015) which are similar in design and infrastructure. In particular, these studies have similar inclusion and exclusion criteria and mandate similar rigorous procedures for the collection of vaccine-HPV-related CIN and cervical cancer data (including frequent Pap testing, colposcopy performed by experienced colposcopists using similar guidelines, diagnosis of biopsy specimens by the same expert panel of pathologists, and HPV typing using similar HPV-localizing type-specific assays). While none of the 4 studies, individually, has adequate sample size to provide strong evidence (i.e., lower bound of the confidence interval for the vaccine efficacy >25%) that Merck's HPV L1 virus-like particle (VLP) vaccine reduces the incidence of vaccine HPV type-related CIN 2/3 and cervical carcinoma, an analysis of the combined data would have adequate power for such a demonstration and would improve the precision of the estimate of the vaccine efficacy.

Study Objectives and Hypotheses

The primary objective of the combined analysis of Protocols 005, 007, 013, and 015 is to demonstrate that intramuscular administration of a 3-dose regimen of Merck's HPV L1 VLP vaccine reduces the incidence of the composite endpoint of HPV 16- and 18-related high-grade cervical abnormalities (CIN 2/3) or HPV 16- and 18-related invasive cervical carcinoma in subjects who are seronegative and negative by a polymerase chain reaction (PCR) assay at baseline and PCR-negative 1 month after completion of the vaccination series for the relevant HPV type. The secondary objective is to demonstrate that intramuscular administration of a 3-dose regimen of Merck's HPV L1 VLP vaccine reduces the incidence of the composite endpoint of all high-grade cervical abnormalities (CIN 2/3) and cervical carcinoma in subjects who are **naïve at baseline** for high-risk HPV types.

The corresponding hypotheses are:

(1) Primary hypothesis: Administration of a 3-dose regimen of Merck's HPV L1 VLP vaccine reduces the incidence of the composite endpoint of HPV 16- or HPV 18-related CIN 2/3 or invasive cervical carcinoma compared with placebo in subjects who are PCR-negative and seronegative at baseline and PCR-negative 1 month after completion of the vaccination series for the relevant HPV type. *(The statistical criterion for success requires that the lower bound of the confidence interval for the vaccine efficacy exclude 25% or lower.)*

(2) Secondary hypothesis: Administration of a 3-dose regimen of Merck's HPV L1 VLP vaccine reduces the incidence of the composite endpoint of any CIN 2/3 or invasive cervical carcinoma compared with placebo in subjects who are **naïve at baseline** for high-risk HPV types. *(The statistical criterion for success requires that the lower bound of the confidence interval for the vaccine efficacy exclude 0%.)*

Efficacy Endpoints

The primary endpoint for this analysis is the composite endpoint of high-grade cervical dysplasia or cervical cancer related to HPV types 16 and 18. This endpoint will occur, if, on any single biopsy (Protocols 005, 007, 013, and 015), Endocervical Curettage (ECC) (Protocols 007, 013, and 015 only) or Loop Electrosurgical Excision Procedure (LEEP)/Conization Tissue Block (Protocols 007, 013, and 015 only), both of the following occur:

- Pathology panel consensus diagnosis of CIN 2, CIN 3, squamous carcinoma in situ, adenocarcinoma in situ, invasive squamous cervical carcinoma, or invasive adenocarcinoma of the cervix, and

- HPV 16 and/or HPV 18 detected in an adjacent section, defined as a positive HPV 16 or HPV 18 Thin-section PCR assay.

In Protocols 005 and 007, before development of the Thin-section PCR assay, the CIN 2/3 or worse endpoint was defined as:

- **A pathology panel consensus diagnosis of CIN 2, CIN 3, squamous carcinoma in situ, adenocarcinoma in situ, invasive squamous cervical carcinoma, or invasive adenocarcinoma of the cervix, and**

- HPV 16 **(Protocols 005 and 007) or HPV 18 (Protocol 007)** detected by Merck's Quantitative HPV PCR assay in biopsy tissue or **a biopsy swab (Protocol 007 only)** taken concurrently from the same lesion in which a Pathology-Panel-confirmed diagnosis of CIN was made, **and**

- **At least one cervicovaginal sample obtained from the subject at the visit antecedent to the biopsy is positive for the same HPV type.**

This definition applied to all biopsies in Protocol 005 and early biopsies in Protocol 007.

The secondary endpoint of interest is the combined incidence of all high-grade cervical dysplasia and cervical cancer. This endpoint will occur, if, on any single biopsy (Protocols 005, 007, 013, and 015), ECC (Protocols 007, 013, and 015 only) or LEEP/Conization Tissue Block (Protocols 007, 013, and 015 only), the pathology panel consensus diagnosis is CIN 2, CIN 3, squamous carcinoma in situ, adenocarcinoma in situ, invasive squamous cervical carcinoma, or invasive adenocarcinoma of the cervix.

Data Analysis and Decision Criterion

The final primary and secondary efficacy analyses will be conducted when fixed numbers of cases of the primary and secondary endpoints have been observed across all 4 studies. Specifically, the final analyses will be conducted when at least 48 cases of the primary endpoint *and* at least 141 cases of the secondary endpoint have been observed.

The primary analysis will be per-protocol. To address the primary hypothesis of the study, a one-sided test of the null hypothesis that the vaccine efficacy (defined as 100[1 - Relative Risk]) is ≤25% will be conducted. The alternative hypothesis is that the vaccine efficacy is >25%. A point estimate of the vaccine efficacy and the corresponding multiplicity-adjusted two-sided confidence interval will be provided. The null hypothesis will be rejected (i.e., success will be achieved) if the lower bound of the confidence interval exceeds 25%. An exact stratified analysis will be used with study as the stratification factor. Such an analysis will not adjust for extraneous factors such as age and number of lifetime sexual partners. Assuming a true vaccine efficacy of 80%, there is 96% power to show the lower bound of the confidence interval for the vaccine efficacy with respect to the primary endpoint excludes 25% when the 4 studies are combined.

The secondary hypothesis will be tested using the same methodology as the primary with a null hypothesis that the vaccine efficacy is ≤0%. Assuming a true vaccine efficacy of 40% against all CIN 2/3 and cervical cancer, the power for the secondary hypothesis is 84%.

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 the primary endpoint have been observed across all 4 studies. The interim analysis will involve a test of the primary hypothesis. It 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 the interim analysis of Protocol 015 meets the primary statistical criterion for success prespecified in that protocol (lower bound of the confidence interval for the vaccine efficacy >0%) *and* the interim analysis of the combined data sets meets the primary criterion for success prespecified in this data analysis plan (lower bound of the confidence interval for the vaccine efficacy >25%), then the vaccine will be submitted for regulatory review as soon as possible thereafter.

The final analysis of the primary endpoint will be conducted regardless of the outcome of the interim analysis. A multiplicity adjustment will be made to account for the 2 separate analyses of the combined data. A two-sided alpha of 0.0146 will be spent at the interim analysis, and a two-sided alpha of 0.0454 will be spent at the final analysis. The power for the interim analysis, assuming different values for the true vaccine efficacy, is given in Table 1.

Table 1

Power for the Interim Analysis of the Combined Data Sets

Vaccine Efficacy Threshold to be Excluded by Lower Bound of Confidence Interval	True Vaccine Efficacy	Power for the Lower Bound of the 98.5% Confidence Interval to Exclude the Vaccine Efficacy Threshold at the Interim Analysis
25% or lower	80%	**69%**
	85%	**87%**
	90%	**97%**

Note that the power for the interim analysis of Protocol 015 is 80%, assuming a true vaccine efficacy of 80%.

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 assess the efficacy of Merck's HPV vaccines, particularly the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, in the reduction of HPV 16- and 18-related cervical intraepithelial neoplasia Grades 2 and 3 (CIN 2/3) and HPV 16- and 18-related cervical carcinoma in young women through a combined analysis of the Phase IIb and Phase III protocols. The protocols covered by this DAP are:

- Protocol 005: Study of Pilot Manufacturing Lot of HPV 16 Virus-Like Particle (VLP) Vaccine in the Prevention of HPV Infection in 16- to 23-Year-Old Females
- Protocol 007: A Placebo-Controlled, Dose Ranging Study of Quadrivalent HPV Virus-Like Particle (VLP) Vaccine in 16- to 23-Year-Old Women
- Protocol 013: A Study to Evaluate the Efficacy of Quadrivalent HPV (Types 6, 11, 16, and 18) L1 Virus-Like Particle (VLP) Vaccine in regards to the Incidence of HPV 6/11-, 16- and 18-related CIN and HPV 6/11-related Genital Warts in 16- to 23-Year Old Women—The FUTURE Study
- Protocol 015: A Randomized, International, Placebo-Controlled, Double Blind Study to Investigate the Safety, Immunogenicity and Efficacy on the Incidence of HPV 16/18-related CIN 2/3 or Worse of Quadrivalent HPV Virus-Like Particle (VLP) Vaccine in 16- to 23-Year Old Women—The FUTURE II Study

B. Description of the Study and Objectives/Hypotheses

1. Study Designs

The study designs of Protocols 005, 007, 013, and 015 are summarized in Table 2. All are prospective, randomized, double-blind, placebo-controlled, parallel, multicenter studies operating under in-house blinding procedures. Different HPV vaccines are administered in Protocol 005 (monovalent) and Protocols 007, 013, and 015 (quadrivalent) (see Table 2). However, vaccine or placebo is administered at 0, 2, and 6 months in each of the studies. Subjects return to the study site for collection of specimens, gynecologic examinations and/or Pap tests at follow-up visits Postdose 3. In Protocols 005, 007, and 013, the follow-up visits occur approximately every 6 months, but the visit schedule differs slightly from protocol to protocol (see Table 2). In Protocol 015, the follow-up visits occur approximately every 12 months.

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

Table 2

Study Design Comparison of Protocols 005, 007, 013, and 015

Design Feature	Protocol 005	Protocol 007	Protocol 013	Protocol 015
General				
Sample size	**2391**	**552**	~5700	~11,500
Study dates	1998 to 2004	2000 to 2004	2001 to **2007**	2002 to **2007**
Study sites	U.S., Multicenter	International, Multicenter	International, Multicenter	International, Multicenter
Study design	Prospective, parallel	Prospective, parallel	Prospective, parallel	Prospective, parallel
Blinding	Double-blind, In-house Blinding	Double-blind, In-house Blinding	Double-blind, In-house Blinding	Double-blind, In-house Blinding
Main efficacy cohort	Baseline HPV 16-naïve subjects (only HPV 16-related endpoints collected)	Baseline HPV 16-naïve subjects (HPV 16 endpoints), HPV 18-naïve subjects (HPV 18 endpoints), and HPV 6/11-naïve subjects (HPV 6/11 endpoints)	Baseline HPV 16-naïve subjects (HPV 16 endpoints), HPV 18-naïve subjects (HPV 18 endpoints), and HPV 6/11-naïve subjects (HPV 6/11 endpoints)	Baseline HPV 16-naïve subjects (HPV 16 endpoints), HPV 18-naïve subjects (HPV 18 endpoints)
Study vaccine	HPV 16 Vaccine 40 µg or Placebo	Quadrivalent HPV Vaccine 20/40/40/20 µg or Placebo	Quadrivalent HPV Vaccine 20/40/40/20 µg, **HPV 16 Vaccine 40 µg** or Placebo	Quadrivalent HPV Vaccine 20/40/40/20 µg or Placebo
Vaccination regimen	0, 2, 6 months	0, 2, 6 months	0, 2, 6 months	0, 2, 6 months
Visit schedule for gynecologic exam, specimen collection and/or Pap tests	Months 0, 7, 12, 18, 24, 30, 36, 42 and 48	Months 0, 7, 12, 18, 24, 30, and 36	Months 0, 3, 7, 12, 18, 24, 30, and 36	Months 0, 7, 12, 24, 36 and 48
Assays performed to ensure subjects are HPV vaccine-type naïve at baseline and through 1-month postdose 3 (Month 7)	Serum RIA and (b)(4) at enrollment; PCR on (b)(4) swab, (b)(4) and (b)(4) swabs and (b)(4) at enrollment and Month 7	Serum **cLIA** at enrollment; PCR on (b)(4) swab, (b)(4) and (b)(4) swab and (b)(4) swabs at enrollment and Month 7	Serum **cLIA** at enrollment; PCR on (b)(4) swab and (b)(4) and (b)(4) swabs at enrollment, Month 3 and Month 7	Serum **cLIA** at enrollment; PCR on (b)(4) swab and (b)(4) and (b)(4) swabs at enrollment and Month 7

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

Table 2 (Cont.)

Study Design Comparison of Protocols 005, 007, 013, and 015

Design Feature	Protocol 005	Protocol 007	Protocol 013	Protocol 015
Inclusion/Exclusion Criteria				
Gender	Women	Women	Women	Women
Age	16 to 23 years	16 to 23 years	16 to 23 years	16 to **26** years
Lifetime male sexual partner number	0 to 5	0 to 4	0 to 4	0 to 4
Previous abnormal Pap	Not Allowed	Not Allowed	Not Allowed	Not Allowed
Previous HPV disease	Not Allowed	Not Allowed	Not Allowed	Not Allowed
Cervical Cancer Screening				
Program structure	No Paps outside of study allowed	No Paps outside of study allowed	No Paps outside of study allowed	No Paps outside of study allowed
ThinPrep™ Pap Test	Yes	Yes	Yes	Yes
Central laboratory reading	5 Regional Labs	(b)(4)	(b)(4)	(b)(4)
Timing of Pap screening	Approximately every 6 months	Approximately every 6 months	Approximately every 6 months	Approximately every 12 months
Screening triage strategy	Voluntary	Voluntary	Mandatory	Mandatory
Minimal Pap abnormality for referral	ASCUS	ASCUS, HPV (+) on HC-II	ASCUS, HPV (+) on HC-II	ASCUS, HPV (+) on HC-II

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

Table 2 (Cont.)

Study Design Comparison of Protocols 005, 007, 013, and 015

Design Feature	Protocol 005	Protocol 007	Protocol 013	Protocol 015
Colposcopy, Biopsy, and LEEP				
Program structure	Colposcopy outside of study not allowed	Colposcopy outside of study not allowed	Colposcopy outside of study not allowed	Colposcopy outside of study not allowed
Requirement for biopsy	All abnormal areas sampled	All abnormal areas sampled	All abnormal areas sampled	All abnormal areas sampled
Biopsy technique	Separate forceps/block for each lesion	Separate forceps/block for each lesion	Separate forceps/block for each lesion	Separate forceps/block for each lesion
Laboratory processing	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Pathology reading (routine)				
Pathology reading (endpoints)				
HPV causality assessment	Merck HPV PCR assay on frozen biopsy specimens	Merck HPV PCR assay on paraffin-embedded specimens	Merck HPV PCR assay on paraffin-embedded specimens	Merck HPV PCR assay on paraffin-embedded specimens
LEEP tissue analyzed	Biopsies from LEEP material[§]	Entire LEEP specimen	Entire LEEP specimen	Entire LEEP specimen

† Starting in Feb-2000.
‡ Until Oct-2000, Pathologists were (b)(4)
§ LEEP Material included in Protocol 005 as of 19-Sep-2000.
RIA = Radioimmunoassay.
cLIA = Luminex immunoassay.
(b)(4)
PCR = Polymerase Chain Reaction.
ASCUS = Atypical Squamous Cells of Undetermined Significance.
HC-II = Hybrid Capture II.
LEEP = Loop Electrosurgical Excision Procedure.

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

With respect to the efficacy evaluation outlined in this DAP, procedures performed at both scheduled and unscheduled visits will provide efficacy data. The procedures performed at scheduled visits for the purpose of efficacy data collection include serum sample collection at enrollment, collection of cervicovaginal specimens at enrollment and Month 7 (and Month 3 in Protocol 013) and Pap testing at Month 7 and all subsequent visits. The procedures that are typically performed at unscheduled visits for the purpose of efficacy data collection are repeat Pap tests, colposcopy, and biopsy following Month 7.

The serum samples collected at enrollment are tested for antibody to HPV vaccine types using a radioimmunoassay (RIA) **or Luminex immunoassay (cLIA)** (b)(4) (b)(4) in Protocol 005). The cervicovaginal specimens are tested for HPV vaccine-type DNA using type-specific PCR assays. The **serology** results at enrollment, along with the PCR results from the cervicovaginal specimens collected at enrollment and Month 7 (and Month 3 in Protocol 013), are used to exclude subjects who are positive for vaccine HPV types at baseline or develop infection before 1 month following the administration of the 3rd dose of the vaccination regimen from the evaluation of vaccine efficacy.

The same procedures for sample collection are used in each of the 4 studies. However, the cervicovaginal specimens that are collected differ slightly from study to study (see Table 2), and Protocol 013 has samples collected at Month 3, whereas Protocols 005, 007, and 015 do not.

In each of the protocols, the results of the Pap tests performed at Month 7 and subsequent visits are used to identify subjects with HPV disease. Protocol-specified guidelines, which are mandatory in Protocols 013 and 015 but not in Protocols 005 and 007, are used to triage subjects with Pap abnormalities to colposcopy. Colposcopy is performed by an experienced colposcopist who has been trained in protocol-specific colposcopy procedures. If a lesion is seen on colposcopy, it is biopsied.

All biopsies in the 4 studies are read by a pathologist at a central laboratory for the purpose of patient management. However, the biopsies are also read by an independent panel of expert pathologists who will provide the final pathologic diagnosis for study purposes. To determine the causal HPV type within a cervical biopsy for efficacy assessments, Merck's type-specific HPV PCR assays are performed on the tissue

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

samples. Frozen tissue samples from the biopsied lesions are tested by PCR in Protocol 005. In Protocols 007, 013, and 015, an HPV type-specific localizing assay (HPV Type-Specific Thinsection PCR Assay) is performed on paraffin-embedded tissue samples.

All of the subjects in Protocol 005 (n=**2391**) will contribute to the combined analysis of HPV vaccine-type-related CIN 2/3 and cervical cancer. However, since a monovalent HPV 16 vaccine was administered in Protocol 005, these subjects will only be eligible to contribute cases of HPV 16-related CIN 2/3 or cervical cancer to the primary analysis.

Protocol 007 is being conducted in 2 parts, Part A and Part B. Since Part A is a small randomized, double-blind, placebo-controlled, multicenter, sequential dose-escalating study that is not operating under in-house blinding procedures, the 52 subjects enrolled in Part A will not contribute to the combined efficacy evaluation outlined in this DAP. Part B of Protocol 007 is a randomized, double-blind, placebo-controlled, multicenter dose-ranging study operating under in-house blinding procedures. A total of 1103 subjects were enrolled and randomized to receive 1 of 3 formulations of quadrivalent (HPV 6, 11, 16, 18) VLP vaccine or placebo. However, since only 1 of the 3 quadrivalent vaccine formulations in Protocol 007 will be used in Phase III, only one-third of the vaccine recipients in Protocol 007 (those receiving the final dose selected for Phase III) and the placebo recipients will be eligible to contribute efficacy data to the analyses outlined in this DAP. Thus, only **277** vaccine recipients and **275** placebo recipients from Protocol 007 will contribute to the analyses. Since quadrivalent HPV vaccine is being administered in Protocol 007, Protocol 007 subjects will contribute cases of HPV 16- and 18-related CIN 2/3 and cervical cancer to the primary analysis.

Approximately 5700 subjects will be enrolled in Protocol 013. Of these, ~5400 subjects will be randomized to receive either quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine or placebo. The additional 300 subjects will be randomized to receive monovalent HPV 16 vaccine for an immunogenicity bridge with Protocol 005. **The 5400 subjects randomized to receive quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine or placebo will contribute cases of HPV 16- and 18-related CIN 2/3 and cervical cancer to the primary analysis. The HPV 16-related CIN 2/3 and cervical cancer cases among the 300 subjects randomized to receive monovalent HPV 16 vaccine will not be included in the combined vaccine efficacy estimate. This is because it would be very difficult to interpret the vaccine efficacy**

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

estimate within Protocol 013 if only the HPV 16-related cases among these 300 subjects were pooled with the HPV 16 AND 18-related cases among the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine recipients for comparison with a placebo group in which the HPV 16 AND 18-related cases will be counted. The HPV 16-related CIN 2/3 and cervical cancer cases among the 300 subjects randomized to receive monovalent HPV 16 vaccine in Protocol 013 will be summarized separately.

All of the 11,500 subjects enrolled in Protocol 015 will be included in the analyses outlined in this DAP. Since quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine will be administered, the subjects in Protocol 015 will contribute cases of HPV 16- and 18-related CIN 2/3 and cervical cancer to the primary analysis.

It should be noted that in Protocols 007 and 013, subjects undergo rigorous procedures for genital wart ascertainment, since genital warts related to the vaccine HPV types are co-primary endpoints with CIN related to the vaccine HPV types. However, development of genital warts does not prevent a subject from becoming a case of CIN in these studies. Subjects who qualify as a case according to the genital wart definition continue to be followed for the CIN endpoints.

2. Primary Objective

To demonstrate that intramuscular administration of a 3-dose regimen of Merck's HPV L1 VLP vaccine reduces the incidence of the composite endpoint of HPV 16- and 18-related high-grade cervical abnormalities (CIN 2/3) or HPV 16- and 18-related invasive cervical carcinoma in subjects who are PCR-negative and seronegative at baseline and PCR-negative 1 month after completion of the vaccination series for the relevant HPV type.

3. Secondary Objective

To demonstrate that intramuscular administration of a 3-dose regimen of Merck's HPV L1 VLP vaccine reduces the incidence of the composite endpoint of all high-grade cervical abnormalities (CIN 2/3) and cervical carcinoma in subjects who are **naïve at baseline** for high-risk HPV types.

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

4. Primary Hypothesis

Administration of a 3-dose regimen of Merck's HPV L1 VLP vaccine reduces the incidence of the composite endpoint of HPV 16- or HPV 18-related CIN 2/3 or invasive cervical carcinoma compared with placebo in subjects who are PCR-negative and seronegative at baseline and PCR-negative 1 month after completion of the vaccination series for the relevant HPV type. *(The statistical criterion for success requires that the lower bound of the confidence interval for the vaccine efficacy exclude 25% or lower.)*

5. Secondary Hypothesis

Administration of a 3-dose regimen of Merck's HPV L1 VLP vaccine reduces the incidence of the composite endpoint of any CIN 2/3 or invasive cervical carcinoma compared with placebo in subjects who are **naïve at baseline** for high-risk HPV types. *(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, and number of lifetime sexual partners will be summarized by study and treatment group, across studies by treatment group, and in total for all subjects enrolled in the 4 studies. In addition, for Protocols 007, 013, and 015, baseline serostatus for HPV 16 and 18 and PCR status for HPV 16 and 18 at enrollment and Month 7 will be presented by study and treatment group, across studies by treatment group, and in total. For Protocol 005, HPV 16 serostatus at enrollment and HPV 16 PCR status at enrollment and Month 7 will be presented by treatment group. Balance among studies and between treatment groups with respect to subject characteristics will be determined by observation.

III. EFFICACY ANALYSES

A. Efficacy Endpoints

1. Primary Endpoint

The primary endpoint for this analysis is the composite endpoint of high-grade cervical dysplasia or cervical cancer related to HPV types 16 and 18. This endpoint will occur, if, on any single biopsy (Protocols 005, 007, 013, and 015), Endocervical Curettage (ECC) (Protocols 007, 013, and 015 only) or Loop Electrosurgical Excision Procedure (LEEP)/Conization Tissue Block (Protocols 007, 013, and 015 only), both of the following occur:

- Pathology panel consensus diagnosis of CIN 2, CIN 3, squamous carcinoma in situ, adenocarcinoma in situ, invasive squamous cervical carcinoma, or invasive adenocarcinoma of the cervix, and

- HPV 16 and/or HPV 18 detected in an adjacent section, defined as a positive HPV 16 or HPV 18 Thin-section PCR assay.

In Protocols 005 and 007, before development of the Thin-section PCR assay, the CIN 2/3 or worse endpoint was defined as:

- **A pathology panel consensus diagnosis of CIN 2, CIN 3, squamous carcinoma in situ, adenocarcinoma in situ, invasive squamous cervical carcinoma, or invasive adenocarcinoma of the cervix, and**

- HPV 16 **(Protocols 005 and 007) or HPV 18 (Protocol 007)** detected by Merck's Quantitative HPV PCR assay in biopsy tissue or **a biopsy swab (Protocol 007 only)** taken concurrently from the same lesion in which a Pathology-Panel-confirmed diagnosis of CIN was made, **and**

- **At least one cervicovaginal sample obtained from the subject at the visit antecedent to the biopsy is positive for the same HPV type.**

This definition applied to all biopsies in Protocol 005 and early biopsies in Protocol 007.

2. Secondary Endpoint

The secondary endpoint of interest is the combined incidence of all high-grade cervical dysplasia and cervical cancer. This endpoint will occur, if, on any single biopsy (Protocols 005, 007, 013, and 015), ECC (Protocols 007, 013, and 015 only) or LEEP/Conization Tissue Block (Protocols 007, 013, and 015 only), the pathology panel consensus diagnosis is CIN 2, CIN 3, squamous carcinoma in situ, adenocarcinoma in situ, invasive squamous cervical carcinoma, or invasive adenocarcinoma of the cervix.

B. Study Participant Populations

1. Primary Endpoint

Four patient populations will be considered for the **primary efficacy endpoint**: 1 per-protocol population and 3 modified intention-to-treat (MITT) populations. The efficacy analysis using the per-protocol population will be the primary analysis. The 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:

a. receive all 3 injections with the correct dose of the correct clinical material,

b. be seronegative by RIA **or cLIA** (and (b)(4) in Protocol 005) to the appropriate HPV types before the first injection and PCR-negative to the appropriate HPV types through Month 7,

c. not receive any nonstudy inactivated vaccine within 14 days of a study vaccine or any nonstudy live virus vaccine within 21 days before or 14 days after a study vaccine,

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

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

B. Study Participant Populations (Cont.)

f. 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,

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

Only subjects who are HPV 16 seronegative at enrollment and HPV 16 PCR-negative from enrollment through Month 7 will be eligible to be counted as cases of HPV 16-related CIN 2/3 or cervical cancer. The same rules apply for HPV 18. **Therefore, to be included in the per-protocol population for the primary efficacy analysis regarding CIN 2/3 and cervical cancer related to the high-risk vaccine HPV types (HPV 16 and 18), subjects are required to be seronegative at enrollment and PCR-negative from enrollment through Month 7 to HPV 16, HPV 18, or both.**

Modified Intention-to-Treat Populations

The first MITT analysis will include all subjects who are seronegative at enrollment and PCR-negative from enrollment through Month 7 to the appropriate HPV types, 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. The **second** MITT analysis will include all subjects who are seronegative and PCR-negative at baseline to the appropriate HPV types, who receive at least 1 dose of HPV 16 monovalent vaccine, quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine, or placebo, and who have any follow-up visit after 1 month following the first injection. Finally, the **third** MITT analysis will include all subjects who receive at least 1 dose of HPV 16 monovalent vaccine, quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine, or placebo and who have any follow-up visit following the first injection, regardless of initial serology and PCR status.

B. Study Participant Populations (Cont.)

2. Secondary Endpoint

The principal approach to the secondary efficacy analysis regarding all CIN 2/3 and cervical cancer will utilize a population similar to the MITT-2 population described above. Only subjects who are HPV 16 seronegative and PCR-negative at enrollment will be eligible to be counted as cases of HPV 16-related CIN 2/3 or cervical cancer. The same rules apply for the other vaccine HPV types (HPV 6, 11, and 18). For each of the non-vaccine HPV types for which PCR assays are available (mostly likely HPV types 31, 45, 52, 58, and 59), only subjects who are PCR-negative at enrollment will be eligible to be counted as cases of CIN 2/3 or cervical cancer related to that type. (No baseline serology testing will be performed for the non-vaccine high-risk HPV types. Therefore, for a given type, all subjects who are PCR-negative at enrollment, even though they may be baseline seropositive for that type, will be eligible to be counted as cases of CIN 2/3 or cervical cancer 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.) **For any non-vaccine HPV type for which a PCR assay is not available, a subject will be required to have a normal Pap test result at enrollment to be eligible to be counted as a case of CIN 2/3 or cervical cancer related to that type. In this case, the normal Pap test result is used as a proxy for the PCR result. Although, it does not ensure that a subject is negative for a given HPV type at baseline, it does give an indication that the subject is free from disease for that type.**

Two supporting analyses of the secondary efficacy endpoint will be conducted to assess the impact of the vaccine on this endpoint from a population benefit point of view. The first will be conducted in a "restricted MITT-2" population. This population will include all subjects who are seronegative and PCR negative at enrollment to all vaccine HPV types, who are PCR negative at enrollment for the non-vaccine HPV types for which PCR assays are available AND who have a normal Pap test result at enrollment. The analysis performed in the restricted MITT-2 population is intended provide a "real world" estimate of the impact of the vaccine with regard to CIN 2/3 or worse among baseline HPV-naïve women. The second supporting analysis will be conducted in the MITT-3 population as described above for the primary endpoint.

B. Study Participant Populations (Cont.)

Pooling of Subjects

With the exception of the 300 monovalent HPV 16 vaccine recipients in Protocol 013, the vaccine and placebo recipients will be pooled across the studies for analysis. However, since the vaccine recipients in Protocol 005 received a monovalent HPV 16 vaccine and the vaccine recipients in Protocols 007 and 015 and 5400 of the subjects in Protocol 013 received a quadrivalent HPV vaccine, the subjects in Protocol 005 will only contribute HPV 16-related disease endpoints to the primary analysis. Similarity in immune responses between recipients of the monovalent HPV 16 vaccine and the quadrivalent HPV vaccine will be established in Protocol 012 (a sub-study of Protocol 013) to justify the pooling of the subjects receiving the monovalent vaccine in Protocols 005 with the subjects receiving the quadrivalent vaccine in Protocols 007, 013, and 015 for analysis.

C. Approaches to Efficacy Analysis

The final primary and secondary efficacy analyses will be conducted when fixed numbers of cases of the primary and secondary endpoints have been observed across all 4 studies. Specifically, the final analyses will be conducted when at least 48 cases of the primary endpoint *and* at least 141 cases of the secondary endpoint have been observed.

To address the primary hypothesis of the study, a one-sided test of the null hypothesis that the vaccine efficacy (defined as 100[1 - Relative Risk]) is ≤25% will be conducted. The alternative hypothesis is that the vaccine efficacy is >25%. A point estimate of the vaccine efficacy and the corresponding multiplicity-adjusted two-sided confidence interval will be provided. The null hypothesis will be rejected (i.e., success will be achieved) if the lower bound of the confidence interval exceeds 25%. An exact stratified analysis will be used with study as the stratification factor. Such an analysis will not adjust for extraneous factors such as age and number of lifetime sexual partners. The secondary hypothesis will be tested using the same methodology with a null hypothesis that the vaccine efficacy is ≤0%.

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 endpoint for the primary analysis is a composite endpoint, any subject who is eligible to be an endpoint according to the HPV 16-related disease definition, the HPV 18-related disease definition, or both will be included in the population at risk for the primary analysis. **It is anticipated that all subjects will be included in the population at risk for the secondary analysis, since all subjects should be eligible to be an endpoint with respect to at least 1**

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

high-risk HPV type. The method that will be used to compute the follow-up time for each subject in the population at risk is described in Section V.D.4. Since a monovalent HPV 16 vaccine was administered in Protocol 005, any cases of HPV 18-related disease that occur in this study will not be counted as endpoints for the analysis of the vaccine efficacy with respect to vaccine HPV types. **(Cases of HPV 16-related disease that occur in the 300 subjects who received monovalent HPV 16 vaccine in Protocol 013 will not be included in the HPV vaccine-type-related disease analysis but will be summarized separately due to the difficulty in interpreting the efficacy estimate within Protocol 013 which would arise were these cases to be pooled with the HPV 16 AND 18-related cases observed in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group for comparison with the HPV 16 AND 18-related cases in the placebo group.)**

For the analysis of the vaccine efficacy with respect to the *all* CIN 2/3 or worse endpoint, the cases of HPV 18-related disease in Protocol 005 and among the 300 subjects administered monovalent HPV 16 vaccine in Protocol 013 will be counted as endpoints. This may lead to an underestimate of the vaccine efficacy with respect the all CIN 2/3 or worse endpoint in these studies. Thus, this approach is conservative. However, since the number of HPV 18-related CIN 2/3 or worse cases that are expected in Protocol 005 and among the 300 subjects administered monovalent HPV 16 vaccine in Protocol 013 is small, the impact of this approach on the overall vaccine efficacy with respect to all CIN 2/3 or worse should be minor.

D. **Combining Studies for the Efficacy Assessment**

1. **Standardization of Procedures for Endpoint Collection**

An analysis that combines Protocols 005, 007, 013, and 015 for the evaluation of the efficacy of the HPV vaccine in reducing HPV 16- and 18-related CIN 2/3 or cervical cancer is justified by the similarity in the protocols with respect to study design and the procedures for endpoint collection.

a. **General Study Design**

With respect to the study populations, female subjects 16 to 23 years of age are being studied in all 4 protocols. The study criteria for inclusion and exclusion are nearly identical in the 4 studies as well. With respect to the treatment plan, the women in each study are randomized to receive HPV vaccine or placebo in a 0-, 2-, and 6-month regimen.

D. Combining Studies for the Efficacy Assessment (Cont.)

b. Cytology

The intervals for Pap screening are similar in the 4 protocols. Protocols 005, 007, and 013 require Pap screening approximately every 6 months, while Protocol 015 requires Pap screening approximately every 12 months. Cytological evaluation for the subjects is performed within the context of the 4 studies using the ThinPrep™ Pap Test. In Protocol 007, 013 and 015, all ThinPrep™ Pap Tests are read in a single central laboratory. In Protocol 005, Pap tests were read at 1 of 5 regional central laboratories. Similar protocol-prescribed guidelines for referral of subjects with Pap test abnormalities to colposcopy and biopsy and similar guidelines for the treatment of confirmed cervical pathology are provided in the 4 protocols. In general, subjects with a diagnosis of Atypical Squamous Cells of Undetermined Significance (ASCUS) or greater on 2 visits were referred for colposcopy early in Protocols 005 and 007. Subjects with a diagnosis of ASCUS or greater combined with a positive Hybrid Capture II (HC-II) HPV test are referred for colposcopy in Protocols 013 and 015 and later in Protocols 005 and 007. These 2 triage guidelines have comparable sensitivity for detection of CIN 2/3 and cervical cancer. The protocol-specified triage guidelines are voluntary in Protocols 005 and 007 and mandatory in Protocols 013 and 015. Thus, there will be more uniformity in triage patterns in Protocols 013 and 015. It is not anticipated, however, that there will be differences in ascertainment of lesions among studies, as the threshold for colposcopy in all protocols was very low. In addition, Protocols 005 and 007 were amended to introduce an exit colposcopy to ensure complete ascertainment of cases in the context of the voluntary triage guidelines.

c. Colposcopy

In all 4 studies, colposcopies are performed at the study site. Subjects who undergo colposcopy also undergo biopsy, if indicated. Colposcopy is performed only by an experienced colposcopist (>50 colposcopies per year for at least 2 years).When biopsies are performed, the slides of cervical biopsy specimens are prepared at a central laboratory and reviewed by a pathologist on site for the purpose of patient management. Therefore, uniform fixation, processing, and sectioning methods are used and are under the control of the single central laboratory for standardization of the reading of cytology and histopathology. The same central laboratory equipment and pathologists are handling the biopsy specimens from all 4 studies.

D. Combining Studies for the Efficacy Assessment (Cont.)

d. Pathology Panel

A pathology panel consisting of up to 4 independent pathologists reviews all cervical biopsy slides and adjudicates all cervical pathology for the purpose of providing the official pathologic diagnosis for the analysis of vaccine efficacy. The SPONSOR and pathology panel follow established guidelines for review of the slides. Each pathology panel member independently reviews the slides, blinded to treatment and the subject's HPV PCR status, to formulate a consensus. The consensus diagnosis of this panel will represent the final diagnosis for study purposes. The membership of the pathology panel will remain basically the same throughout the 4 studies, ensuring that the same pathologists are reading the biopsies (there was 1 substitution in 2000, prior to the initiation of Protocols 007, 013, and 015).

e. HPV Assays

Similar assays are being used for HPV analysis in all 4 protocols:

1) Comparable PCR assays are used to measure whether subjects are infected with vaccine HPV types at enrollment and to detect the onset of new HPV infection during the vaccination period. A (b)(4) PCR assay was used at the beginning of Protocols 005 and 007. This assay was later replaced by a (b)(4) PCR assay that was also used in Protocols 013 and 015. A cross-validation of the 2 assays, performed by MRL, has shown that the assays produce comparable results.

2) **Serology assays using comparable methodology were used to measure HPV type-specific antibodies. In Protocol 005, a competitive radioimmunoassay (cRIA) and an (b)(4) (b)(4) were used. A competitive Luminex immunoassay (cLIA) was used in Protocols 007, 013, and 015. All assays were type-specific. All assays measured anti-HPV levels by competition against a known neutralizing assay.**

D. Combining Studies for the Efficacy Assessment (Cont.)

3) Similar localizing PCR assays are used to determine the causal HPV type within cervical biopsy specimens. For Protocol 005, DNA for PCR analysis was obtained from frozen tissue specimens immediately adjacent to biopsies performed for the purpose of pathologic diagnosis. For Protocols 007, 013, and 015, a single paraffin-embedded biopsy specimen is being used for both pathologic diagnoses and PCR assays. Here, adjacent sections are stained for H&E (pathology diagnosis) and PCR analysis (determination of causal HPV type).

2. Assessment of Homogeneity

Although the 4 studies being combined to address the objectives of this DAP are similar in many ways, there are small differences among them that should be acknowledged. For example, Protocols 007, 013, and 015 are international studies, while Protocol 005 is conducted strictly in the United States. In Protocol 013, the additional study visit at Month 3 may cause more subjects to be excluded from the analysis due to PCR positivity for the vaccine HPV types than in Protocols 005, 007, and 015. In Protocols 005 and 007, colposcopies and biopsies are performed based on voluntary Pap triage guidelines, whereas Protocols 013 and 015 have mandatory Pap triage guidelines. Protocol 015 requires Pap screening every 12 months, while Protocols 005, 007, and 013 require Pap screening every 6 months. This could prove to be a less sensitive screening plan for ascertaining endpoints. Protocols 007, 013, and 015 study a quadrivalent HPV vaccine, while Protocol 005 studies a monovalent HPV 16 vaccine. To assess statistically the homogeneity in the studies, an exact test of the homogeneity in relative risks among the 4 studies will be conducted before the studies are combined for an overall estimate of the vaccine efficacy. Assuming the relative risk is homogeneous among the studies, the common relative risk, and hence, the common vaccine efficacy, will be estimated using an exact stratified approach.

While small differences and imbalances will exist among the individual studies, it is expected that the overall vaccine efficacy with respect to the endpoints described in this DAP will be high and that these differences will have no impact on the overall study conclusions or on the ability of the studies to be combined in a single analysis. Nevertheless, any differences or imbalances observed among the studies will be described in the combined study report.

IV. INTERIM ANALYSES/DATA AND SAFETY MONITORING BOARDS

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 the primary endpoint have been observed across all 4 studies. The interim analysis will involve a test of the primary hypothesis. **A test of the secondary hypothesis will also be conducted in only the restricted MITT-2 population and the MITT-3 population.**

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. By the time the required numbers of cases are observed, Protocols 005 and 007 should be complete, and the complete data from these studies should be screened and cleaned. However, for all of the studies, the critical database fields for identifying protocol violators, identifying cases, and conducting the primary analysis will be identified, and all critical data that are in-house will be screened prior to the interim analysis. A separate document outlining the critical data fields and detailed screening plan will be written.

The interim analysis of the data from the combined studies will be performed by a designated unblinded statistician unrelated to any of the studies. The unblinded statistician will provide the results of the analysis to a data and safety monitoring board (DSMB) along with the results of the interim analysis of the CIN 2/3 study (Protocol 015). If the interim analysis of Protocol 015 meets the primary statistical criterion for success prespecified in that protocol (lower bound of the confidence interval for the vaccine efficacy >0%) *and* the interim analysis of the combined data sets meets the primary criterion for success prespecified in this data analysis plan (lower bound of the confidence interval for the vaccine efficacy >25%), then the DSMB will communicate this information to the HPV vaccine project team at the SPONSOR, and the project team will proceed with submission for regulatory review. At that time, for Protocols 005, 007, and 015, any remaining unscreened data in the official clinical database (the non-critical data) that were collected prior to the interim analysis will be screened and cleaned by a designated clinical, statistical, and data management team. The database will be audited and a copy will be unblinded and frozen.

IV. INTERIM ANALYSES/DATA AND SAFETY MONITORING BOARDS (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 (Protocol 013's endpoints are CIN 1 or worse and genital warts; the combined analysis endpoint is CIN 2/3 or worse), 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 that study have been observed. 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. Once the required numbers of primary endpoints are observed in Protocol 013, the complete data in the official clinical database will be screened and cleaned by the designated clinical, statistical, and data management team. The database will be audited and a copy will be unblinded and frozen.

Once the databases for the 4 studies are unblinded and frozen, the designated statistical team will analyze the trial data and prepare the submission for regulatory review. The results will then be disclosed to the regulatory agency as part of the submission.

It is important to note that the CIN 2/3 endpoints in the *complete* data set from Protocol 013 will be included in the submission. These may or may not be the same Protocol 013 CIN 2/3 endpoints that are included in the combined CIN 2/3 interim analysis. If the required numbers of primary endpoints for Protocol 013 are observed *before* the combined CIN 2/3 interim analysis is performed, then the Protocol 013 CIN 2/3 endpoints from the complete data set will be included in the interim analysis as well. However, if the required numbers of primary endpoints in Protocol 013 do not accrue by the time the combined CIN 2/3 interim analysis is performed, the Protocol 013 CIN 2/3 cases that are included in the interim combined analysis will not be from the complete data set. They will be preliminary numbers. Therefore, the CIN 2/3 cases from Protocol 013 that contribute to the *decision* to proceed to an early submission may be fewer in number than those that are actually included in the submission, and they may reflect a slightly different efficacy contribution from Protocol 013 to the overall efficacy estimate from the 4 studies.

IV. INTERIM ANALYSES/DATA AND SAFETY MONITORING BOARDS (CONT.)

If either the interim analysis of the CIN 2/3 study or the interim analysis of the combined data sets fails to meet the statistical criterion for success at the interim time point, the DSMB will communicate this information to the HPV vaccine project team at the SPONSOR, and the project team will not proceed with a submission to regulatory authorities at that time.

The final analysis of the combined studies will be performed when at least 48 cases of the primary endpoint and at least 141 cases of the secondary endpoint are observed regardless of the outcome of the interim analysis. This will allow for an assessment of longer-term vaccine efficacy and will allow a sufficient number of cases of CIN 2/3 or worse due to any cause to accrue for the secondary analysis. A multiplicity adjustment will be made to account for the 2 separate analyses of the combined data. A two-sided alpha of 0.0146 will be spent at the interim analysis, and a two-sided alpha of 0.0454 will be spent at the final analysis.

V. STATISTICAL TECHNICAL ISSUES

A. Planned Statistical Power and Sample Size

The attrition rate in each protocol is expected to be no more than 15% through Month 7 and no more than 6% per year thereafter. In addition, it is expected that ~18% of the subjects in each study will be seropositive at enrollment or PCR-positive prior to or at Month 7 for each of HPV 16 and HPV 18. It is assumed that ~8% of the subjects in each study will not be eligible for either the HPV 16- or 18-related disease endpoints. **Furthermore, it is assumed that nearly every subject in each study will be eligible to be an endpoint case for the secondary analysis, since every subject should be PCR-negative at baseline to at least 1 high-risk HPV type for which she will be tested.** With **2391** subjects enrolled in Protocol 005, **552** subjects enrolled in the dosage groups of interest in Protocol 007, 5700 subjects enrolled in Protocol 013, and 11,500 subjects enrolled in Protocol 015, the expected numbers of evaluable subjects in each study are given in Table 3 along with the numbers of cases of each endpoint that are expected to be observed in the placebo arm. The expected numbers of cases are based on the following assumptions:

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

- the rate of CIN 2/3 or worse is 0.19% per year for HPV 16, 0.038% per year for HPV 18, 0.02% per year for each of HPV 31 and 45, 0.01% per year for each of HPV 52 and 58, and 0.015% per year for all other high-risk HPV types combined.
- HPV 16 and 18 comprise 50% of all CIN 2/3 or worse.
- all subjects followed beyond Month 7 are eligible to be endpoints and any subject who discontinues the study after Month 7 is at risk for half of the interval in which she discontinued.
- for the HPV 16- and 18-related endpoints, all cases occur in the placebo recipients.
- the durations of the studies are: 4 years for Protocol 005, 3 years for Protocol 007, 4 years for Protocol 013, and 4 years for Protocol 015.

Table 3

Expected Numbers of Primary and Secondary Endpoints in Protocols 005, 007, 013, and 015

Protocol	Number of Subjects Enrolled[a]	Number of Subjects Evaluable for HPV 16- and 18-Related Endpoints[b]	Number of Subjects Evaluable for All CIN 2/3 or Worse Endpoint[c]	Expected Number of Cases of HPV 16/18-Related CIN 2/3 or Cervical Cancer[d]	Expected Number of Cases of CIN 2/3 or Cervical Cancer[d]
005	**2391**	1870[e]	2032	5[e]	15
007	**552**[f]	430	466	1	1
013	5700	4456	4844	13	36
015	11,500	8992	9774	29	89
Total	19,842	15,748	17,116	48	141

[a] Note that while the number of subjects enrolled includes the subjects in the vaccine and placebo groups combined, all of the primary endpoint cases are assumed to occur in the placebo group to be conservative. This means that the number of cases is based on approximately half of the number of subjects enrolled in each study.

[b] Assumes that ~15% of the subjects in each study will drop out prior to Month 7 and that ~8% of the subjects in each study will not be eligible for either the HPV 16- or HPV 18-related disease endpoints.

[c] **Excludes only subjects who drop out of each study through Month 7, since all subjects are expected to be PCR-negative at baseline to at least 1 of the high-risk HPV types for which they are tested.**

[d] Assumes that: (1) the rate of CIN 2/3 or worse is 0.19% per year for HPV 16, 0.038% per year for HPV 18, 0.02% per year for each of HPV 31 and 45, 0.01% per year for each of HPV 52 and 58, and 0.015% per year for all other high-risk HPV types combined; (2) HPV 16 and 18 comprise 50% of all CIN 2/3 or worse; (3) all subjects followed beyond Month 7 are eligible to be endpoints and any subject who discontinues the study after Month 7 is at risk for half of the interval in which she discontinued; (4) for the HPV 16- and 18-related endpoints, all cases occur in the placebo recipients; and (5) the durations of the studies are: 4 years for Protocol 005, 3 years for Protocol 007, 4 years for Protocol 013, and 4 years for Protocol 015.

[e] Includes only HPV 16 endpoints, since an HPV 16 monovalent vaccine was administered in Protocol 005.

[f] Includes only the subjects in Protocol 007 receiving placebo or the quadrivalent formulation selected for Phase III.

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

In order to avoid problems with imprecise incidence and efficacy estimates, the interim and final analyses of the primary and secondary hypotheses will be conducted when fixed numbers of cases of the primary and secondary endpoints have been observed across all 4 studies. The interim analysis will be conducted at the time that at least 33 cases of the primary endpoint are observed and will involve a test of the primary hypothesis. The final analysis will be conducted when at least 48 cases of the primary endpoint *and* at least 141 cases of the secondary endpoint are observed. Table 4 shows the power for the test of the primary hypothesis at the interim and final analyses, assuming varying true vaccine efficacies. For the purpose of the power calculations, the true vaccine efficacy is assumed to be 80% (this is conservative based on the Protocol 005 primary analysis). Based on this assumption, there is 96% power to show that the lower bound of the confidence interval for the vaccine efficacy is >25% at the final analysis with a two-sided α=0.0454. Assuming that there is equal follow-up in the 2 treatment groups, a 37/11 split (~70% observed efficacy) will be statistically significant.

Table 4

Power Sensitivity Analysis

Analysis	α-level	Observed Number of Cases	Lower Bound of Confidence Interval for Vaccine Efficacy	True Vaccine Efficacy	Power
Interim	0.0146	33	25%	80%	**69%**
				85%	**87%**
				90%	**97%**
Final	0.0454	48	25%	80%	96%
				85%	99%
				90%	>99%

Assuming a true vaccine efficacy of 40% in reducing all high-grade CIN and cervical cancer, if 141 cases of CIN 2/3 or cervical cancer are observed across the 4 studies **at the final analysis of the secondary endpoint**, the power for the secondary hypothesis is 84%. **It is anticipated that there will be approximately 180 cases of high-grade CIN due to any HPV type in the restricted MITT-2 population at the interim analysis. With 180 cases and an assumed true vaccine efficacy of 40%, the power for the interim analysis of the secondary endpoint is 50% with the multiplicity adjustment. However, if the true vaccine efficacy is 52%, the power for the interim analysis is 90%.**

B. Method of Assigning Study Participants to Treatment Groups

Excluding the 300 subjects receiving the monovalent HPV 16 VLP vaccine in Protocol 013, participants in each 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

Protocols 005, 007, 013, and 015 are double-blinded studies operating under in-house blinding procedures. Therefore, the subjects enrolled in the studies, the investigators and study personnel, the laboratory personnel conducting the PCR, RIA, **cLIA** and (b)(4) assays on the clinical samples, the Pathology Panel, and the clinical, data management, and statistical personnel involved with the protocols at the SPONSOR will be blinded to the treatment group assignments of the subjects through the primary efficacy evaluations.

The statistical, clinical, and data management personnel at the SPONSOR will be unblinded to the *grouped* efficacy data for Protocol 005 when ~31 cases of sustained HPV 16 PCR positivity (the primary endpoint of interest in Protocol 005) have been observed. The individual treatment allocations of the subjects will remain blinded for the duration of the study, although high efficacy would effectively unblind the ~31 cases.

In addition, in Protocol 013 (the CIN/Wart efficacy study), the duration of the primary efficacy phase of the study will be ~3 years. However, the primary time point for the immunogenicity analyses for the concomitant administration and monovalent HPV 16 vaccine bridging substudies is Month 7 (1 month following completion of the full vaccination regimen). Similarly, in Protocol 015 (the CIN 2/3 efficacy study), the duration of the primary efficacy phase of the study will be ~4 years. However, the primary time point for the immunogenicity analysis for the consistency lot substudy is Month 7. The immunogenicity analysis for any or all of the substudies may be conducted when all subjects in the substudy have completed the Month 7 follow-up. In both Protocol 013 and 015, in order to keep the data for the efficacy evaluations blinded while unblinding the immunogenicity and safety data for the consistency lot, concomitant administration and monovalent bridging substudies, 2 separate clinical, statistical, and data management teams will be formed to screen and clean the data from the immunogenicity substudies and the larger efficacy studies. For each study, the clinical, statistical, and data management personnel on both teams will perform the screening and cleaning of data through Month 7, a process that 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

C. Blinding/Unblinding (Cont.)

the clean database will be made, and this copy will be unblinded for the clinical, statistical, and data management teams that are responsible for the immunogenicity and safety analyses. Only the teams responsible for the immunogenicity and safety analyses will have access to the allocation schedules and the unblinded database. The primary database for both studies will remain blinded for the efficacy analysis. Only the second team will be responsible for screening and cleaning the data for the efficacy analysis. No member of the previously unblinded team (who participated in the immunogenicity analyses) will be allowed to participate in this effort. 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.

Protocol 015 will also have an interim analysis that will coincide with the interim analysis of the combined studies described in this DAP (see Section IV). Both interim analyses will be performed by a designated unblinded statistician. If the interim analysis of Protocol 015 meets the primary statistical criterion for success prespecified in that protocol *and* the interim analysis of the combined data sets meets the primary criterion for success prespecified in this DAP, the quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine will be submitted to regulatory authorities for review as soon as possible. The interim results from both the analysis of Protocol 015 and the analysis of the combined studies will then be disclosed to all personnel at the SPONSOR responsible for preparing the regulatory submission. At this time, the screening, cleaning, unblinding, and analysis of the data in the 4 studies will take place as outlined in Section IV. Following the unblinding of the data for the preparation of the submission, the clinical, statistical, and data management personnel assigned to the HPV vaccine project at the SPONSOR will most likely have access to the individual treatment assignments of the subjects in Protocols 013 and 015, even though those studies will continue. Therefore, if the early submission occurs, the remainder of Protocols 013 and 015 will be considered extension phases. The purpose of the extension phases will be to collect data on the longer-term efficacy of the vaccine with respect to the primary endpoint and to allow a sufficient number of cases of CIN 2/3 and cervical cancer due to any cause to accrue across all of the studies for the secondary analysis outlined in this DAP.

C. Blinding/Unblinding (Cont.)

It is important to note that throughout the efficacy phase of all 4 studies and the extension phase of Protocols 013 and 015, the laboratory personnel, the pathology panel, the investigators, site personnel, and subjects will remain blinded to the individual treatment allocations of the subjects. The data that 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. Thus, 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 4 studies. It is also important to note that at the time of the early submission, Protocols 013 and 015 will be complete for the purposes of addressing their primary objectives.

If either the interim analysis of Protocol 015 or the interim analysis of the combined data sets fails to meet the statistical criterion for success at the interim time point, the quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine will not be submitted for regulatory review at that time. The results from the interim analyses will remain blinded to everyone except the designated unblinded statistician and the DSMB until the end of the studies (i.e., until the complete data have been screened, cleaned, and audited for analysis).

D. Statistical Methods

1. Vaccine Efficacy

A one-sided test of H_0: $\pi = 0.25$ versus H_1: $\pi > 0.25$ will be conducted, where $\pi = 1 - RR$ is the vaccine efficacy, and RR is the relative risk of the vaccine compared with placebo. Assuming homogeneity of the relative risk among the 4 studies, a multiplicity-adjusted two-sided exact confidence interval for the common vaccine efficacy will be used to test the null hypothesis. An exact conditional procedure will be used under the assumption that the number of cases in the vaccine group in each study, C_v, and the number of cases in the placebo group, C_p, are independent Poisson random variables with means λ_v and λ_p. (The relative risk of the vaccine is λ_v/λ_p.) Assuming the follow-up times in the vaccine group and placebo group are k_v and k_p, respectively, the number of cases in the vaccine group C_v, given the total number of cases observed, $T = C_v + C_p$, is binomially distributed with parameters, $C_v + C_p$, and $p = k_v\lambda_v/(k_v\lambda_v + k_p\lambda_p)$, where p is the probability that a subject in the vaccine group is a case. The point estimate for p is $C_v/(C_v + C_p)$.

D. Statistical Methods (Cont.)

2. Test of Homogeneity of Relative Risk

Assuming the relative risk for the *ith* study is $RR_i = \lambda_{vi}/\lambda_{pi}$, the test of homogeneity will test the null hypothesis, H_0: $RR_1 = RR_2 = RR_3 = RR_4$ against the alternative hypothesis that at least 1 pair of relative risks is unequal. The test will be conducted using the method of Martin and Austin [1]. Let T_i be the total number of cases in each study ($T_i = C_{vi} + C_{pi}$) and let C_{v+} be the total number of cases in the vaccine group across all of the studies ($C_{v+} = C_{v1} + C_{v2} + C_{v3} + C_{v4}$). Then, conditioning on the T_i and C_{v+}, the conditional probability, under the null hypothesis, for the joint distribution of the cases in the vaccine group across the studies is given by

$$\Pr(\mathbf{C}_v \mid \mathbf{T}, C_{v+}) = \frac{\prod_{i=1}^{3} \binom{T_i}{C_{vi}} (k_{vi})^{C_{vi}} (k_{pi})^{T_i - C_{vi}}}{\sum_{\mathbf{C}_v \in S} \left(\prod_{i=1}^{3} \binom{T_i}{C_{vi}} (k_{vi})^{C_{vi}} (k_{pi})^{T_i - C_{vi}} \right)}$$

where S is the set of all 4 x 2 contingency tables with marginal column sums C_{v+} and $C_{p+} = C_{p1} + C_{p2} + C_{p3} + C_{p4}$ and row sums T_1, T_2, T_3 and T_4. The p-value of the test, then, is the sum of the probabilities of all of the 4 x 2 tables more extreme than the observed table (i.e., having a smaller probability than the observed table).

3. Estimate of Common Vaccine Efficacy

The exact multiplicity-adjusted confidence interval for the common vaccine efficacy will be computed from an exact multiplicity-adjusted confidence interval for RR, the common relative risk for the studies. The confidence interval for the relative risk will be constructed based on the methodology for stratified Poisson samples described in the (b)(4) (b)(4) Manual [2]. This methodology produces results that are the same as those obtained by the method proposed by Martin and Austin [1].

4. Computation of Follow-Up Time

Follow-up for CIN 2/3 and cervical cancer in each study 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. For cases, the final visit will the visit at which CIN 2/3 or cervical cancer was detected. This value will be converted to person years by dividing by 365.25. To obtain the total follow-up time in each treatment group in the 4 studies, k_{vi} and k_{pi}, the

D. Statistical Methods (Cont.)

person years will be summed over all subjects in the given treatment group and study.

Although the primary analysis is per-protocol and HPV type-specific, all subjects who are eligible for the per-protocol analysis based on at least 1 of the 2 HPV types being analyzed (HPV 16 or 18) will contribute follow-up time to the totals. **For the secondary analysis, all subjects who are eligible for analysis based on at least 1 high-risk HPV type will contribute follow-up time to the totals.**

5. Potential Bias

a. Ascertainment Bias

All of the studies in the combined analysis require pelvic examinations which include an examination for genital warts. A genital wart examination introduces the potential for ascertainment bias, particularly in Protocols 007 and 013, where the examination for genital warts is quite rigorous. In all of the Phase III studies, subjects are triaged to colposcopy and biopsy based on the results of the Pap tests performed approximately every 6 months or every year, depending on the study. However, colposcopy is frequently performed based solely on a discovery of genital warts as well. In studies in which the quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP vaccine is administered, this could introduce bias if the vaccine is efficacious against genital warts. If the vaccine is efficacious against genital warts, warts 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 2/3 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 2/3 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

D. Statistical Methods (Cont.)

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.

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 an endpoint, 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 diagnoses less severe disease than CIN 2 or no disease on the same lesion. Though this situation is expected to occur infrequently, it could cause some of the subjects with the most endpoint potential to be censored before becoming endpoints. 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 lab or pathology panel diagnosis of each biopsy.

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).

D. Statistical Methods (Cont.)

With respect to counting cases of CIN 2/3 and cervical cancer for the combined analyses, if a subject has a biopsy (Protocols 005, 007, 013, and 015), ECC (Protocols 007, 013, and 015 only) or LEEP/conization specimen (Protocols 007, 013, and 015 only) 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 **required serology result** for a particular vaccine HPV type *will not* be eligible to be cases of CIN 2/3 or cervical cancer related to that HPV type in the primary analysis.

- With respect to missing PCR results for cervicovaginal specimens, a subject's eligibility for analysis depends on the number of missing results.

  – In Protocols 005 and 007, the PCR results for 3 cervicovaginal specimens collected at enrollment and 3 cervicovaginal specimens collected at Month 7 are used to determine a subject's eligibility for analysis. For a given vaccine HPV type, subjects who are missing PCR results for all 3 specimens or 2 out of the 3 specimens at enrollment or Month 7 will not be eligible to be cases of CIN 2/3 or cervical cancer related to that HPV type in the primary analysis. Subjects who are missing 1 of the 3 PCR results at enrollment or Month 7 will be eligible to be cases of CIN 2/3 or cervical cancer related to that HPV type. In this situation, if either of the 2 results present for the given HPV type is positive, the subject will be considered positive. If both are negative, the subject will be considered negative. (This is a conservative approach.)

D. Statistical Methods (Cont.)

- In Protocol 013, the PCR results for 2 cervicovaginal specimens collected at enrollment, 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 enrollment, Month 3, or Month 7 will not be eligible to be cases of CIN 2/3 or cervical cancer related to that HPV type in the primary analysis.

- In Protocol 015, the PCR results for 2 cervicovaginal specimens collected at enrollment and 2 cervicovaginal specimens collected at Month 7 are used to determine each subject's eligibility for analysis. Subjects who are missing one or both of the PCR results for a given vaccine HPV type at enrollment or Month 7 will not be eligible to be cases of CIN 2/3 or cervical cancer related to that HPV type in the primary analysis.

- If the PCR result from a biopsy sample taken between enrollment 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 a case of CIN 2/3 or cervical cancer 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 will be applied for the secondary analysis.

E. Multiplicity

There is only 1 primary efficacy hypothesis for the study. It will be tested with an interim analysis at the time that at least 33 endpoint cases have been observed and at a final analysis when at least 48 endpoint cases have been observed. In order to control the overall type I error rate at α=0.05 two-sided, the α-levels used at the interim and final analyses must be adjusted to account for the multiple, correlated analyses. The effective α-levels at the interim and final analyses were computed using the power boundaries of Wang and Tsiatis [3]. Using an alpha boundary shape of 0 (representing the O'Brien-Fleming boundary), a two-sided alpha of 0.0146 will be spent at the interim analysis, and a two-sided alpha of 0.0454 will be spent at the final analysis.

E. Multiplicity (Cont.)

The secondary hypothesis of the study will be tested at the interim analysis with approximately 180 endpoint cases in the secondary, supportive populations and the final analysis with at least 141 endpoint cases in the primary population. In order to control the overall type I error rate at α=0.05 two-sided, the secondary hypothesis will be tested at the α=0.001 level (two-sided) at the interim analysis and the α=0.049 level (two-sided) at the final analysis.

VI. GROUND RULES FOR ANALYSIS

A. Definition of Time Points

Each of the subjects in each study will receive 3-doses of HPV vaccine or placebo. The vaccine or placebo will be administered at 0, 2, and 6 months. For the per-protocol analyses, there will be no restrictions placed on the timing of the 3 vaccination visits or any of the follow-up visits with the exception of the Month 7 visit. The postvaccination clinical samples collected at the Month 7 visit will only be considered as valid for establishing the PCR status of a subject if they are obtained 14 to 72 days following the Month 6 vaccination.

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

With the exception of the Month 7 visit, multiple efficacy measurements within a day range are not possible for this analysis, as no day ranges are imposed on the visits, scheduled or unscheduled. Since the visits in all 4 protocols are labeled, if multiple efficacy measurements are taken within the acceptable day range for the Month 7 visit, the values for the visit that is labeled "Month 7" by the study site will be the values that are used to determine the subject's Month 7 PCR status. As part of the routine screening process, the data will be screened prior to analysis to make sure that only 1 visit for each subject is labeled as "Month 7."

C. Definition of Baseline Value

For the serum samples, the baseline value(s) for a study participant is (are) the assay result(s) 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 16 and/or 18 at baseline and throughout the vaccination phase of the studies (through Month 7) are: the HPV 16 results for the (b)(4) and (b)(4) swab, the (b)(4) and the (b)(4) swab at enrollment and Month 7 in Protocol 005, the HPV 16 and 18 results for the (b)(4) and (b)(4) swab, the (b)(4) swab, and the (b)(4) swab at enrollment and Month 7 in Protocol 007, the HPV 16 and 18 results for the (b)(4) and (b)(4) swab and the (b)(4) swab at enrollment, Month 3, and Month 7 in Protocol 013, and the HPV 16 and 18 results for the (b)(4) and (b)(4) swab and the (b)(4) swab at enrollment and Month 7 in Protocol 015.

D. Description of Data Handling Procedures Prior to Analysis

For each study, all data will be screened and cleaned prior to unblinding. This includes identification of subjects excluded from the per-protocol analyses. All data handling guidelines and actions will 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

The per-protocol analysis of efficacy will exclude data according to the following rules:

1. 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.
2. Incorrectly randomized subjects shall be excluded.
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 (however, Protocol 005 and Protocol 007 prior to Amendment 007-03 required such subjects to discontinue the study).

4. 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 and without knowledge of each individual's case status.
5. 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 and without knowledge of each individual's case status.
6. 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.
7. Subjects receiving any immunosuppressives shall be excluded with the exception of subjects using topical or inhaled steroids.
8. Subjects who receive any nonstudy inactivated vaccine within 14 days 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 a study vaccine.

VII. PRESENTATION AND FORMAT OF RESULTS

A. Outline of Results Section

The "Results" portion of the report will contain sections for:

1. Subject Characteristics
2. Subject Accounting
3. Efficacy

B. Decimals and Rounding

All percentages and confidence intervals will be reported to 1 decimal place. 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: HPV VLP Vaccine	Group 2: Placebo

VIII. REFERENCES

1. Martin DO, Austin H. Exact estimates for a rate ratio. Epidemiology 1996;7:29-33.

2. (b)(4)

3. Wang SK, Tsiatis AA. Approximately optimal 1-parameter boundaries for groups sequential trials. Biometrics 1987;43:193-9.