Official Protocol Title:	A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds)
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SPONSOR:

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TITLE:

A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds)

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: III

US IND NUMBER: 13447

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

Protocol V503-002-20 is an extension of Protocol V503-002-10. Protocol V503-002-20 will assess long-term immunogenicity, safety, and effectiveness of 9-valent HPV L1 VLP vaccine, when administered to 9- to 15-year-old girls and boys through active follow-up of study subjects for up to 10 years post-dose three.

OTHER CHANGES INCLUDED IN THE AMENDMENT:

The protocol template has been updated to conform to the current Merck standard.

Section 1.3 – The rationale for the long term follow-up was added.

Section 1.4 – The study design for the long term follow-up was added.

Section 1.5 – A description of the subject population for the long term follow-up was added.

Section 1.6 – A statement was added that no study vaccination will be provided in the long term follow-up.

Section 1.7 – Fifteen additional visits (from Month 42 through Month 126) for the long term follow-up were added to the study flow chart.

Section 2.1 – Primary and secondary objectives were added for the long term follow-up

Section 2.2 – Previous inclusion criteria do not apply. One inclusion criterion was added for the long term follow-up.

Section 2.3 – Previous exclusion criteria do not apply. One exclusion criterion was added for the long term follow-up.

Section 2.4 – The summary of study design was updated for the long term follow-up.

Section 2.5 – The measurements were updated for the long term follow-up.

Section 2.6 – The safety measurements were updated for the long term follow-up.

Section 2.7 – The "Statistical Analysis Plan Summary" was updated for analysis of information during long term follow-up.

Section 3.1.1 – The rationale for the long term follow-up was added.

Section 3.2 – Study procedures were updated for the long term follow-up.

Section 3.3.1.3 – Pseudovirion-based neutralization assay was added.

Section 3.3.2 – PCR assay for HPV 35, 39, 51, 56, and 59 was added.

Section 3.3.2.2 – "Preparation and Disposition of Thinsections of Biopsy Tissue" was added.

Section 3.3.3 – "Responsibility of the HPV Vaccine Program Pathology Panel" was added.

Section 3.5 – "Data Analysis" section was updated, explaining the plan for analysis of information obtained during the long term follow-up.

Table of Contents

1. SUMMARY

1.1 TITLE

A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds) – Long Term Effectiveness, Immunogenicity, and Safety Study in Subjects Vaccinated Between 9 to 15 Years of Age.

1.2 INDICATION

Prevention of cervical, vulvar, and vaginal cancers and related precancers, external genital lesions, Pap test abnormalities, and persistent infection caused by human papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

1.3 SUMMARY OF RATIONALE

V503 is a prophylactic 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle (VLP) vaccine[1] that is comprised of VLPs of the 4 HPV types (Type 6, 11, 16, and 18) represented in GARDASIL™[2], plus the VLPs of 5 additional oncogenic HPV types (Type 31, 33, 45, 52, and 58). This vaccine offers the potential of significant prophylactic cancer coverage in addition to that already provided by GARDASIL™, with an increase in overall cervical cancer coverage from approximately 70% to 90%. This is in addition to the potential of coverage for genital warts provided by VLPs of HPV Types 6 and 11.

Protocol V503-002 was a 12-month study to evaluate the immunogenicity and tolerability of 9-valent HPV L1 VLP vaccine in preadolescent and adolescent girls and boys, 9 to 15 years of age with a comparison to young women, 16 to 26 years of age. All enrolled subjects received a 3-dose regimen of 9-valent HPV L1 VLP vaccine (at Day 1, Month 2, and Month 6), were evaluated for immunogenicity at Month 7 (28 days post-dose 3) and followed for safety from Day 1 through Month 12. The safety and immunogenicity data from the study will be used to bridge V503 efficacy findings for the 9 vaccine HPV types in young women, 16 to 26 years of age, to preadolescents and adolescents.

Protocol V503-002-10 was a study extension to continue to evaluate safety and assess persistence of antibody responses to 9-valent HPV L1 VLP vaccine for an additional 2 years in preadolescent and adolescent subjects initially enrolled in Protocol V503-002.

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[1]The 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle (VLP) vaccine will hereafter be referred to as 9-valent HPV L1 VLP vaccine in this protocol

[2] GARDASIL [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A. GARDASIL is also known as SILGARD in some countries. SILGARD is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

The young women 16 of 26 years of age enrolled in the base study did not continue in the V503-002-10 study extension. Antibody persistence and long term vaccine effectiveness in that demographic group is to be assessed in a different study (Protocol V503-001).

Protocol V503-002-20 is a second study extension to evaluate longer-term immunogenicity and safety of V503 in subjects who were enrolled in Protocol V503-002 when they were between 9 and 15 years of age. In addition, data permitting, the extension will evaluate the effectiveness of 9-valent HPV L1 VLP vaccine in preventing persistent infection, cervical, vulvar, vaginal, perineal, perianal, and penile intraepithelial preinvasive and invasive disease, and external genital lesions caused by HPV types targeted by 9-valent HPV L1 VLP vaccine.

1.4 SUMMARY OF STUDY DESIGN

The proposed study will extend the study up to Month 126 for preadolescent and adolescent girls and boys between the ages of 9 to 15 years at randomization. All subjects who were enrolled in Protocol V503-002, received 3 doses of the 9-valent HPV L1 VLP vaccine and consent/assent to participate in Protocol V503-002-20 will be eligible. All subjects will be followed up for 10 years post-dose 3. No subject will receive study vaccinations during the proposed long term follow-up study.

The purpose of this study extension is to collect data on long term immunogenicity, safety, and effectiveness of the vaccine. Until subjects reach 16 years of age, serum samples and safety information will be collected annually. Starting at age 16, visits will be twice a year and effectiveness endpoints will be collected to assess HPV persistent infection and disease.

Interim analyses will be conducted at Month 72 and Month 96 to assess the feasibility of continuing through 10 years of follow-up. The decision to continue with the effectiveness component of the study will depend on the ability to collect sufficient effectiveness data through Months 72 and 96 and as anticipated through the remainder of the study.

1.5 SAMPLE

All subjects who were enrolled in Protocol V503-002 between the ages of 9 and 15 years and received 3 doses of 9-valent HPV L1 VLP vaccine are eligible for enrollment in this extension. Protocol V503-002 enrolled 2604 subjects between the ages of 9 to 15 years. Among them, 2552 subjects received 3 doses of 9-valent HPV L1 VLP vaccine.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

No study vaccinations will be administered within the context of Protocol V503-002-20.

1.7 STUDY FLOW CHART

Event/Test	Month 42	48	54	60	66	72	78	84	90	96	102	108	114	120	126
Visit windows [1] (For clinical use only)	**6 months post month 36 ±4wks**	**6 months post month 42 ±4wks**	**All visits should be scheduled 6 months apart ±4wks Contact Sponsor if subject will be late for specimen collection visits**												
Obtain Informed Consent/Assent (may be obtained at Month 36)	+														
Review Inclusion/Exclusion Criteria	+														
FEMALE – <16 y/o															
Review Serious Adverse Experiences/ Review Medical History [2]	+		+		+		+		+		+		+		+
Update Sexual History (optional, only if subject volunteers information)[3]	+		+		+		+		+		+		+		+
Pregnancy Testing (optional , if indicated) [4]	+		+		+		+		+		+		+		+
Collect Blood for Immunogenicity Testing [5]	+		+		+		+		+		+		+		+
FEMALE – Not Sexually Active: ≥16 y/o and <21 y/o (Pelvic specimen collection – in serial order) [6]															
Review Serious Adverse Experiences/ Review Medical History [2]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Update Sexual History	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pregnancy Testing (optional , if indicated) [4]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Collect Blood for Immunogenicity Testing [5]	+		+		+		+		+		+		+		+
Labial/Vulvar/Perineal/Perianal (LVPP) Swabs for HPV PCR	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perform External Genital Lesion Examination	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urine for Chlamydia/Gonorrhea Testing	+		+		+		+		+		+		+		+
FEMALE – Sexually Active: ≥16 y/o and <21 y/o (Pelvic specimen collection – in serial order) [6]															
Review Serious Adverse Experiences/ Review Medical History [2]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Update Sexual History	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pregnancy Testing (optional , if indicated) [4]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Collect Blood for Immunogenicity Testing [5]	+		+		+		+		+		+		+		+
Labial/Vulvar/Perineal/Perianal (LVPP) Swabs for HPV PCR [7]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endo/Ectocervical (EEC) Swab for HPV PCR [7]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pap Test [8] (Thin Prep™ for cytology; includes annual chlamydia/gonorrhea testing) (optional, if indicated)	+		+		+		+		+		+		+		
Pap Test [8] (Thin Prep™ for cytology; includes annual chlamydia/gonorrhea testing) (mandatory)															+
Perform External Genital Lesion Examination	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urine for Chlamydia/Gonorrhea Testing [9]	+		+		+		+		+		+		+		
STI Testing (local laboratory testing, if indicated) [10]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Event/Test	Month 42	48	54	60	66	72	78	84	90	96	102	108	114	120	126
Visit windows[1]	**6 months post month 36 ±4wks**	**6 months post month 42 ±4wks**	**All visits should be scheduled based on Month 42 ±4wks Contact sponsor if subject will be late for specimen collection visits**												
FEMALE – Age: ≥21 y/o (Pelvic specimen collection – in serial order)[6]															
Review Serious Adverse Experiences/ Review Medical History [2]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Update Sexual History	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pregnancy Testing (optional , if indicated) [4]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Collect Blood for Immunogenicity Testing [5]	+		+		+		+		+		+		+		+
Labial/Vulvar/Perineal/Perianal (LVPP) Swabs for HPV PCR [7]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endo/Ectocervical (EEC) Swab for HPV PCR [7,11]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pap Test [8,11] (Thin Prep™ for cytology; includes annual chlamydia/gonorrhea testing)	+		+		+		+		+		+		+		+
Perform Pelvic Exam [11,12]	+		+		+		+		+		+		+		+
Perform External Genital Lesion Examination	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STI Testing (local laboratory testing, if indicated) [10]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALE – <16 y/o															
Review Serious Adverse Experiences/ Review Medical History [2]	+		+		+		+		+		+		+		+
Update Sexual History (optional, only if subject volunteers information)[3]	+		+		+		+		+		+		+		+
Collect Blood for Immunogenicity Testing [5]	+		+		+		+		+		+		+		+
MALE Age: ≥16 y/o (Genitourinary sample collection – in serial order)[6]															
Review Serious Adverse Experiences/ Review Medical History [2]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Update Sexual History	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Collect Blood for Immunogenicity Testing [5]	+		+		+		+		+		+		+		+
Perform External Genital Lesion Examination	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penile/Glans Penis File and Wetted Swab for HPV PCR [7]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Scrotal File and Wetted Swab for HPV PCR [7]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perineal/Perianal File and Wetted Swab for HPV PCR [7]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urine for Chlamydia/Gonorrhea Testing	+		+		+		+		+		+		+		+
STI Testing (local laboratory testing, if indicated) [10]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

[1] To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days. Study visits should be based on Month 42 and have a ±4wks visit window. With regards to protocol study visit windows, the following situations require consultation between the investigator and the SPONSOR and written documentation of the collaborative decision: a subject needs to be scheduled earlier than the start of a visit window, the study site is considering skipping a visit, or a study site needs significant guidance on scheduling visit windows. If a subject is very late for a visit such that she is in the next visit window, schedule future visits a minimum of 4 months apart until the visits are within the protocol-specified window. All data will be analyzed regardless of visit windows.

[2] Limited new medical history will be collected. See protocol details in Section 3.2.2.5.

[3] If a subject <16 years of age volunteers information relating to their sexual debut, then sexual history will be collected. In such subjects, chlamydia/gonorrhea testing can be conducted on urine at the investigator's discretion.

[4] The serum pregnancy test or urine pregnancy test (sensitive to 25 mIU/mL β-hCG) will be performed per the manufacturer's instructions. All materials used for serum and urine pregnancy testing will be provided by the study sites. Pregnancy testing is optional and will be conducted if indicated. Completion of protocol-specified study procedures in pregnant subjects is at the investigator's discretion.

[5] Serum must be shipped as specified by the SPONSOR/Central Laboratory. The retention serum vial must remain at the site until the SPONSOR notifies the study site to ship the samples.

[6] See the protocol details for prerequisites for pelvic sample collection and the preferred order in which to collect specimens.

[7] Type-specific HPV Polymerase Chain Reaction (PCR) testing to be performed at MRL. The 2 LVPP swabs are placed in one container of specimen transfer medium (STM) and 1 EEC swab is placed in another container (separate from the LVPP swabs) of STM. Penile/glans penis, scrotal and perineal/perianal swabs are placed in 3 separate containers of STM. Swabs must be shipped as specified by the SPONSOR/Central Laboratory.

[8] Pap test to be analyzed by the SPONSOR-designated Central Laboratory.

[9] Subjects who have a Pap test performed do not need to have their urine tested for chlamydia and gonorrhea.

[10] The Pap test fluid will be evaluated for chlamydia and gonorrhea at the specified visits, but additional local laboratory tests for chlamydia and gonorrhea may be performed at other visits. Other sexually transmitted infection (STI) tests, including HSV, hepatitis B, syphilis, and HIV, may be performed at any visit as needed.

[11] The requirement for EEC swab, Pap test and pelvic exam may be waived in sexually naïve subjects at the discretion of the investigator based on local standard of care.

[12] Collect pelvic study specimens prior to performing the bimanual pelvic examination. See the protocol details for prerequisites for pelvic sample collection.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary Objective

(1) Objective: To evaluate the anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 responses generated following administration of a 3-dose regimen of 9-valent HPV L1 VLP vaccine up to 10 years post-dose 3.

2.1.2 Secondary Objectives

(1) Co-Secondary Objective: To estimate the long-term effectiveness of 9-valent HPV L1 VLP vaccine, when administered to 9- to 15-year-old girls, with respect to the combined incidence of persistent HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 infection for a duration of 6 months (within ± 1 month windows) or longer and HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58-related Cervical Intraepithelial Neoplasia (CIN), Adenocarcinoma In Situ (AIS), Vulvar Intraepithelial Neoplasia (VIN), Vaginal Intraepithelial Neoplasia (VaIN), genital warts, and cervical/vaginal/vulvar cancer.

(2) Co-Secondary Objective: To estimate the long-term effectiveness of 9-valent HPV L1 VLP vaccine, when administered to 9- to 15-year-old boys, with respect to the combined incidence of persistent HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 infection for a duration of 6 months (within ± 1 month windows) or longer and HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58-related Penile Intraepithelial Neoplasia (PIN), genital warts, and penile/perineal/perianal cancer.

2.1.3 Safety Objective

Objective: To describe the incidence of serious adverse experiences (deemed to be vaccine-related or procedure-related) in subjects who received 9-valent HPV L1 VLP vaccine at 9 to 15 years of age.

Effectiveness, immunogenicity, and safety summaries will be provided for estimation purposes only. Thus, there are no formal hypotheses for the study extension.

2.2 SUBJECT/PATIENT INCLUSION CRITERIA

- Subject was enrolled in Protocol 002 between 9 and 15 years of age and received 3 doses of 9-valent HPV L1 VLP vaccine.

2.3 SUBJECT/PATIENT EXCLUSION CRITERIA

- Subjects who are concurrently enrolled in clinical studies that would involve or interfere with the collection of genital specimens.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

Protocol V503-002-20 is an international, multicenter study designed to evaluate the long-term immunogenicity, safety, and effectiveness of 9-valent HPV L1 VLP vaccine in subjects who were enrolled in Protocol V503-002 when they were between 9 and 15 years of age and received 3 doses of 9-valent HPV L1 VLP vaccine. Under the base study (Protocol V503-002), subjects were administered a 3-dose regimen of 9-valent HPV L1 VLP vaccine and assessed for immunogenicity (at Day 1 and Month 7) and safety (Day 1 through Month 12). Under Study Extension V503-002-10, subjects continued to be followed for immunogenicity and safety through Month 36. Subjects will complete the Month 36 visit (which is the last visit in Protocol V503-002-10) before starting in Protocol V503-002-20. The long term follow-up period under Protocol V503-002-20 will start at the Month 42 visit and end at the Month 126 visit (approximately 7.5 years later and approximately 10 years post-dose 3).

Visit schedule and study endpoints will vary depending on age and gender.

- Prior to reaching 16 years of age, subjects will have an annual visit. Serum samples will be obtained and safety information will be collected as outlined in Section 2.6

- Starting at age 16 years, visits will be twice a year. In addition to serum samples (collected yearly) and safety information, visits will include the collection of sexual history, genital examination and genital clinical specimens. Genital examination and types of clinical specimens collected will be age and gender specific, and in females, depend in part on sexual activity, as described below:

    1. For female subjects 16 to 20 years of age who are not sexually active, each visit will include external genital lesion examination and collection of labial/vulvar/perineal/perianal (LVPP) swabs. Chlamydia/gonorrhea testing will be performed annually based on urine sample.

    2. For female subjects 16 to 20 years of age who are sexually active (defined as having engaged in vaginal penetration), each visit will include external genital lesion examination and collection of LVPP and endo/ectocervical (EEC) swabs. Chlamydia/gonorrhea testing will be performed annually based on urine sample. Pap tests are not required in subjects less than 21 years of age (consistent with the 2012 screening guidelines from the American Society for Colposcopy and Cervical Pathology [ASCCP] [1]), but may be performed annually per investigator's discretion if required per local standard of care. The last visit (Month 126) will also include a mandatory Pap test.

    3. For female subjects who are at least 21 years of age, each visit will include external genital lesion examination and collection of LVPP and EEC swabs. Pelvic examination and a Pap test (with annual chlamydia/gonorrhea testing)

will be performed annually. The requirement for EEC swab, Pap test and pelvic examination may be waived in sexually naïve subjects at the discretion of the investigator based on local standard of care.

4. For male subjects, each visit will include external genital lesion examination and collection of penile and glans penis swabs, scrotal swabs, perineal/perianal swabs. Chlamydia/gonorrhea testing will be performed annually based on urine sample.

If applicable, tissue samples to assess HPV disease will be collected as outlined in Section 2.5 for histological examination.

All genital specimens (swabs and tissue samples) will be tested by Polymerase Chain Reaction (PCR) for HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 to examine the impact of vaccination on the rates of infection and disease due to these types.

2.4.2 Treatment Plan

No study vaccinations will occur within the context of Protocol V503-002-20.

2.5 LIST OF IMMUNOGENICITY AND EFFECTIVENESS MEASUREMENTS

2.5.1 Immunogenicity Measurements

Serum will be collected for analysis of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 responses. Serum will be analyzed to assess persistence of antibody responses at Month 66, Month 90, and Month 126 in the same subjects as in Protocol V503-002-10 (including all enrolled preadolescent and adolescent boys, and a subset of approximately 600 preadolescent and adolescent girls), and to support assay development work.

Serum may also be analyzed for exploratory analyses to study parameters of persistence of antibody response (as outlined in Section 2.7.1) and assess the relationship between long-term antibody response and breakthrough disease (as outlined in Section 2.7.2).

2.5.2 Effectiveness Measurements

Endpoints are gender specific.

2.5.2.1 Female Endpoints

LVPP and EEC swabs will be tested for detection of HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 by PCR assay. PCR analysis of the swabs will be used to determine persistent HPV infection endpoints.

A thorough external genital wart/lesion inspection will be performed at routine visit intervals. External genital warts/lesions will be biopsied.

Management of subjects 16 to 20 years of age with abnormal Pap test should be consistent with local standards of care and may include, at the investigator's discretion, observation or colposcopy using a protocol-mandated triage algorithm as outlined below.

Subjects ≥ 21 years of age with abnormal Pap test will be referred to colposcopy using a protocol-mandated triage algorithm. The colposcopist will obtain cervical biopsies of areas of the most severe abnormalities, may decide to take additional biopsies of areas with less severe abnormalities, and may choose to perform an endocervical curettage (ECC) if no cervical dysplasia is observed. A subject may need subsequent cervical definitive therapy per the protocol-mandated cervical definitive therapy guidelines. Vaginal lesions will be biopsied if they are observed during a Pap test, colposcopy, or at any other time. In addition, subjects with histologically confirmed HPV-related external genital warts (e.g., condyloma acuminata, VIN, cancer) or vaginal warts (e.g., condyloma acuminata, VaIN, cancer) will be referred to colposcopy if the biopsies were not obtained during a colposcopy.

Tissue obtained from biopsy and cervical definitive therapy procedures will be analyzed by MRL HPV Thinsection PCR assay (detection of HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and by a consensus diagnosis from the HPV Vaccine Program Pathology Panel to determine clinical disease efficacy endpoints.

2.5.2.2 Male Endpoints

Penile and glans penis swabs, scrotal swabs, and perineal/perianal swabs will be tested for detection of HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 by PCR assay. PCR analysis of the swabs will be used to determine persistent HPV infection endpoints.

A thorough external genital wart/lesion inspection will be performed at routine visit intervals. External genital warts/lesions will be biopsied.

Tissue obtained from biopsy procedures will be analyzed by MRL HPV Thinsection PCR assay (detection of HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and by a consensus diagnosis from the HPV Vaccine Program Pathology Panel to determine clinical disease efficacy endpoints.

2.6 LIST OF SAFETY MEASUREMENTS

The following serious adverse experiences will be collected for the duration of the study:

- Death of a study subject
- Serious adverse experiences (as defined in Section 3.4) judged by the study investigator to be related to prior administration of 9-valent HPV L1 VLP vaccine.
- Serious adverse experiences (as defined in Section 3.4) judged by the study investigator to be related to a study procedure.

Pregnancy information and infant serious adverse experiences will also be collected.

2.7 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 3.5.

2.7.1 Immunogenicity Analyses

Immunogenicity summaries are planned to occur at three time points, to include follow-up data through Month 72, Month 96, and at the end of the study at Month 126. Geometric mean titers (GMTs) and seropositivity rates for each vaccine HPV type will be summarized by gender, and age group (determined by age at enrollment), along with associated 95% confidence intervals. Longitudinal plots of anti-HPV levels will be provided for each HPV type. The primary analysis will be per-protocol.

In addition, exploratory analyses regarding the kinetics and persistence of the antibody response may be conducted, with particular interest in the effect of age at first vaccination on duration of anti-HPV levels. Modeling techniques may be used to study the relationship between anti-HPV persistence and factors such as time since vaccination, age at vaccination, age at sexual debut, and GMT at 1 month post-dose 3.

2.7.2 Effectiveness

At the time of the first interim analysis (Month 72), summaries of the incidence of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 related persistent infection for a duration of ≥6 months (within ± 1 month windows) and cervical, vulvar, vaginal, perineal, perianal, and penile intraepithelial preinvasive and invasive disease, and external genital lesions will be provided, separately for males and females. Similar summaries of the incidence rates of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58-related persistent infection for a duration of ≥6 months (within ± 1 month windows) and disease will be provided to include follow-up data through the second interim analysis at Month 96 and at the end of the study at Month 126.

All subjects will contribute to the effectiveness summaries. Summaries will be provided by gender and age group (based on age at enrollment). The primary analysis group will be those who have received 3 doses of 9-valent HPV L1 VLP vaccine within one year. Subjects will be considered breakthrough cases related to a given HPV type provided they were negative to the respective HPV type by serology prior to vaccination and were sexually naïve through the 3rd dose of 9-valent HPV L1 VLP vaccine**.** Sexual naïveté, an inclusion criterion for the base study, is being used as a way to limit analysis of the prophylactic effect of the vaccine to subjects who were not infected prior to completion of the vaccination series. There are no PCR data from Protocol V503-002 subjects until subjects reach their 16th birthday. Therefore, the only data available to assess possible prior infection are pre-vaccination serum anti-HPV levels and sexual history. Cases in subjects with evidence of HPV exposure or infection prior to vaccination (i.e., seropositivity to the relevant HPV type(s) pre-vaccination or sexual activity prior to completion of the vaccination series) or in subjects who did not receive 3 doses of 9-

valent HPV L1 VLP vaccine within one year will not be considered breakthrough cases (vaccine failures). Such cases will be summarized separately.

At each analysis time point, the cumulative (from the start of this extension) incidence rate for effectiveness endpoints will be computed, along with the associated 95% confidence intervals. Time-to-event plots will also be provided by gender if >5 cases are observed. In addition, exploratory analyses will be conducted to characterize subjects who become cases of persistent infection or disease endpoints in the long-term effectiveness follow-up period. Baseline demographic characteristics, pre-vaccination anti-HPV serology status, and post-vaccination immunogenicity profiles will be considered. Incidence rates for the same endpoints caused by HPV types not contained in the vaccine will also be summarized, when such data are available. An additional analysis of persistent infection for a duration of 12 months (within ± 1 month windows) or more may be conducted.

2.7.3 Safety analysis

All subjects who received at least one dose of 9-valent HPV L1 VLP vaccine and have long-term study follow-up data will be included in the safety summaries. Listings of serious adverse experiences and deaths, and a pregnancy summary will be provided.

2.7.4 Power and sample size

The sample size for this long-term follow-up study is fixed by the number of Protocol 002 participants who are eligible and willing to participate in the extension. There is no formal hypothesis that will be tested in this long-term follow-up study. A total of approximately 2600 subjects, 9 to 15 years of age, were enrolled in the V503-002 base study.

2.7.5 Interim Analysis

Interim analyses will be conducted at Month 72 and Month 96 to assess the feasibility of obtaining 10 full years of follow-up. The decision to continue with the effectiveness component of the study will depend on the ability to collect sufficient effectiveness data observed through Months 72 and 96, and anticipated through the remainder of the study. Summaries of the incidence of persistent infection and cervical, vulvar, vaginal, perineal, perianal, and penile intraepithelial preinvasive and invasive disease, and external genital lesions related to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be provided separately for males and females.

3. PROTOCOL DETAILS

3.1 RATIONALE

3.1.1 Introduction to Human Papillomavirus

HPV infection causes benign and malignant dysplastic disease, localized primarily in the anogenital area and aerodigestive tract, in both men and women [2; 3; 4].

3.1.1.1 Disease Burden

Cervical Cancer and Precancerous Dysplasia. Nearly 100% of cervical cancers are caused by HPV infection [5; 6]. Cervical cancer is the second most common cancer in women worldwide [7], with approximately 530,000 new cases diagnosed each year and 275,000 annual deaths [8; 9]. Most (~80%) of the cases occur in developing countries. In developed countries, cervical cancer screening programs have reduced the incidence of cervical cancer by 75% due to the detection, follow-up, and treatment of premalignant lesions. Despite this success, ~10,000 cases of cervical cancer still occur annually in the US, causing over 3000 annual deaths [10; 11], and more than 30,000 cases of cervical cancer still occur annually in the European Union, causing over 13,000 annual deaths [12].

Anogenital Warts. Anogenital warts are generally benign, exophytic, hyperkeratotic lesions appearing over the vulva, urethra, vagina, perineum, and anus in women, and on the penile shaft (most common site of lesions), scrotum, perineum, and anus in men. In general, the lesions do not cause any physical discomfort [13]. Some patients experience itching, burning, bleeding, moisture, irritation or soreness, especially with lesions in the perianal region. Patients are often distressed by unsightly lesions. Treatment consists of chemical or physical ablation and is often unsuccessful. Recurrence rates are high [14].

Anal, Vulvar, Vaginal and Penile Cancer. Most anal cancers, and ~50% of vulvar, vaginal and penile cancers, are caused by HPV. Rates of anal cancer (men and women) and HPV-related vulvar and vaginal cancers are increasing [5; 15].

Recurrent Respiratory Papillomatosis. RRP is a rare but severe disease that is manifested as rapidly-growing exophytic warts in the upper airway, most often in the larynx, causing severe respiratory and speech impairment. Repeated surgical excision is often needed. The disease tends to recur despite repeated treatment and can lead to death by blocking the airway. RRP is primarily caused by HPV Types 6 and 11. The disease occurs in both children and young adults [16; 17; 18; 19; 20].

Other HPV-associated malignancies. HPV causes ~25 to 30% of cancers of the oral cavity, oropharynx, and larynx [21]. When oropharyngeal cancers are considered alone, the percentage caused by HPV is notably higher. HPV may also be associated with cancers involving the aerodigestive tract, including cases of lung and esophageal cancers [22; 23], as well as bladder cancers [24].

3.1.1.2 Biology of Human Papillomavirus

HPV consist of a family of small, nonenveloped icosahedral capsid viruses containing double-stranded DNA composed of 8 early transcribed open reading frames, two late open reading frames, and a non-coding long control region [25]. The Late (L) genes encode the 2 capsid proteins (L1, major capsid protein) and L2 (minor capsid protein). Even though present in mature viral particles, L2 proteins are not necessary for capsid formation. Proteins encoded on the early (E) portion of the genome are involved in viral DNA synthesis. E6 and E7 proteins induce epithelial cell hyperproliferation by inhibiting cell cycle regulatory proteins, a likely mechanism by which all HPV types cause aberrant proliferation of infected cells [26; 27].

The HPV family of viruses represents nearly 100 related epitheliotropic DNA viruses that have been classified by types and species [28]. HPV types (also referred to as genotypes) are defined based on DNA sequencing [10]. Overall, 40 HPV types can infect the anogenital tract. Although all HPV types appear to disrupt the cell cycle regulator mechanisms, true oncogenic potential is limited to a subset of HPV types. Clinically, HPV types are classified into high-risk (HR) types (cancer-causing: i.e., in descending order of frequency in tumor specimens HPV 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 39, 51, 73, 66, 68) [10], and low-risk (LR) types (causing generally benign lesions: e.g., HPV 6, 11, 42, 43, 44).

Phylogenetically, HPV are classified into several species. HPV types targeted by prophylactic HPV vaccines belong to Species A7, A9, and A10. Species A7 and A9 contain most of the HR types. The A7 Species includes HPV 18, 39, 45, 59, and 68. The A9 Species includes HPV 16, 31, 33, 35, 52, and 58. HPV 16 and 18 are responsible for most (~70%) cases of cervical cancer, with an additional ~20% due to HPV Types 31, 33, 45, 52, and 58 [8]. The proportion of cervical cancers caused by types other than HPV 16 varies by region. For example, in Western countries, HPV 18 is the second most common cause of cervical cancer. However, in East Asia, HPV 52 and 58 are responsible for a higher proportion of cervical cancers than HPV 18. Species A10 contains LR HPV Types 6 and 11, which are responsible for over 90% of anogenital warts and RRP cases.

HPV infection and replication is entirely intraepithelial. The basal cell of the epithelium is the primary target of HPV infection. A minor lesion in the epithelium is enough to allow HPV to access this layer of cells [29]. Viral replication occurs only at a low level in the basal cells. High-level viral protein expression is achieved in the middle or upper layers of the epithelium. These layers of epithelial cells are normally terminally differentiated. However, with the up-regulation of viral proteins E6 and E7 that takes place during HPV infection, these cells are maintained in a mitotically active state that is conducive to viral DNA and protein synthesis [30]. Viral assembly takes place only in terminally differentiated cells at the epithelium surface. Viral shedding occurs through the routine desquamation of dead epithelial cells [31; 32; 33].

3.1.1.3 Epidemiology of HPV Infection and Disease

3.1.1.3.1 HPV Infection

The cumulative lifetime risk for HPV infection in sexually active women exceeds 50%. Available data suggest that HPV infection is also very prevalent in men [34; 35]. HPV infection is transmitted via contact with an infected individual or a contaminated object and occurs most often during sexual activity. Sixty percent (60%) of sexual partners of infected individuals develop lesions 4 weeks to 8 months after exposure [36]. HPV is often acquired immediately after sexual debut. The risk of HPV infection is strongly correlated with the number of lifetime sexual partners [37; 38]. Men and women in their late teens and early twenties are at the highest risk for HPV infection, as early sexual activity is accompanied with a higher likelihood of having new sexual partners, thus increasing the risk of exposure to the virus. The incidence of HPV infection in women increases with age during the teen years and peaks in the early 20's and declines gradually thereafter [6; 39]. In contrast, there does not appear to be such an association between HPV prevalence and age in men. This difference between genders may reflect stronger immune response to HPV in women, as suggested by findings of higher prevalence of anti-HPV antibodies in women than in men across all ages [40]. Most cervical HPV infections resolve spontaneously. On average, HPV infection persists for 4 to 20 months. However, a small proportion of infections persist beyond 1 to 2 years. Infection with HR types tends to last longer than infection with low-risk (LR) types [41; 42; 43; 44; 45].

3.1.1.3.2 Cervical HPV Disease

Infection with HPV is generally asymptomatic and not recognized until lesions are identified. Most HPV lesions are self-limited: for instance, early HPV disease causes low-grade cervical dysplasia (Cervical Intraepithelial Neoplasia Grade 1 [CIN 1]) which resolves in most cases without clinical sequelae. In some cases however, HPV infection persists, leading to CIN 2/3 and cervical cancer [39]. CIN 2/3 encompasses moderate and high-grade cervical dysplasia and cervical carcinoma in situ. It is the immediate precursor to cervical cancer with high rates of progression to cervical cancer and low rates of regression to normal [46]. Determinants of progression versus clearance of HPV disease are not well defined. Pap test screening programs have sharply reduced cervical cancer incidence [47] by allowing early detection and excision of CIN 2/3 lesions prior to cancer development [48; 49]. These benefits have not been shared in populations with sporadic screening, especially in the developing world and among the disadvantaged in the US [50].

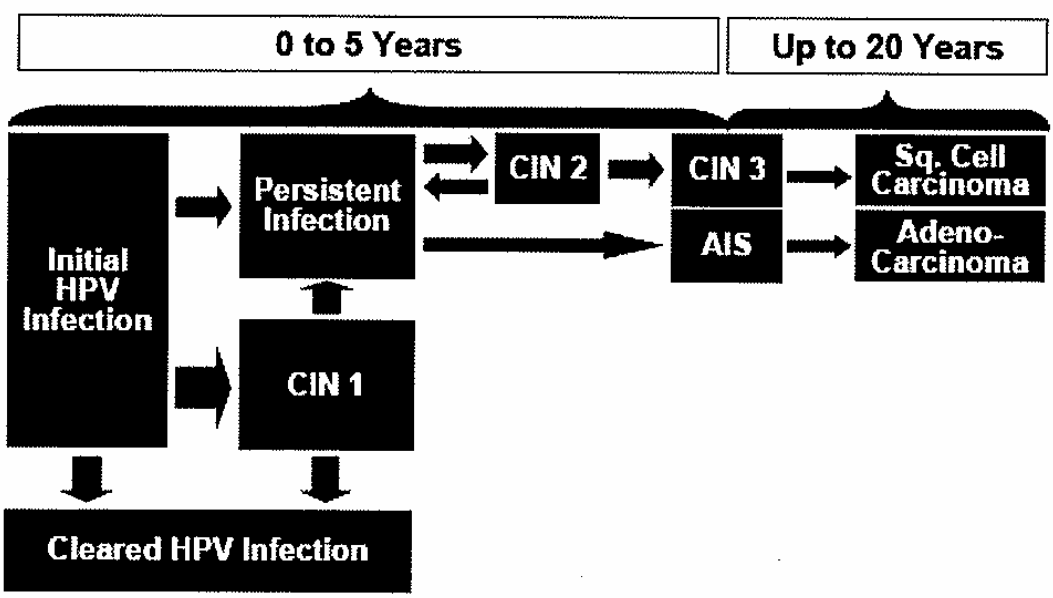
It appears that viral persistence, rather than transient viral infection, plays a key role in cervical carcinogenesis [51; 52; 53; 54; 55]. Risk of CIN and invasive cervical cancer (ICC) is strongly associated with persistent infection with HR types [56; 57; 39; 58; 59; 60]. Persistent detection of HR HPV DNA is a predictor for progression to cervical cancer [39; 61; 62]. The risk of development of cervical lesions, which is highest for HPV 16, has also been demonstrated for other HR HPV types. The risk of progression to CIN increases with duration of viral persistence. However, a long period of infection

(e.g., > 1 year) is often not required for CIN development [63]. A strong association between 3 to 6 months persistent infection and subsequent development of CIN1 or worse has been demonstrated [64]. Based on all these observations, persistent infection with at least 1 HR type is considered a key intermediate step for progression to cervical cancer.

The natural history of cervical HPV disease is represented schematically in Figure 3-1.

Figure 3-1

Natural History of Infection with High-Risk HPV Types (e.g., HPV 16 and HPV 18)



3.1.1.3.3 Non-Cervical HPV Disease

Infection with HPV is also associated with vulvar, vaginal, anal, penile, oral, and oropharyngeal cancers [2; 3]. Each of these HPV-related diseases is much less frequent than cervical cancer. But taken together, they represent a significant human health and economic burden [34; 65]. Of particular concern, the incidence of anal cancer has been increasing over the past several decades [66]. The risk of anal cancer is increased in men and women with a high number of sexual partners, current smokers, and among men who are not exclusively heterosexual or women by having sexual intercourse [67]. Anal cancer is preceded by high-grade anal intraepithelial neoplasia (AIN) [68; 69]. Over 80% of anal cancers and over 90% of high-grade anal neoplasia contain HR-HPV [70]. The high proportion of HPV-positive tumors suggests that HPV infection is necessary for developing anal cancer. HPV vaccination could prevent most anal cancers and precancers.

3.1.1.3.4 Aspects of HPV Infection and Disease Specific to Men

Only a few prospective studies have examined the incidence and duration of genital HPV infection in men. These studies indicate that HPV infection in men is self limited and a risk factor for HPV genital disease. Most HPV infections in men appear to clear within 12 months with a median time of clearance ranging from 5.9 to 7.5 months [71; 72]. HPV 16 infections tend to last longer and clear at an average of 12.2 months [72]. HPV testing positive for HPV 6 or 11 is the strongest predictor of developing genital warts [73]. HPV 16 infection is a recognized risk factor for penile cancer [74].

3.1.1.4 Prophylactic HPV Vaccines

3.1.1.4.1 Immune Response to HPV Natural Infection and HPV Vaccination

By remaining exclusively intraepithelial, HPV largely avoids exposure to the host immune system and evades immune recognition, which allows HPV infection to proceed [10; 75; 76]. Other mechanisms inhibiting the immune response are also used by HPV to avoid immune surveillance and control [77]. Accordingly, immune responses to natural viral infection are poor. In particular, low-level antibody responses to HPV become detectable only several months after the infection and in only approximately 50% of the subjects [78]. Nonetheless, most HPV infections are eventually cleared. It is thought that naturally acquired immune responses contribute to the clearance of infection, although the mechanisms are not well elucidated [79]. Those infections that are not cleared (especially the high-risk types) can result in dysplasia and cancer.

Prophylactic HPV vaccines have been developed based on VLPs which are produced by self-assembly of recombinant HPV L1 capsid proteins expressed in a heterologous cell substrate. VLPs mimic the overall structure of HPV virions, thus keeping capsid proteins in their native antigenic conformation. HPV vaccines are delivered intramuscularly and induce high levels of type-restricted neutralizing antibodies to L1 and seroconversion in virtually 100% of the vaccinated subjects.

3.1.1.4.2 Quadrivalent HPV (qHPV) Vaccine

3.1.1.4.2.1 Phase III Clinical Studies

As of July 2012, the quadrivalent (Type 6, 11, 16, 18) HPV L1 VLP vaccine (qHPV vaccine) was approved and marketed under the name GARDASIL™/SILGARD™ in over 120 countries. A 0.5-mL dose of vaccine contains 20 µg HPV Type 6 L1 VLP, 40 µg HPV Type 11 L1 VLP, 40 µg HPV Type 16 L1 VLP, 20 µg HPV Type 18 L1 VLP, and 225 µg of the adjuvant Amorphous Aluminum Hydroxyphosphate Sulfate (AAHS).

In clinical trials in 16 to 26-year-old women, qHPV vaccine was over 94% efficacious in preventing the development of: HPV 16- and 18-related CIN 2/3 and adenocarcinoma in situ (obligate cervical cancer precursors); HPV 16- and 18-related Vulvar Intraepithelial Neoplasia (VIN) 2/3 and Vaginal Intraepithelial Neoplasia (VaIN) 2/3 (obligate precursors to HPV-related vulvar and vaginal cancer, respectively); HPV 6- and 11-related external genital lesions (including condyloma acuminata); HPV 6-, 11-, 16-, and

18-related CIN; and HPV 6-, 11-, 16-, and 18-related persistent infection [80]. Efficacy was maintained for at least 5 years post-vaccination onset [81]. The vaccine also afforded some cross-protection against other oncogenic HPV types [82; 83; 84]. However, cross-protection was incomplete and limited to only a few types. In addition, in a Phase III study (V501 Protocol 020), the qHPV vaccine was over 89% efficacious in preventing the development of HPV 6- or 11-related genital warts in 16- to 26-year-old males [85], and 77.5% efficacious in preventing AIN in 16- to 26-year-old men-having-sex-with-men (MSM) [86].

3.1.1.4.2.2 Ecological Studies

Australia has been the first country to introduce a fully funded national HPV vaccination program. The program, targeted to adolescent females 12 to 13 years of age, was started in April 2007. In addition, up to 31-Dec-2009, a catch-up vaccination program was offered to girls and women, 14 to 26 years of age [87]. Within approximately 3 years following implementation of this qHPV vaccination program, a decline was observed in the diagnosis of genital warts among young Australian women [88]. Moreover, a decrease was noted in incidence of high-grade cervical abnormalities in girls less than 18 years of age [89]. A subsequent study reported the near disappearance of genital warts in young women and young heterosexual men within approximately 4 years following implementation of this vaccination program [90]. Overall, these observations suggest a rapid, beneficial effect of mass vaccination with qHPV vaccine. Dramatic fall in disease incidence following vaccine introduction, a typical pattern previously observed after introduction of mass vaccination with a number of new vaccines, appears also verified with qHPV vaccine. The decline in genital warts among Australian men (who are not part of the mass vaccination program) indicates that the concept of herd protection, previously noted with other vaccines, is also applicable to prophylactic HPV vaccination.

3.1.1.4.3 V503: 9-valent Prophylactic HPV Vaccine

The 9-valent HPV L1 VLP vaccine formulated with AAHS consists of highly purified VLPs of the L1 capsid proteins from HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. Like for GARDASIL™, the L1 capsid proteins in the vaccine are individually expressed in *Saccharomyces cerevisiae* yeast. The HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 L1 VLPs final aqueous products consist of recombinant L1 polypeptides for their respective viral types that have self-assembled into VLPs. Following fermentation, the VLPs are isolated from lysed yeast cells by standard techniques, then highly purified, and then adsorbed onto AAHS without the addition of preservative. After preparation of the Monovalent Bulk Adsorbed Products, the bulks are mixed to create the 9-valent HPV L1 VLP vaccine with the desired concentrations of each monovalent L1 VLP. The 9-valent HPV L1 VLP vaccine is not a live virus vaccine. It is not capable of causing viral infection.

HPV 16 and 18 cause approximately 70% of cervical cancers worldwide. Approximately 20% of additional cervical cancers are caused by HPV 31, 33, 45, 52, and 58. The addition of HPV 31, 33, 45, 52, and 58 L1 VLPs to the 4 types already present in qHPV vaccine will thus increase overall cervical cancer coverage from approximately 70% to approximately 90% [91; 92]. Assuming at least 90% vaccine efficacy, this coverage may

provide 80% or greater reduction in cervical cancer risk (matching or exceeding the efficacy of most cervical cancer screening programs). A small increase in coverage of anal, vulvar, and vaginal cancers and precancers is also anticipated.

3.1.2 Rationale for This Study

3.1.2.1 Rationale for Assessment of Long Term Effectiveness

Protocol V503-002, a 12-month immunogenicity and safety study of V503 in preadolescent and adolescent girls and boys, showed that V503 is highly immunogenic and generally well-tolerated in the study population. Girls and boys enrolled in V503-002 are being followed for 24 additional months under Study Extension V503-002-10, to assess persistence of antibody responses and long term safety.

Taken together, the Protocol V503-002 base study and V503-002-10 study extension will provide immunogenicity and safety data through approximately 36 months of study follow-up. Efficacy data were not collected in V503-002 and V503-002-10 because evaluation of sexual history and gynecological/genital examination is limited in young adolescents by social, cultural, and legal constraints. Nonetheless, data on the long term immunogenicity, safety, and effectiveness of V503 administered to preadolescent and adolescent girls and boys will support ongoing use of the vaccine in this important target population.

In the current protocol, immunogenicity and safety information will be collected for all subjects, and effectiveness endpoints will be assessed in subjects who have reached 16 years of age. Collection of efficacy data will be dependent on age and gender. Data permitting, the protocol will evaluate the long term effectiveness of V503 in preventing HPV persistent infection as well as HPV disease caused by HPV types targeted by V503, including external genital warts in both genders; cervical, vulvar, and vaginal intraepithelial neoplasia, and associated cancers in female subjects; penile, perineal, and perianal intraepithelial neoplasia, and associated cancers in male subjects.

3.1.2.2 Rationale for Including Male Subjects

HPV vaccination could contribute to reducing the burden of HPV diseases in males. The qHPV vaccine is highly efficacious to prevent genital warts as well as anal cancer and precancers in males. Additional benefits of vaccination may include coverage of other HPV-related cancers (i.e., head and neck cancer, penile cancer) for which prophylactic vaccine efficacy has not been studied but is biologically plausible. In contrast to cervical cancer in women, there is no widespread screening program for any of the HPV-related cancers in men. Thus, prophylactic vaccination is the only realistic preventive measure for HPV diseases in men, in both developed and developing countries.

A number of observations suggest that HPV transmission is a risk for development of HPV disease in both men and women. Male factors, such as lack of circumcision (which promotes chronic HPV infection in men), type-specific HPV infection, and viral load of such infection, are important correlates for HPV infection and disease in their female partners [93; 94; 95; 96]. Penile lesions are frequent in sexual partners of women with

CIN [97; 98]. Regression of penile lesions is significantly slower in men whose partners are infected with the same HPV type [99]. Husbands of women with cervical cancer or cervical carcinoma in situ have a higher HPV prevalence than husbands of control women [100]. The risk of cervical cancer is also increased by certain behaviors of male partners, such as having multiple sex partners and contact with prostitutes [101; 102]. Thus, vaccination of men could promote herd protection and lead to a substantial reduction of HPV-related diseases in both males and females [35].

Previous public health experience has shown that gender-restricted vaccination programs are substantially less effective than universal vaccination. It is likely that the most effective means to reduce the burden of HPV disease through vaccination is to vaccinate both males and females. As illustrated by the Australian experience, the concept of herd protection is applicable to HPV prophylactic vaccination. Thus, in the setting of a protective intervention that provides less than 100% protection to the entire female population (i.e., less than 100% efficacy and/or less than 100% coverage), reducing the burden of HPV disease would likely be enhanced by gender neutral vaccination through the establishment of herd protection.

3.2 STUDY PROCEDURES

3.2.1 Prerequisites for Study Visits With Gynecological or Genitourinary Specimen Collection

All subjects 16 years of age and older will have gynecological (female subjects) or genitourinary (male subjects) specimens collected during study visits. This section summarizes prerequisites for visits with collection of such specimens. Deviations from these prerequisites require consultation between the investigator and the SPONSOR and written documentation of the collaborative decision. See the Administrative Binder for a summary of deviations that require documentation in this study

For visits that include collection of study specimens, study personnel should verify by questioning the subject and/or by examination that:

1. *(All subjects)* – The subject has refrained from sexual activity (including anal, oral, vaginal, or genital/genital contact, whether same sex or opposite sex) for 2 calendar days prior to any visit that includes collection of labial/vulvar/perineal and perianal (LVPP) swabs, endo/ectocervical (EEC) swabs or external genital swabs, a Pap test, and/or biopsies/definitive therapy specimens.

2. *(Female subjects only)* – The subject has refrained from douching/vaginal cleansing and using vaginal medications or preparations for 2 calendar days prior to any visit that includes collection of LVPP/EEC swabs, a Pap test, and/or biopsies/definitive therapy specimens.

3. *(Female subjects only)* – The subject does not have visible blood in the vagina. As a guide, a study visit that includes collection of LVPP/EEC swabs, a Pap test, and/or biopsies/definitive therapy specimens should not be scheduled between the time

period of 2 days prior to menses (if date of menses can be predicted) to 2 days after menses. If, despite using these collection timeframe guidelines, visible blood is noted in the vagina, then the specimens may be collected.

4. *(Female subjects only)* – The subject does not have gross purulent cervicitis at a study visit that includes collection of LVPP/EEC swabs, a Pap test, and/or cervical biopsies/definitive therapy specimens.

5. *(Male subjects only)* – The subject has refrained from shaving his genital region (and/or applying any post-shave solutions or lubricants) a minimum of 1 day prior to the visit as this may interfere with the collection of skin cells. If the subject has shaved, or applied lotions or lubricants within 24 hours, the scheduled visit, exam, and specimen collection will be postponed until this criterion has been met.

If the subject does not meet the requirements listed above, the study visit (including specimen collection and/or study vaccination) should be re-scheduled. If the subject has gross purulent cervicitis, the re-scheduled study visit should occur after the condition is diagnosed and treated according to the study site's standards and practices.

3.2.2 Summary of Scheduled Study Visit Procedures

The Study Flow Chart summarizes procedures for scheduled study visits and items appear in the order they should be performed. This section provides clarifications to the scheduled study visit procedures (presented in order of the Study Flow Chart).

3.2.2.1 Calculation of Schedule Visit Windows

The visit windows provided in this protocol are for site scheduling purposes. The visit windows used for exclusion from analyses are provided in the Statistical Analysis Plan (Section 3.5). The Day 1 visit was defined as the day that the first study vaccination was given during the V503-002 Base Study. The Month 6 visit (when the third vaccination was given during the Base Study) was based on Day 1 and had a ±4 weeks visit window. The Month 36 visit in Extension 002-10 was based on Month 6 and had ±4 weeks visit window. The Month 42 visit in Extension 002-20 is based on Month 36 and has ±4 weeks visit window. The other study visits in Extension 002-20 are each based on Month 42 and have a ±4 weeks visit window. To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days.

3.2.2.2 Informed Consent

Written consent will be obtained for each subject (or, for minors, from the parent/legal guardian and the subject) prior to enrollment, study data collection, or performance of study procedures. A copy of the signed informed consent form will be given to each subject for his or her records. Verification of the subject's identity and age is to be determined prior to obtaining written consent. Any government-issued photo identification will suffice for verification purposes and should be documented in the subject's file.

The assent/consent for the V503-002-20 Extension can be collected at the Month 36 visit (if possible), or can be administered prior to serum collection at the Month 42 visit.

3.2.2.3 Randomization/Allocation

Subjects were randomized in the Protocol V503-002 Base Study and will retain their baseline and allocation numbers from those studies.

A single patient/subject cannot be assigned more than 1 allocation number.

3.2.2.4 Patient ID Card

All subjects/patients will be given a card, at the time of screening, identifying them as participants in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

3.2.2.5 History and Medication

No study vaccinations will be administered during the follow-up period. If an investigator discovers that a subject received an additional dose of any marketed HPV vaccine unintentionally outside the context of the study, this should be reported to the Sponsor.

Limited new medical history information will be collected to include:

- Events of acquired immunodeficiency
    - HIV infection
    - Hematological malignancies (e.g, leukemia, lymphoma)
    - Immunosuppressive therapy or procedure such as radiation therapy, cytotoxic or immunosuppressive chemotherapy, high-dose corticosteroids (at least 2 weeks), immunosuppressive monoclonal antibody therapy (e.g., anti-CD20, anti-TNF-alpha), splenectomy, or any other therapy or procedure known to interfere with the immune response.
- Administration of a marketed HPV vaccine outside the context of the study.
- Any gynecological or genitourinary procedure or condition that may interfere with the evaluation of vaccine effectiveness (e.g., subject had hysterectomy, subject has more than 1 cervix uteri).
- Any condition that may be relevant to the evaluation of the vaccine.

3.2.2.6 Sexual History and Contraception Information

At the first visit after a subject reaches 16 years of age, the subject's lifetime sexual history will be collected. For subjects who are sexually active, additional information will be collected to determine the age at sexual debut, the date of last sexual event, the

lifetime number of sex partners, the number of new or current sexual partners, and use of contraception. In this context, sexual activity is defined as having had vaginal and/or anal penetration and/or oral sex and/or genital to genital contact.

If a subject <16 years of age volunteers information relating to their sexual debut, then information similar to that described above will be gathered.

3.2.2.7 Pregnancy Testing (Female Subjects If Indicated)

A serum or urine pregnancy test can be performed if the investigator suspects pregnancy. Although pregnancy does not exclude a subject from participation in this study, completion of protocol-specified study procedures in pregnant subjects is at the investigator's discretion.

3.2.2.8 Serum Collection

All subjects will have serum drawn at Months 42, 54, 66, 78, 90, 102, 114, and 126. For collection of serum samples, the study site must adhere to the procedures described in this protocol, must follow instructions provided by the SPONSOR/Central Laboratory, and must use the materials provided by the SPONSOR/Central Laboratory as described in Section 3.2.4.1.1.

3.2.2.9 Optional Testing for Sexually Transmitted Infections

Local laboratory testing for Sexually Transmitted Infections (STIs), including chlamydia, gonorrhea, HSV, syphilis, hepatitis B, and HIV may be performed at any visit at the discretion of the investigator if clinically indicated. For these additional local laboratory tests for chlamydia and gonorrhea, the study site will collect samples using their own materials. Subjects who test positive for STIs may remain in the study. All subjects who test positive for STIs should be referred for counseling and treatment. It is important to document all tests for STIs on the appropriate eCRF as discussed in the eCRF Entry Guidelines. Testing for STIs should be done after gynecologic and genitourinary examination and sample collection.

3.2.2.10 Gynecological or Genitourinary Examination and Sample Collection

There will be no gynecological or genitourinary examination and sample collection in subjects who are less than 16 years of age.

Once a subject becomes 16 years of age, gynecological or genitourinary examination and sample collection will be performed at every study visit. Gynecological examination and sample collection in female subjects will be different in subjects 16 to 20 years of age who are not sexually active, subjects 16 to 20 years of age who are sexually active, and subjects ≥21 years of age. In this context, 'sexually active' is defined as having had vaginal penetration. Genitourinary examination and sample collection will be conducted in all male subjects 16 years or older regardless of sexual history.

3.2.2.11 Gynecological Examination and Sample Collection (Female Subjects 16 to 20 Years of Age, Not Sexually Active)

3.2.2.11.1 External Genital Swabs (Female Subjects 16 to 20 Years of Age, Not Sexually Active)

Two (2) LVPP swabs for HPV Polymerase Chain Reaction (PCR) assay will be collected at each study visit. For collection of swabs, the study site must adhere to the procedures described in this protocol, must follow instructions provided by the SPONSOR/Central Laboratory, and must use the materials provided by the SPONSOR/Central Laboratory (see Section 3.2.4).

3.2.2.11.2 External Genital Lesion Examination (Female Subjects 16 to 20 Years of Age, Not Sexually Active)

After obtaining study specimens (LVPP swabs), and after a change of gloves, an external genital examination should be performed using a good light source and a hand-held magnifying glass (4x to 5x power) or, optionally, a colposcope with low-power magnification. The following guidance should be used for all external genital lesion examinations performed within the study:

1. The examiner should ask the subject if she has noticed any bumps, lesions, or unusual symptoms (e.g., itching, discomfort, dyspareunia, dysuria).

2. The labia should be spread, and the condition of the hymen and vulvovaginal skin and clitoris are to be examined and noted. Note abnormalities, such as abnormal hair growth distributions, abnormalities of the skin, rashes, lacerations, or bruises.

3. The examination should include a systematic inspection of the entire external genitalia (periurethral, perineal, perianal, and vulvar regions) for apparent cutaneous and subcutaneous lesions or wart-like growths.

4. Acetic acid is not to be used routinely. It may be used for confirmation of a suspected lesion.

5. All observations should be recorded into the subject's chart. Medical conditions and lesions should be recorded on the appropriate eCRFs.

External genital lesions should be classified and managed as described in Section 3.2.3.1.2.

3.2.2.11.3 Urine Specimen for Chlamydia and Gonorrhea Testing (Female Subjects 16 to 20 Years of Age, Not Sexually Active)

This test is to be performed at Months 42, 54, 66, 78, 90, 102, 114, and 126. Urine should be collected after all routine swabs are obtained. For collection of urine samples, the study site must adhere to the procedures described in this protocol as described in Section 3.2.4.1.2.

3.2.2.12 Gynecological Examination and Sample Collection (Female Subjects 16 to 20 Years of Age, Sexually Active)

3.2.2.12.1 Gynecological Examination (Female Subjects 16 to 20 Years of Age, Sexually Active)

An external genital examination will be performed at each study visit. A complete gynecological examination is not required but may be performed at Months 42, 54, 66, 78, 90, 102, 114, and 126 at the discretion of the investigator based on local standard of care. A sterile, non-lubricated, single use, individually wrapped, plastic speculum should be used. If lubrication of the speculum is needed, only use sterile saline or sterile water. All study samples (See Section 3.2.4) must be taken from the pelvic area before any further examination is performed, to prevent contamination of study samples.

If the subject has gross purulent cervicitis at a visit with specimen collection (LVPP/EEC swabs, a Pap test, and/or cervical biopsy/definitive therapy specimens), the visit should be re-scheduled for a time after the condition is diagnosed and treated according to the study site's standards and practices.

Gynecologic conditions other than gross purulent cervicitis, such as vaginitis, bacterial vaginosis, and vaginal yeast infections, do not require a visit to be re-scheduled. These conditions should be diagnosed and treated according to the study site's standards and practices and treatment should be given after study sample collection.

3.2.2.12.2 Genital/Cervical Swabs, Pap Test, and Sexually Transmitted Infection (STI) Testing (Female Subjects 16 to 20 Years of Age, Sexually Active)

Two (2) LVPP swabs and 1 EEC swab for PCR assay will be collected at each study visit. A ThinPrep™ Pap test for liquid-based cytology Pap testing is not required, but may be performed at Months 42, 54, 66, 78, 90, 102, and 114 at the discretion of the investigator based on local standard of care. In that case, tests for chlamydia and gonorrhea will be performed on the Pap test fluid. A ThinPrep™ Pap test is required at Month 126. For collection of swabs and the ThinPrep™ Pap test, the study site must adhere to the procedures described in this protocol, must follow instructions provided by the SPONSOR/Central Laboratory, and must use the materials provided by the SPONSOR/Central Laboratory (see Section 3.2.4).

A non-lubricated, single use, individually wrapped, plastic speculum should be used for pelvic specimen collection. If lubrication of the speculum is needed, only use sterile saline or sterile water. During the Pap test, an inspection for vaginal lesions should be performed. Any vaginal lesion that is, in the investigator's opinion, HPV-related (e.g., condyloma acuminata or VaIN) should be classified and managed as described in Section 3.2.3.1.2.

ThinPrep™ Pap tests will be submitted to the SPONSOR-designated Central Laboratory. Cytology specimens will be evaluated using The Bethesda System-2001. For a diagnosis of atypical squamous cells of undetermined significance (ASC-US), the Central

Laboratory will perform reflex testing for high-risk/low-risk HPV probes (Digene Hybrid Capture II™ Assay) on residual ThinPrep™ material. The Pap test diagnoses generated by the Central Laboratory will be reported to the study sites for subject management, which may include, at the investigator's discretion and based on local standards of care, observation or referral to colposcopy according to a protocol-mandated triage algorithm (see Table 3-1). All Pap test reports must be reviewed and signed by a physician (M.D./D.O.) investigator/sub-investigator.

As noted in Section 3.2.2.9, local laboratory testing for STIs may be performed at any visit at the discretion of the investigator if clinically indicated. Any STI sampling of the cervix or external genital region should occur after the swabs and Pap test are obtained.

3.2.2.12.3 External Genital Lesion Examination (Female Subjects 16 to 20 Years of Age, Sexually Active)

After obtaining all study specimens (swabs and Pap test), and after a change of gloves, an external genital examination should be performed using a good light source and a hand-held magnifying glass (4x to 5x power) or, optionally, a colposcope with low-power magnification. The following guidance should be used for all external genital lesion examinations performed within the study:

1. The examiner should ask the subject if she has noticed any bumps, lesions, or unusual symptoms (e.g., itching, discomfort, dyspareunia, dysuria).

2. The labia should be spread, and the condition of the hymen and vulvovaginal skin and clitoris are to be examined and noted. Note abnormalities, such as abnormal hair growth distributions, abnormalities of the skin, rashes, lacerations, or bruises.

3. The examination should include a systematic inspection of the entire external genitalia (periurethral, perineal, perianal, and vulvar regions) for apparent cutaneous and subcutaneous lesions or wart-like growths.

4. Acetic acid is not to be used routinely. It may be used for confirmation of a suspected lesion.

5. All observations should be recorded into the subject's chart. Medical conditions and lesions should be recorded on the appropriate eCRFs.

External genital lesions should be classified and managed as described in Section 3.2.3.1.2.

3.2.2.12.4 Urine Specimen for Chlamydia and Gonorrhea Testing (Female Subjects 16 to 20 Years of Age, Sexually Active)

This test is to be performed at Months 42, 54, 66, 78, 90, 102, 114, and 126. Urine should be collected after all routine swabs are obtained. For collection of urine samples, the study site must adhere to the procedures described in this protocol as described in Section

3.2.4.1.2. Subjects who have a Pap test performed do not need to have their urine tested for chlamydia and gonorrhea.

3.2.2.13 Gynecological Examination and Sample Collection (Female Subjects ≥21 Years of Age)

3.2.2.13.1 Gynecological Examination (Female Subjects ≥21 Years of Age)

An external genital examination will be performed at each study visit. A complete gynecological examination will be performed at Months 42, 54, 66, 78, 90, 102, 114, and 126. A sterile, non-lubricated, single use, individually wrapped, plastic speculum should be used. If lubrication of the speculum is needed, only use sterile saline or sterile water. All study samples (See Section 3.2.4) must be taken from the pelvic area before the bimanual pelvic examination is performed to prevent contamination of study samples.

If the subject has gross purulent cervicitis at a visit with specimen collection (LVPP/EEC swabs, a Pap test, and/or cervical biopsy/definitive therapy specimens), the visit should be re-scheduled for a time after the condition is diagnosed and treated according to the study site's standards and practices.

Gynecologic conditions other than gross purulent cervicitis, such as vaginitis, bacterial vaginosis, and vaginal yeast infections, do not require a visit to be re-scheduled. These conditions should be diagnosed and treated according to the study site's standards and practices and treatment should be given after study sample collection and/or after study vaccination.

3.2.2.13.2 Genital/Cervical Swabs, Pap Test, and Sexually Transmitted Infection (STI) Testing (Female Subjects ≥21 Years of Age)

Two (2) LVPP swabs and 1 EEC swab for PCR assay will be collected at each study visit. A ThinPrep™ Pap test for liquid-based cytology Pap testing will be collected at Months 42, 54, 66, 78, 90, 102, 114, and 126. Tests for chlamydia and gonorrhea will be performed on the Pap test fluid. For collection of swabs and the ThinPrep™ Pap test, the study site must adhere to the procedures described in this protocol, must follow instructions provided by the SPONSOR/Central Laboratory, and must use the materials provided by the SPONSOR/Central Laboratory (see Section 3.2.4).

A non-lubricated, single use, individually wrapped, plastic speculum should be used for pelvic specimen collection. If lubrication of the speculum is needed, only use sterile saline or sterile water. During the Pap test, an inspection for vaginal lesions should be performed. Any vaginal lesion that is, in the investigator's opinion, HPV-related (e.g., condyloma acuminata or VaIN) should be classified and managed as described in Section 3.2.3.1.2.

ThinPrep™ Pap tests will be submitted to the SPONSOR-designated Central Laboratory. Cytology specimens will be evaluated using The Bethesda System-2001. For a diagnosis of atypical squamous cells of undetermined significance (ASC-US), the Central Laboratory will perform reflex testing for high-risk/low-risk HPV probes (Digene Hybrid

Capture II™ Assay) on residual ThinPrep™ material. The Pap test diagnoses generated by the Central Laboratory will be reported to the study sites for subject management, and subjects will be referred to colposcopy according to a protocol-mandated triage algorithm (see Table 3-1). All Pap test reports must be reviewed and signed by a physician (M.D./D.O.) investigator/sub-investigator.

As noted above (Section 3.2.2.9), local laboratory testing for STIs may be performed at any visit at the discretion of the investigator if clinically indicated. Any STI sampling of the cervix or external genital region should occur after the swabs and Pap test are obtained.

3.2.2.13.3 External Genital Lesion Examination (Female Subjects ≥21 Years of Age)

After obtaining all study specimens (swabs and Pap test), and after a change of gloves, an external genital examination should be performed using a good light source and a hand-held magnifying glass (4x to 5x power) or, optionally, a colposcope with low-power magnification. The following guidance should be used for all external genital lesion examinations performed within the study:

1. The examiner should ask the subject if she has noticed any bumps, lesions, or unusual symptoms (e.g., itching, discomfort, dyspareunia, dysuria).

2. The labia should be spread, and the condition of the hymen and vulvovaginal skin and clitoris are to be examined and noted. Note abnormalities, such as abnormal hair growth distributions, abnormalities of the skin, rashes, lacerations, or bruises.

3. The examination should include a systematic inspection of the entire external genitalia (periurethral, perineal, perianal, and vulvar regions) for apparent cutaneous and subcutaneous lesions or wart-like growths.

4. Acetic acid is not to be used routinely. It may be used for confirmation of a suspected lesion.

5. All observations should be recorded into the subject's chart. Medical conditions and lesions should be recorded on the appropriate eCRFs.

External genital lesions should be classified and managed as described in Section 3.2.3.1.2.

3.2.2.14 External Genital Lesion Examination and Sample Collection (Male Subjects ≥16 Years of Age)

An external genital examination should be performed using a good light source and a hand-held magnifying glass (4x to 5x power) or, optionally, a colposcope with low-power magnification (2x to 4x), and non-sterile gloves.

The external genital lesion examination (including penile, scrotal, perineal and perianal examination) should be completed prior to collecting external genital swabs. The guidance provided below should be used for all external genital lesion examinations performed within the study.

3.2.2.14.1 Penile and Scrotal Examination (Males Subjects ≥16 Years of Age)

1. The subject should be lying supine on the examination table.

2. The examiner should inquire as to whether the subject has shaved his genital region and/or applied any post-shave lotion or lubricants within 24 hours (1 Day) prior to the visit.

3. The examiner should inquire as to whether the subject has noticed any bumps or lesions or unusual symptoms (e.g., itching or dysuria). Begin with the inspection of the penile shaft, glans penis and urethral meatus, noting and recording evidence of abnormalities, including any abnormalities of the skin, rashes, minor lacerations, or bruises, etc.

4. The entire penis is to be palpated, region by region, for apparent cutaneous and subcutaneous lesions or wart-like growths.

5. After completing the inspection of the penis, continue with a careful examination of the scrotum. The testes should be palpated for asymmetry and/or palpable lesions.

6. The examination is to be performed using the hand-held magnifying glass and/or colposcope and should include the penile shaft, glans penis, and urethral meatus, and scrotum.

7. At the investigator's discretion, low-power magnification with the colposcope may be used for better visualization of an identified lesion.

8. Acetic acid is not to be used routinely. It may be used for confirmation of a suspected lesion.

3.2.2.14.2 Perineal and Perianal External Genital Lesion Inspection (Males Subjects ≥16 Years of Age)

The subject should lie on his left lateral side with his knees tucked up toward his chest or the prone knee-chest position that allows comfortable access for examination.

1. The examiner should inquire as to whether the subject has noticed any bumps or lesions or unusual symptoms (e.g., itching and/or dyspareunia).

2. Inspect the anus, perianal and perineal areas for the presence of anogenital warts.

3. The perianal and perineal regions are to be palpated for apparent cutaneous and subcutaneous lesions or wart-like growths.

4. The examiner should spread the contiguous skin by the use of his/her thumbs and note the condition of the anus.

5. The examination is to be performed using the hand-held magnifying glass and/or colposcope and should include the perianal and anal region

6. At the investigator's discretion, low-power magnification with the colposcope may be used for better visualization of an identified lesion.

7. Acetic acid is not to be used routinely. It may be used for confirmation of a suspected lesion.

3.2.2.14.3 External Genital Swabs (Male Subjects ≥16 Years of Age)

One (1) penile/glans swab, 1 scrotal swab, and 1 perineal/perianal swab for HPV PCR assay will be collected at each study visit following completion of the external genital examination.

For collection of swabs, the study site must adhere to the procedures described in this protocol, must follow instructions provided by the SPONSOR/Central Laboratory, and must use the materials provided by the SPONSOR/Central Laboratory (see Section 3.2.4).

3.2.2.14.4 Urine Specimen for Chlamydia and Gonorrhea Testing (Male Subjects ≥16 Years of Age)

This test is to be performed at Months 42, 54, 66, 78, 90, 102, 114, and 126. Urine should be collected after all routine swabs are obtained. For collection of urine samples, the study site must adhere to the procedures described in this protocol as described in Section 3.2.4.1.2.

3.2.3 Summary of Unscheduled Study Visits/Follow-up Procedures

3.2.3.1 Unscheduled Study Visits and Follow-up Procedures in Female Subjects

3.2.3.1.1 Colposcopy, Cervical Biopsy, and Cervical Definitive Therapy

Female subjects with abnormal ThinPrep™ Pap tests will be referred to colposcopy and biopsy according to the protocol-mandated triage algorithm. In addition, female subjects with histologically confirmed HPV-related external genital warts (e.g., condyloma acuminata, VIN, cancer) or vaginal warts (e.g., condyloma acuminata, VaIN, cancer) will be referred to colposcopy if the biopsies were not obtained during a colposcopy. If a colposcopy is required per the protocol-mandated triage algorithm, the colposcopy must be performed within 2 months of receipt of the abnormal result by the study investigator. If abnormalities of the cervix are found during colposcopy, cervical biopsies will be taken of the areas with the most severe abnormalities. The colposcopist may decide to take additional biopsies from areas with less severe abnormalities. If no cervical dysplasia is observed, the colposcopist may choose to perform an endocervical curettage (ECC). A vaginal exam is required during all study colposcopies. Additional Pap testing during the

unscheduled colposcopy study visit is not allowed and is considered a deviation from the protocol-mandated triage algorithm. A summary of colposcopy referral is given in Table 3-1.

Table 3-1

Protocol-Mandated Triage Algorithm for Referral to Colposcopy

ThinPrep™ Pap Result	**Action**
Negative for intraepithelial lesion or malignancy (includes reactive, reparative, inflammatory, etc.)	Routine visit interval as specified by the protocol.
Atypical Squamous Cells – Undetermined Significance (ASC-US)	Central laboratory performs reflex HPV testing on residual ThinPrep™ material (High Risk and Low Risk Probe, Hybrid Capture II, DIGENE™). If at least 1 probe is positive or if no result is obtained, the subject will be referred for colposcopy. If both probes are negative, the subject will return for Pap screening at the routine visit interval.
Atypical Squamous Cells – cannot exclude HSIL (ASC-H)	Referral to colposcopy.
Low-grade Squamous Intraepithelial Lesion (LSIL)	Referral to colposcopy.
High-grade Squamous Intraepithelial Lesion (HSIL)	Referral to colposcopy.
Atypical Glandular Cells (to include atypical endocervical, endometrial, NOS; Adenocarcinoma in Situ, adenocarcinoma, etc.)	Referral to colposcopy.
Unsatisfactory	Repeat ThinPrep™ Pap test as soon as possible, but not less than 4 weeks from the Pap test that had the unsatisfactory finding.
External Genital Biopsy Result	**Action**
HPV-related (e.g., condyloma acuminata, VIN, cancer)	Referral to colposcopy if the biopsy was not obtained at a colposcopy.
Vaginal Biopsy Result	**Action**
HPV-related (e.g., condyloma acuminata, VaIN, cancer)	Referral to colposcopy if the biopsy was not obtained at a colposcopy.

Notes:
Additional guidance for the protocol-mandated triage algorithm, including follow-up for discordant cases, is given in the Mandatory Regimen for Triage Attachment.

Deviations to the protocol-mandated triage algorithm for colposcopy, including repeat Pap tests at unscheduled colposcopy study visits, require consultation between the investigator and the SPONSOR and written documentation of the collaborative decision. Deviations that require this documentation include a colposcopy that is performed for another medical reason, such as unresolved post-coital bleeding that persists after completion of the appropriate work-up. In addition, if a deviation is discovered by the SPONSOR or study investigator after an error is made, retrospective written documentation is required. See the Administrative Binder for a summary of deviations that require documentation in this study.

If the Pap test diagnosis is AGC (to include AIS, atypical endocervical cells, adenocarcinoma, etc.), ASC-H, or HSIL and the subsequent biopsy diagnosis is CIN 1 or less, then this is defined as a discordant case. A discordant diagnosis will require a review of the results by the Sponsor-designated Central Laboratory. Upon completion of the review, a consultation report will be sent to the investigator. If the results are amended upon completion of this review, the protocol-mandated colposcopy triage algorithm (Table 3-1) and guidelines for cervical definitive therapy (Table 3-2) should be followed. If the discordant results are reviewed but not amended, see Table 3-2 and the Mandatory Regimen for Triage Attachment (Figure 4) for guidelines.

Subjects will be referred for cervical definitive therapy according to Table 3-2. If cervical definitive therapy is performed, on the day of the procedure, pre-definitive cervical biopsies must be taken of the areas with the most severe abnormalities prior to performing the cervical definitive therapy. Loop Electrosurgical Excision Procedure (LEEP) is the preferred method for cervical definitive therapy. LEEP has contraindications for subjects with the following conditions: allergy to all local anesthetics; pregnancy; severe acute cervicitis (severe acute cervicitis should be diagnosed and treated, and excision conducted after the infection has resolved); obvious invasive cancer; significant glandular neoplasia (AGUS favor neoplasia, AIS, Adenocarcinoma); and microinvasive cancer. In addition to LEEP, laser conization is also acceptable if it is the standard of care at the study site. Cold-knife conization and ablative cervical definitive therapy (e.g., cervical cryotherapy or cervical laser vaporization) should be reserved for rare instances where cervical definitive therapy is required and LEEP or laser conization is not indicated. LEEP, laser conization, and cold-knife conization are study procedures, but ablative cervical definitive therapy is not a study procedure because this procedure is not tissue preserving.

Table 3-2

Protocol-Mandated Guidance for Referral to Cervical Definitive Therapy

<table>
<tr><th colspan="2">Biopsy Results that Require Cervical Definitive Therapy</th></tr>
<tr><td colspan="2">Cervical biopsy result or ECC result of CIN 2†, CIN 3, Adenocarcinoma in Situ (AIS), or cervical cancer.</td></tr>
<tr><td colspan="2">Cervical biopsy (including ECC, if taken) result of CIN 1 on at least 2 consecutive biopsies for a duration of 18 months or longer†.</td></tr>
<tr><th colspan="2">Discordant Case Guidance for Cervical Definitive Therapy
(After Discordant Case Review Confirms Discrepancy)</th></tr>
<tr><td rowspan="2">High Grade Pap Result (AGC [to include AIS, atypical endocervical cells, adenocarcinoma, etc.)], ASC-H, or HSIL), negative vaginal examination, cervical biopsy/ECC is CIN 1 (or less) or if no lesion is seen and cervical biopsy/ECC is not taken:</td><td>If colposcopic examination was unsatisfactory- Cervical Definitive Therapy required.</td></tr>
<tr><td>If colposcopic examination was satisfactory- See Attachment (Mandatory Regimen for Triage, Figure 4) for guidance. ‡</td></tr>
<tr><td colspan="2">† Management of women ≤ 20 years of age should be consistent with local standards of care and may include observation in these instances.
‡ Two repeat High Grade Pap diagnoses (regardless of whether they are consecutive or not) without a confirmed cervical biopsy or ECC diagnosis of CIN 2, CIN 3, or cervical cancer will be referred to definitive therapy.
General Notes:
Pre-definitive cervical biopsies must be obtained on the day of the cervical definitive therapy procedure and must be taken before the cervical definitive therapy procedure is performed.
Ablative cervical definitive therapy is not a study procedure.
Deviations to the protocol-mandated guidance for referral to cervical definitive therapy and the footnotes in this table require consultation between the investigator and the SPONSOR and written documentation of the collaborative decision. In addition, if a deviation is discovered by the SPONSOR or study investigator after an error is made, retrospective written documentation is required. See the Administrative Binder for a summary of deviations that require documentation in this study.</td></tr>
</table>

If cervical biopsies, pre-definitive cervical biopsies, endocervical curettage (ECC) specimens, or cervical definitive therapy specimens are obtained, they must be sent to the SPONSOR-designated Central Laboratory for analysis. Separate biopsy forceps must be used for each of the discrete lesions that are biopsied. See Section 3.2.4 for detailed guidance on colposcopy, biopsy, ECC, and cervical definitive therapy procedures.

Subjects who undergo cervical biopsy and/or cervical definitive therapy will continue to be followed through the completion of scheduled study visits. The interval between a cervical biopsy and/or cervical definitive therapy and the next scheduled visit that includes a pelvic exam must be at least 2 months. Follow-up care after cervical definitive therapy will occur according to the study site's standards and practices.

Colposcopy, biopsy, and ECC procedures must be performed by an experienced health care professional (>50 colposcopies per year for at least 2 years). The cervical definitive therapy provider should be an experienced physician (defined as performing 20 LEEP procedures per year for at least 2 years) and must have documented formal instruction [i.e., residency or postgraduate course or American Society for Colposcopy and Cervical Pathology (ASCCP) training course]. To ensure that colposcopy practices and skill levels are standardized across study sites, and that colposcopists at all sites develop a uniform approach to all study colposcopies, study colposcopists will be required to participate in colposcopic standardization training. The purpose of this training is to evaluate the colposcopic practices at all study sites, to standardize colposcopy and biopsy practices, and to provide a guide for all aspects of the protocol related to colposcopy and histological sampling of the cervix. An alternative to the SPONSOR-organized colposcopy training, the "Comprehensive Colposcopy Course" given by the ASCCP, will be accepted as equivalent for the purpose of standardization to participate in this study, provided it has been taken within the previous year.

3.2.3.1.2 External Genital Lesion and Vaginal Lesion Diagnosis and Follow-Up

External genital lesions or vaginal lesions may be identified during a scheduled visit exam, Pap test, colposcopic examination, or at any other time during the study. For the purposes of this study, lesions that require access via the introitus (with the exception of the cervix, which is considered a separate location) are to be defined as vaginal lesions. Lesions that are external to the introitus are to be defined as external genital lesions. To classify the location of external genital lesions, the external genital area will be further divided into the following 4 regions:

- periurethral (includes the clitoris)
- perineal
- perianal
- vulvar (includes all areas other than the periurethral, perineal or perianal regions)

It is important to make an accurate evaluation of any identified external genital lesions. The practitioner must classify a lesion as condyloma acuminata, other HPV-related lesion (e.g., a flat wart, a papular wart, a keratotic wart, VIN, Bowenoid papulosis, Bowen's disease) or a non HPV-related lesion. If lesions are identified, they must be documented on the appropriate eCRF.

External genital lesions suspected to be possibly, probably, or definitely HPV-related (i.e., clinical impression of condyloma acuminata or other HPV-related lesion) or of unknown etiology are to be biopsied. Separate biopsies should be performed if external genital lesions are at different locations (periurethral, perineal, perianal, or vulvar region) or if more than one external genital lesion is at the same location and has a different morphology. An additional external genital lesion biopsy should be obtained if a new HPV-related lesion (or lesion of unknown etiology) appears and is of differing morphology and/or differing location from the initial lesion(s). A recurrent lesion should not be biopsied. A recurrent external genital lesion is defined as a lesion that has both of the following characteristics: (1) appears within 2 months of the complete resolution of an initial lesion(s) and (2) has the same location and a similar morphology as the initial lesion(s). If an HPV-related lesion or a lesion of unknown etiology appears after 2 months of complete resolution of the initial lesion(s), a biopsy of the lesion should be taken.

Vaginal lesions suspected to be possibly, probably, or definitely HPV-related (i.e., condyloma acuminata or other HPV-related lesion) or of unknown etiology are to be biopsied. Separate biopsies should be performed for each vaginal lesion with a different morphology. An additional vaginal biopsy should be obtained if a new potentially or definitely HPV-related lesion (or lesion of unknown etiology) appears and is of differing morphology from the initial lesion(s). A recurrent lesion should not be biopsied. A recurrent vaginal lesion is defined as a lesion that has both of the following characteristics: (1) appears within 2 months of the complete resolution of an initial lesion(s) and (2) has a similar morphology as the initial lesion(s). If an HPV-related lesion or a lesion of unknown etiology appears after 2 months of complete resolution of the initial lesion(s), a biopsy of the lesion should be taken.

External genital lesion biopsies and vaginal lesion biopsies must be sent to the SPONSOR-designated Central Laboratory for analysis. Separate biopsy forceps must be used for each of the discrete lesions that are biopsied. Biopsy of an external genital lesion or vaginal lesion should ideally be performed on the same day that the lesion is first observed, because the lesion may resolve before the subject returns for a biopsy procedure if it is performed at a later time. See Section 3.2.4 for detailed guidance on these procedures.

Subjects with histologically confirmed HPV-related external genital warts (e.g., condyloma acuminata, VIN, cancer) or vaginal warts (e.g., condyloma acuminata, VaIN, cancer) will be referred to colposcopy if the external genital or vaginal biopsies were not obtained during a colposcopy (see Section 3.2.4). Subjects who undergo external genital lesion biopsy, vaginal lesion biopsy, and any subsequent treatment for the lesions will

continue to be followed through the completion of scheduled study visits. After a biopsy is obtained, management and treatment of external genital lesions and vaginal lesions are at the investigator's discretion and according to the study site's standards and practices. If excision is chosen as the method of treatment, all excised tissue is to be submitted to the SPONSOR-designated Central Laboratory for analysis. The interval between the external genital lesion biopsy/excision or vaginal lesion biopsy/excision and the next scheduled visit involving a pelvic exam must be at least 2 months. External genital lesion biopsy/excision and vaginal lesion biopsy/excision must be performed by an experienced health care professional.

3.2.3.1.3 Processing of Tissue Specimens in the Context of the Study

Extra visits that are associated with tissue excision (cervical, vaginal, external genital, and cervical definitive therapy samples) will be considered part of the study. Any specimens collected will be obtained as described in the protocol and collected and shipped as described in the Laboratory Manual provided by the SPONSOR/Central Laboratory. Slides of tissue specimens will be prepared at the SPONSOR-designated Central Laboratory and reviewed by a pathologist, and reports will be provided to the study sites for subject management.

All tissue slides will be reviewed by the HPV Vaccine Program's expert Pathology Panel (See Section 3.3.3). The consensus diagnosis of HPV Vaccine Program Pathology Panel will represent the final diagnosis for study purposes and not for subject management. Also, all tissue will be tested at MRL for detection of HPV types by PCR assay (See Section 3.3.2). The SPONSOR and the HPV Vaccine Program Pathology Panel will follow established guidelines for review of the slides. The investigator will be notified of any histological diagnosis made by the HPV Vaccine Program Pathology Panel that is more severe than the one made by the SPONSOR-designated Central Laboratory.

3.2.3.1.4 Pap Tests and Tissue Specimens Taken Outside the Context of the Study

Cervical, vaginal, and external genital tissue samples and Pap tests collected outside the context of the study are **strongly discouraged**. For procedures with sample collection, "outside the context of the study" is defined as processing of samples at a local laboratory rather than through the SPONSOR-designated Central Laboratory. For procedures without sample collection, such as a colposcopy without biopsy, "outside the context of the study" means a procedure performed by a non-study clinician. If a subject undergoes a study procedure outside the context of the study, all efforts will be made to obtain and send the following to the SPONSOR: (1) Pap or colposcopy/operative report; (2) diagnostic slides (for tissue biopsies only); (3) local pathology report; and (4) tissue block for diagnostic slide preparation and HPV analysis

3.2.3.2 Unscheduled Study Visits/Follow-up Procedures in Male Subjects

3.2.3.2.1 External Genital Lesion Diagnosis

After a thorough external genital lesion examination, the investigator's clinical impression should be recorded. If a lesion, in the investigator's opinion, is possibly, probably, or definitely HPV infection-related or the diagnosis is unknown, it should be biopsied for further evaluation. For multiple lesions, select one external lesion to biopsy that is most representative of the morphology or anatomic location, and is most accessible. A second biopsy is indicated, if a lesion is identified in a separate region (anterior region includes penis and scrotum and posterior region includes perineal and perianal region) or a lesion is identified with different morphology in the same region. For each biopsy, different instruments are to be used to prevent cross-contamination between specimens. At the investigator's discretion, the lesion(s) may be surgically removed (therapeutic excision). In that case, the entire specimen must be submitted for analysis. All specimen(s) excised should be submitted to the central laboratory designated by the SPONSOR for analysis. For the genital wart/lesion biopsy, the external genital lesion biopsy kit provided by the SPONSOR central laboratory is to be used. Slides of the wart/lesion biopsy will be reviewed by a pathologist for the purpose of management of the subject. Management of anogenital warts is a study procedure, but the decision regarding the modality of therapy will be left to the discretion of the investigator, per the site's standard and practices. Excision of the wart/lesion is the preferred study treatment. All excised tissue is to be submitted to the central laboratory for analysis. If more than one biopsy is performed, then use separate instruments for each biopsy. Each biopsy should be placed in individual formalin containers. Treatment of anogenital warts by topical medications or cryotherapy is an acceptable study procedure. A biopsy of the identified lesion/lesions (e.g., morphology differs among identified lesions or more than one lesion is identified) must be obtained prior to administering treatment.

The investigator should provide a clinical impression of the lesion, which should include one of the following: condyloma acuminata, other HPV-related lesion (e.g., Bowenoid papulosis, Bowen's disease), or other non-HPV related lesions.

The location of all lesions that are being submitted for biopsy should be clearly identified on the study operative report form located in the administrative binder.

The location and anatomical area of each biopsied wart/lesion should be identified and noted (as per the lab kit requisition supplied by the SPONSOR and should also be recorded on the workbook/case report form).

3.2.3.2.2 Processing of Tissue Specimens in the Context of the Study

Extra visits that are associated with external genital tissue excision will be considered part of the study. Any specimens collected will be obtained as described in the protocol and collected and shipped as described in the Laboratory Manual provided by the SPONSOR/Central Laboratory. Slides of tissue specimens will be prepared at the

SPONSOR-designated Central Laboratory and reviewed by a pathologist, and reports will be provided to the study sites for subject management.

All tissue slides will be reviewed by the HPV Vaccine Program's expert Pathology Panel (see Section 3.3.3). The consensus diagnosis of HPV Vaccine Program Pathology Panel will represent the final diagnosis for study purposes and not for subject management. Also, all tissue will be tested at MRL for detection of HPV types by PCR assay (See Section 3.3.2). The SPONSOR and the HPV Vaccine Program Pathology Panel will follow established guidelines for review of the slides. The investigator will be notified of any histological diagnosis made by the HPV Vaccine Program Pathology Panel that is more severe than the one made by the SPONSOR-designated Central Laboratory.

3.2.4 Procedures for Collection and Handling of Study Specimen

For scheduled study visits, consult the Study Flow Chart for the specific samples needed for each visit and the order of sample collection. The following Sections describe the step-by-step procedures for collection of study specimens, a description of supplies needed, and the guidelines for handling specimens.

Samples should be shipped, labeled, and handled as instructed by the SPONSOR/Central Laboratory. Specimen collection supplies provided by the SPONSOR/Central Laboratory must be used by the site without substitution.

Within 30 minutes of collection, place serum and gynecological/genitourinary swabs in a freezer at -20°C (or lower) until the samples are shipped on dry ice. If the samples thaw, contact the SPONSOR. Thawed serum/swab samples require written documentation, including details such as allocation number, visit interval, date of collection, and sample accession numbers (see the Administrative Binder for a summary of deviations that require documentation in this study).

For collection of pelvic specimens in female subjects (EEC swab, Pap test, cervical biopsy/definitive therapy), a non-lubricated, single use, individually wrapped, plastic speculum should be used. If lubrication of the speculum is needed, only use sterile saline or sterile water may be used.

3.2.4.1 Study Procedures Applicable to both Female and Male Subjects

3.2.4.1.1 Serum for Anti-HPV Measurements at Scheduled Visits

For each visit that requires a serum specimen for anti-HPV measurements, a 10-mL (non-heparinized, non-serum separator, red-top tube provided by the SPONSOR-designated Central Laboratory) blood specimen will be collected and should be separated to avoid hemolysis. A minimum of 3.0 mL of serum should be aliquoted to a vial provided by the SPONSOR-designated Central Laboratory. An additional 1.5 mL of serum ("Retention Serum") should be aliquoted to a vial provided by the SPONSOR-designated Central Laboratory and labeled with the "Retention Serum" label provided by the SPONSOR-designated Central Laboratory.

"Serum" vials will be stored at the site at -20°C (or lower) until shipped on dry ice to the address noted on SPONSOR-designated Central Laboratory contact information page. The freezer used to store the vials must be a non-frost-free freezer. All available serum should be used for conducting assays specified in the clinical protocol. Serum may also be used during the clinical trial, for further HPV immunologic testing in addition to tests specified in the protocol.

"Retention Serum" vials will remain stored at the site at -20°C (or lower). The freezer used to store the vials must be a non-frost-free freezer. The site should ship "Retention Serum" separately from the "Serum" sample. If "Retention Serum" is sent to the SPONSOR-designated Central Laboratory, it may also be used for further HPV immunologic testing, in addition to tests specified in the protocol.

Serum testing is to be completed before the end of study (final report of study results).

3.2.4.1.2 Urine Specimen for Chlamydia and Gonorrhea Testing

Chlamydia and gonorrhea testing will be performed by a local laboratory using supplies provided by the site.

3.2.4.2 Study Procedures Applicable to Female Subjects Only

3.2.4.2.1 Labial/Vulvar/Perineal and Perianal (LVPP) Swabs for HPV PCR

Use female swabs and Specimen Transport Medium (STM) vials supplied by the SPONSOR-designated Central Laboratory. When collecting swab specimens, remember to keep all swab tips and swab shafts (i.e., the portion that will be placed in the STM) untouched.

1. Remove female swabs from packaging.

2. Using the first swab, swab back and forth in a tight zigzag motion from the clitoral prepuce down to the posterior fourchette on first one side and then the other, so two parallel zigzag paths down the perineum will allow collection between the folds of the labia minora and majora.

3. With the second swab, swab the perianal area.

4. Place both swabs in the appropriately labeled collection/transport tube containing STM. Break off the end of the shafts protruding from the tube by bending them sharply against the rim of the tube. The shafts are pre-scored to facilitate breakage.

5. Securely cap the collection/transport tube containing the specimen.

6. Ensure proper labeling, store the sample at -20°C (or lower), and ship the sample as specified in the Administrative Binder.

3.2.4.2.2 Endo/Ectocervical (EEC) Swab for HPV PCR

Use female swabs and Specimen Transport Medium (STM) vials supplied by the SPONSOR-designated Central Laboratory. When collecting swab specimens, remember to keep all swab tips and swab shafts (i.e. the portion that will be placed in the STM) untouched.

1. Remove one female swab from its packaging.

2. Introduce the swab into the cervical os with enough pressure to maintain contact with the epithelium, but not to induce bleeding. Twirl the swab only 1 to 2 times, and then use a back-and-forth swiping motion across the ectocervix from anterior to posterior cervical lip (top to bottom).

3. Place the swab into the collection/transport tube containing the STM. Break off the end of the shaft protruding from the tube by bending it sharply against the rim of the tube. The shaft is pre-scored to facilitate breakage.

4. Securely cap the collection/transport tube containing the specimen.

5. Ensure proper labeling, store the sample at -20°C (or lower), and ship the sample as specified in the SPONSOR/Central Laboratory.

3.2.4.2.3 Pap Test (ThinPrep™) Specimen Collection

Use PreservCyt™ supplied by the SPONSOR-designated Central Laboratory.

1. Using a plastic spatula, scrape the ectocervix in a 360° arc for 2 full rotations, being sure to include the squamocolumnar junction in the portion sampled. Place the spatula into the open PreservCyt™ vial, using vigorous shaking and swishing of the spatula to rinse all of the cellular debris from the spatula. It is acceptable to leave the spatula in the open PreservCyt™ vial until the cytobrush collection is completed.

2. Insert a cytobrush[3] into the cervical os, and slowly rotate 1/2 full turn one direction. DO NOT OVER-ROTATE. Do not insert deeper than the length of the brush head. Place the cytobrush immediately into the PreservCyt™ vial.

3. Use the spatula to rub against the cytobrush in order to dislodge as much cellular debris from the cytobrush and spatula as possible. Swish and rinse the cytobrush, and knock it against the side of the PreservCyt™ vial at least 10 times to release enough

[3] The use of a cytobrush (Cytobrush™) for ThinPrep™ Pap test collection is contraindicated in women who are 10 weeks pregnant or more, according to the current manufacturer's label. The use of a broom (Wallach Papette™) for ThinPrep™ Pap test collection is not contraindicated in pregnancy, according to the current manufacturer's label. The use of a Wallach Papette™ instead of Cytobrush™ will be allowed if the investigator decides to perform a ThinPrep™ Pap test during pregnancy.

epithelial cells for an adequate Pap test sample. In order to minimize adherence of cellular debris to the collection devices, the rinsing and swishing procedures should be performed within 2 minutes of collection.

4. Remove the spatula and the cytobrush from the PreservCyt™ vial and twist the cap on the vial securely.

5. Ensure proper labeling of the sample as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory. Store PreservCyt™ vials containing the specimens at room temperature until they are shipped to the Central Laboratory. According the manufacturer's instructions, ThinPrep™ specimens must be processed within 21 days of collection to preserve sample integrity. To meet this requirement, specimens must be shipped according to instructions and time intervals specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

6. Prior to removal of the speculum, inspect the lateral walls of the vagina for vaginal lesions. Then collapse the speculum and rotate 90 degrees and re-open the blades to inspect the anterior and posterior walls of the vagina for vaginal lesions. If vaginal lesions are present, use the guidance given in the protocol to classify vaginal lesions and to obtain required biopsies (see Sections 3.2.3.1.2). Collapse and remove the speculum.

7. Change gloves and perform a systematic inspection of the entire external genitalia using a good light source and a hand-held magnifying glass (4x to 5x power) or, optionally, a colposcope with low-power magnification. If external genital lesions are present, use the guidance given in the protocol to classify external genital lesions and to obtain required biopsies (see Sections 3.2.3.1.2 and 3.2.4.2.4).

3.2.4.2.4 External Genital Lesion Biopsy and Vaginal Lesion Biopsy

Use the appropriate eCRFs to note locations, clinical impressions, and biopsy numbers during the procedure. Use the specimen collection kits (labels/requisition) and formalin fixative container provided by the SPONSOR-designated Central Laboratory. The external genital biopsy kit should be used for external genital biopsies and the vaginal biopsy kit should be used for vaginal biopsies.

1. Cleanse the biopsy area with antiseptic solution. Using a 30-gauge needle and a syringe of 1 to 2 mL of 1% lidocaine or bacteriostatic saline, infiltrate below the epidermis of the lesion.

2. Elevate the lesion and remove tangentially with fine (iris) scissors or a scalpel blade to obtain the specimen.

3. Place the biopsy piece in the fixative container and ensure proper labeling of the sample as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

4. If multiple biopsies are obtained, each specimen must be placed in a separate container of fixative. To prevent cross-contamination, a different set of instruments is to be used for each biopsy taken. A maximum of 6 external genital lesion biopsies and 3 vaginal biopsies should be obtained.

5. If the biopsy procedure does not remove the entire lesion(s) and surgical excision is chosen as a treatment method, the excised tissue is to be submitted to the Central Laboratory in a separate container of fixative and labeled as an additional biopsy.

6. To promote hemostasis after the procedure, apply gentle pressure. Monsel's solution may be used. For larger areas, a single interrupted suture may be used. Electrocauterization is to be avoided, but the decision is left to the discretion of the practitioner.

7. Advise the patient to keep the area clean and to expect spotting for 3 days with healing by 1 week.

On the day of collection, ship the sample at room temperature as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

3.2.4.2.5 Colposcopy Guidelines

In order for a colposcopy to be considered satisfactory, the entire transformation zone, including all of the squamocolumnar junction, and the limits of all lesions must be visualized.

1. Assist patient to dorsal lithotomy position.

2. Insert speculum and visualize the entire cervix through the colposcope at low power.

3. Use optional visualization adjuncts (i.e., condom or rubber glove finger "tube" over speculum, lateral side-wall retractor) if necessary to enhance colposcopic visualization.

4. Remove mucus and debris by liberally applying 5% acetic acid to the cervix using cotton balls and ring forceps, large cotton swabs, or by spray technique. Avoid use of 4×4 gauze pads.

5. Reapply acetic acid (or Lugol's solution) to the cervix for a minimum of 60 seconds. Thereafter, reapply acetic acid every 3 to 5 minutes or when the columnar epithelium is no longer blanched white.

6. Identify the entire squamocolumnar junction (360°), if able.

7. Identify acetowhite cervical lesions if present.

8. Assess the severity of each cervical lesion using green filter as needed to examine the vascular patterns.

9. As a guide, use the Reid Colposcopic Index (RCI), which is provided in the Administrative Binder, to classify any identified cervical lesions.

10. Obtain cervical biopsies and, if medically indicated, performed an endocervical curettage (ECC) sample collection (see below for cervical biopsy and ECC procedures).

11. Prior to removal of the speculum, inspect the lateral walls of the vagina with the colposcope. If clinically indicated, apply 5% acetic acid or Lugol's solution to the entire epithelium and then view by low power colposcopic magnification, noting acetowhite (or brownish if Lugol's solution used) vaginal lesions. Collapse the speculum and rotate 90 degrees and re-open the blades to inspect the anterior and posterior walls of the vagina for vaginal lesions (again using the 5% acetic acid or Lugol's solution if clinically indicated). If vaginal lesions are present, use the guidance given in the protocol to classify vaginal lesions and to obtain required biopsies (see Sections 3.2.3.1.2 and 3.2.4.2.4) Collapse and remove the speculum.

12. Change gloves and perform a systematic inspection of the entire external genitalia using a good light source and a hand-held magnifying glass (4x to 5x power) or, optionally, a colposcope with low-power magnification. If external genital lesions are present, use the guidance given in the protocol to classify external genital lesions and to obtain required biopsies (see Sections 3.2.3.1.2 and 3.2.4.2.4).

3.2.4.2.6 Procedures for Cervical Biopsy

A colposcopy should precede all biopsies. Use the appropriate CRFs to note locations, clinical impressions, and biopsy numbers during the procedure. Use the cervical biopsy kit (labels/requisition) and formalin fixative provided by the SPONSOR-designated Central Laboratory.

1. Each discrete abnormal area that is observed on colposcopy should be biopsied. The most severe area of abnormality of a lesion observed on colposcopy should be biopsied.

2. Apply local anesthesia, if this is the local standard of care.

3. If taking multiple biopsies, start with the most posterior (i.e. lower) lesion first. This will prevent contamination of subsequent biopsy sites by the flow of blood from the previous biopsy sites.

4. Place biopsy forceps over the abnormal lesion (usually near the squamocolumnar junction).

5. Open forceps jaws to sufficient extent.

6. Check to make sure the forceps are properly aligned (fixed end of forceps jaw towards cervical os).

7. Rotate biopsy handles to place lesion in the center of biopsy jaw angle if necessary.

8. Exert moderate pressure with biopsy forceps to push cervix backwards until cervix is fixed in position.

9. Squeeze handles together quickly and firmly to close forceps jaws and excise lesion.

10. Lock biopsy jaws to secure tissue (if locking mechanism available) or just hold tightly, then pass the forceps to the assistant.

11. Confirm by colposcopic visualization that an appropriate and adequate biopsy was collected. The biopsy should be perpendicular to the epithelium and deep enough to sample the entire epithelium along with a small amount of stroma (at least 2 mm) for histology.

12. Tamponade biopsy site with cotton swab.

13. Place the biopsy piece in the fixative container and ensure proper labeling of the sample as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

14. Repeat the biopsy procedure for each additional biopsy performed using a different pair of forceps. If multiple biopsies are obtained, each specimen must be placed in a separate fixative container. A maximum of 4 cervical biopsies should be obtained. Collect all biopsy specimens prior to establishing hemostasis, if possible.

15. Obtain complete hemostasis with directed silver nitrate stick or Monsel's (ferric subsulfate) paste application.

16. Instruct subject to: (1) take nonsteroidal anti-inflammatory drugs for uterine cramping (provided no allergy), (2) report significant bleeding immediately, and (3) refrain from use of vaginal products, douching, tampons, and sexual intercourse for 3 to 7 days.

17. On the day of collection, ship the sample at room temperature as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

If no lesion is noted on colposcopy, and the subject was referred based on a cytological abnormality, then endocervical curettage (ECC) may be performed.

3.2.4.2.7 Procedures for Endocervical Curettage (ECC)

Use the cervical biopsy kit (labels/requisition) and formalin fixative provided by the SPONSOR-designated Central Laboratory. A curet must be used (not a cytobrush) when obtaining the ECC specimen. The decision to perform an ECC will be made by the study investigator according to local standards and practices.

1. Obtain an ECC specimen either before or after endocervical biopsies (based on local standard of care).

2. Insert open basket endocervical curet into cervical os.

3. Apply gentle pressure at the distal tip of curet against the endocervical canal and pull the curet from inside to outside with pressure, while simultaneously rotating the curet in a circular direction. The curet should advance no more that 20 mm up the canal and should be rotated completely 2 to 3 times. Avoid sampling ectocervical lesions that extend proximally into the endocervical canal, if possible.

4. Spin the curet rapidly to trap epithelium in the basket and remove the curet from the canal. Scraped material remaining in the canal can be retrieved with small forceps.

5. Place the ECC specimen into the fixative vial (or place the ECC specimen on paper or Telfa and transfer it to the fixative vial) and ensure proper labeling of the sample as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

6. On the day of collection, ship the sample at room temperature as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

3.2.4.2.8 Procedures for Loop Electrosurgical Excision Procedure (LEEP) and Top Hat Method

LEEP used for cervical definitive therapy has contraindications for subjects with the following conditions: allergy to all local anesthetics; pregnancy; severe acute cervicitis (severe acute cervicitis should be diagnosed and treated, and excision conducted after the infection has resolved); obvious invasive cancer; significant glandular neoplasia (AGUS favor neoplasia, AIS, Adenocarcinoma); and microinvasive cancer.

The LEEP is a cervical definitive therapy method that uses a shallow pass to remove the cervical transformation zone. It may be a single or multiple pass and is ~8 mm deep. A "top hat" cone implies a deeper wedge resection, ~15 to 25 mm deep. It is performed by the "top hat" method of successively more internal and smaller loops.

Use the appropriate CRFs to note clinical impressions and biopsy numbers during the procedure. Use the definitive therapy kit (labels/requisitions) and formalin fixative provided by the SPONSOR-designated Central Laboratory. The LEEP should be done under colposcopic control. All instruments used for the procedure must be nonconductive.

1. Assist subject into dorsal lithotomy position.

2. Place dispersive pad near operative site (thigh) and plug into electrosurgical unit (ESU).

3. Place vaginal speculum and secure smoke evacuation tubing.

4. Set electrosurgical unit parameters (power, cut/blend) and test safety systems.

5. Identify cervical pathology by colposcopic examination.

6. If appropriate, apply half-strength Lugol's solution to cervix and identify transformation zone limits.

7. Give local anesthesia if no allergy—4 quadrant (locations 3, 6, 9, 12 o'clock) intracervical injection of lidocaine with epinephrine.

8. Obtain pre-definitive cervical biopsies of the areas with the most severe abnormalities (2- to 3-mm size per location) and use the cervical biopsy labels/requisition provided within the definitive therapy kit (see Section 3.2.4.2.6 for cervical biopsy guidelines).

9. Select appropriate loop electrode size to remove transformation zone and lesion, insert into hand piece and plug hand piece into electrosurgical unit.

10. Activate smoke evacuator.

11. Initiate excision by depressing "cut" switch if using handpiece, cut down (perpendicular to tissue), across transformation zone and straight out at opposite side of transformation zone (depth of 8 mm) and avoid vaginal sidewall contact.

12. Repeat cut procedure (reduced power) along endocervical canal with smaller 10 x 10 loop electrode if top hat conization is necessary.

13. Hand excised tissue to assistant and dictate its orientation. Orient the tissue by placing a suture at the 12 o'clock location. Place tissue in the fixative container and ensure proper labeling of the sample as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory. Note: If the top hat procedure is performed, the tissue from each loop or "pass" should be placed in separate labeled fixative containers.

14. Inspect endocervical canal opening and perform ECC, if medically indicated. Use the ECC label/requisition provided within the definitive therapy kit (see Section 3.2.5.6 for ECC guidelines).

15. Fulgurate base of the excision with coagulation using the ball or paddle electrode until adequate hemostasis and fulgurate 5 mm of the ectocervical margin. If lesion extends beyond the excision, ablate the area and record the ablation on the appropriate CRF and source document.

16. If hemostasis is inadequate, pack base of excision with Monsel's (ferric subsulfate) paste or in rare event suture may be required.

17. Remove blood from posterior fornix.

18. Deactivate ESU and smoke evacuator.

19. Remove dispersive pad and vaginal speculum.

20. Assist subject up from table.

21. Instruct subject to: (1) take nonsteroidal anti-inflammatory drugs as needed (provided no allergy), (2) refrain from use of vaginal products, douching, tampons, and sexual intercourse for 2 to 4 weeks, and (3) report significant bleeding and signs of infection (fever, pain) immediately.

22. On the day of collection, ship the sample at room temperature as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

3.2.4.2.9 Procedure for Laser Conization

Laser Conization is a cervical definitive therapy procedure that uses a laser beam to excise tissue, using small depressor instruments or hooks to position the cone for optimal excision.

Use the appropriate CRFs to note clinical impressions and biopsy numbers during the procedure. Use the definitive therapy kit (labels/requisitions) and formalin fixative provided by the SPONSOR-designated Central Laboratory.

1. Assist subject into dorsal lithotomy position.

2. Place vaginal speculum and secure smoke evacuation tubing.

3. Set laser unit parameters (power, optical focusing of the laser beam) and test safety systems.

4. Identify cervical pathology by colposcopic examination.

5. If appropriate, apply half-strength Lugol's solution to cervix and identify transformation zone limits.

6. Give local anesthesia if no allergy—4 quadrant (3, 6, 9, 12 o'clock) intracervical injection of lidocaine with epinephrine. If needed paracervical injection of the anesthetic may also be used. General anesthesia may be provided if so preferred. If general anesthesia is preferred, intracervical injection of lidocaine with epinephrine may still be used if there is no allergy to the components of the injection.

7. Obtain pre-definitive cervical biopsies of the areas with the most severe abnormalities (2- to 3-mm size per location) and use the cervical biopsy labels/requisition provided within the definitive therapy kit (see 3.2.5.5 for cervical biopsy guidelines).

8. Activate smoke evacuator.

9. Initiate excision by marking the border of the area to be excised with the laser beam.

10. Cut the cone by the laser beam, using small depressor instruments or hooks to position the cone for optimal excision with the laser beam.

11. Hand excised tissue to assistant and dictate its orientation. Orient the tissue by placing a suture at the 12 o'clock location. Place tissue in the fixative container and ensure proper labeling of the sample as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

12. Inspect endocervical canal opening and perform ECC, if medically indicated. Use the ECC label/requisition provided within the definitive therapy kit (see Section 3.2.4.2.7 for ECC guidelines).

13. Use the defocused laser beam in the wound area until adequate hemostasis, and vaporize 5 mm of the ectocervical margin. If lesion extends beyond the excision, ablate the area and record the ablation on the appropriate CRF and source document.

14. If hemostasis is inadequate, inject more lidocaine with adrenaline or in rare event suture may be required.

15. Remove blood from posterior fornix.

16. Remove dispersive pad and vaginal speculum and deactivate smoke evacuator.

17. Assist subject up from table.

18. Instruct subject to: (1) refrain from use of vaginal products, douching/ vaginal cleansing, tampons, and sexual intercourse for 2 weeks, and (2) report significant bleeding and signs of infection (fever, pain) immediately and (3) take nonsteroidal anti-inflammatory drugs as needed (provided no allergy)

19. On the day of collection, ship the sample at room temperature as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory.

3.2.4.2.10 Cold-Knife Conization

Cervical cold-knife conization should be performed only when the LEEP or laser conization procedures are not indicated. A cervical cold-knife conization specimen represents a conically shaped section of the cervix that will vary in size according to the lesion. A broad, shallow conization would be performed for a predominantly exocervical lesion and a narrow, deep conization is appropriate for a predominantly endocervical lesion. Pre-definitive biopsies should be obtained prior to the cervical cold-knife conization. Use the appropriate CRFs to note clinical impressions and biopsy numbers during the procedure. Use the definitive therapy kit (labels/requisitions) for pre-definitive biopsy/ECC (if indicated)/definitive therapy tissue and use the formalin fixative provided by the SPONSOR-designated Central Laboratory. The samples should be

labeled/shipped as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory (ship at room temperature, ship on day of collection).

3.2.4.2.11 Ablative Cervical Definitive Therapy

Ablative cervical definitive therapy is not a study procedure, because this procedure is not tissue preserving. If a subject undergoes ablative cervical definitive therapy (e.g., cervical cryotherapy or cervical laser vaporization) or a hysterectomy during the study, obtain pre-definitive biopsy specimens. Use the definitive therapy kit (labels/requisitions) for pre-definitive biopsy/ECC (if indicated) and use the formalin fixative provided by the SPONSOR-designated Central Laboratory. The samples should be labeled/shipped as specified in the Laboratory Manual that is provided by the SPONSOR/Central Laboratory (ship at room temperature, ship on day of collection).

3.2.4.3 Study Procedures Applicable to Males Subjects Only

3.2.4.3.1 Penile File and Wetted Swab for HPV PCR

1. The subject should be lying supine on the examination table. In order to prepare the subject for the specimen collection with nail file, the examiner should demonstrate a nail file (not kept in sterile condition) prior to the procedure, and ask the subject to rub it on his hands.

2. Remove the nail file from the packaging; remove the male swab from the packaging, then twist the top off of the sterile saline ampule, and wet the entire head of the male swab with the sterile saline, but do not over moisten. If necessary, squeeze the head of the swab to remove excess liquid (while maintaining sterility), as too much liquid may wash cells off the skin instead of collecting them on the swab. If the swab is dripping saline, it is too wet. Only one file and one swab are to be used in the penile sampling.

3. In circumcised men, the examiner wearing gloves should hold the tip of the penis with the thumb and index finger of the non-dominant hand. The file should be held in the dominant hand and in a tight up and down motion (or back and forth motion), move the file over the left and right side of the penile shaft, encompassing the whole shaft, and then gently rub the glans. Sufficient pressure should be applied in order to cause blanching of the skin. If blanching is not observed, pressure should be increased in order to collect the required DNA. Subsequently, the examiner should hold the swab in the dominant hand and in a tight up and down motion, gently swab the shaft and glans following the same route. As with the file, sufficient pressure should be used with the male swab to blanch the skin while moving it over the area of loosened cellular debris. The swab should also be twisted or rotated in order to increase surface area exposure for collection of cellular debris.

4. In uncircumcised men, the examiner wearing gloves should hold the tip of the penis with the thumb and index finger of the non-dominant hand. The file should be held in the dominant hand and in a tight up and down motion (or back and forth motion), gently move the file over the left and right side of the penile shaft, including the outer

foreskin. The examiner should retract the foreskin, and hold the penis with the thumb and the index finger, and gently rub the file over the glans. Sufficient pressure should be applied in order to cause blanching of the skin. If blanching is not observed, pressure should be increased in order to collect the required DNA. Then follow with a wetted swab and rub the penile shaft, the outer foreskin, and then retract the foreskin, and swab the glans, following the same route as the file**.** As with the file, sufficient pressure should be used with the male swab to blanch the skin while moving it over the area of loosened cellular debris. The swab should also be twisted or rotated in order to increase surface area exposure for collection of cellular debris.

5. Discard the file in a Biohazard Sharps Container.

6. Place the swab in an STM vial and break the pre-scored handle. Do not add saline to the STM vial either before or after swabbing.

7. Securely cap the collection/transport tube containing the specimen.

8. Place the appropriate label for the Penile Sample on the STM vial.

3.2.4.3.2 Scrotal File and Wetted Swab for HPV PCR

1. The subject should be lying supine on the examination table. Remove the nail file from the packaging; remove the male swab from the packaging, then twist the top off of the sterile saline ampule, and wet the entire head of the male swab with the sterile saline, but do not over moisten. If necessary, squeeze the head of the swab to remove excess liquid (while maintaining sterility), as too much liquid may wash cells off the skin instead of collecting them on the swab. If the swab is dripping saline, it is too wet. Only one file and one swab are to be used in the scrotal sampling.

2. With the non-dominant hand, lift and move the penis off of the scrotum, and gently rub the file over the entire scrotum with a tight up and down motion (or back and forth motion), moving from left to right. Sufficient pressure should be applied in order to cause blanching of the skin. If blanching is not observed, pressure should be increased in order to collect the required DNA. It is important to stretch or pull the skin taut in order to allow enough pressure to be applied by the nail file. If necessary, the subject can assist with this activity by holding the skin at the bottom of the scrotum while the file (and subsequently the wetted swab) is moved across the area. The subject should not perform the filing or swabbing procedure.

3. Subsequently, with the non-dominant hand, lift the penis, and gently rub the wetted swab over the entire scrotum with a tight up and down motion, moving from left to right. As with the file, sufficient pressure should be used with the male swab to blanch the skin while moving it over the area of loosened cellular debris. The swab should also be twisted or rotated in order to increase surface area exposure for collection of debris. Only one file and one swab are to be used in the scrotal sampling.

4. Discard the file in a Biohazard Sharps container.

5. Place the swab in an STM vial and break the pre-scored handle. Do not add saline to the STM vial either before or after swabbing.

6. Securely cap the collection/transport tube containing the specimen.

7. Place the appropriate label for the Scrotal Sample on the STM vial.

3.2.4.3.3 Perineal/Perianal File and Wetted Swab for HPV PCR

1. The subject should lie on his left lateral side with his knees tucked up towards his chest or in the prone knee chest position that allows comfortable access for examination. Remove the nail file from the packaging. Remove the male swab from the packaging, then twist the top off of the sterile saline ampule, and wet the entire head of the male swab, but do not over moisten. If necessary, squeeze the head of the swab to remove excess liquid (while maintaining sterility), as too much liquid may wash cells off the skin instead of collecting them on the swab. If the swab is dripping saline, it is too wet. Only one file and one swab are to be used in the perineal/perianal sampling.

2. If the subject is in the left lateral position, the subject should lift their right leg, so that the perineal area is able to be visualized. Gently rub the file over the right and left side of the perineal and perianal area. It is important to spread the buttocks apart for ample sampling of the perianal region. Sufficient pressure should be applied in order to cause blanching of the skin. If blanching is not observed, pressure should be increased in order to collect the required DNA. The examiner should gently swab the perineal area. Using the non-dominant hand, the examiner should spread the buttocks to better visualize the perianal area and the anus. The swab should be held in the dominant hand, and starting 3 to 5 cm from the anus, begin swabbing in a circular motion until the entrance of the anus is reached. As with the file, sufficient pressure should be used with the male swab to blanch the skin while moving it over the area of loosened cellular debris. The swab should also be twisted or rotated in order to increase surface area exposure for collection of debris.

3. Discard the file in a Biohazard Sharps container.

4. Place the swab in an STM vial and break the pre-scored handle. Do not add saline to the STM vial either before or after swabbing.

5. Securely cap the collection/transport tube containing the specimen.

6. Place the label for the Perianal Sample on the STM vial.

3.2.4.3.4 External Genital Lesion Biopsy

After a thorough examination, the investigator's clinical impression should be recorded. If a lesion, in the investigator's opinion, is possibly, probably, or definitely HPV infection-related or the diagnosis is unknown, it should be biopsied for further evaluation. For multiple lesions, select one external lesion to biopsy that is most representative of the morphology or anatomic location, and is most accessible. A second biopsy is indicated, if a lesion is identified in a separate region (anterior region includes penis and scrotum and posterior region includes perineal and perianal region) or a lesion is identified with different morphology in the same region. For each biopsy, different instruments are to be used to prevent cross-contamination between specimens. At the investigator's discretion, the lesion(s) may be surgically removed (therapeutic excision). In that case, the entire specimen must be submitted for analysis. All specimen(s) excised should be submitted to the central laboratory designated by the SPONSOR for analysis. For the genital wart/lesion biopsy, the external genital lesion biopsy kit provided by the SPONSOR central laboratory is to be used. Slides of the wart/lesion biopsy will be reviewed by a pathologist for the purpose of management of the subject. Management of anogenital warts is a study procedure, but the decision regarding the modality of therapy will be left to the discretion of the investigator, per the site's standard and practices. Excision of the wart/lesion is the preferred study treatment. All excised tissue is to be submitted to the central laboratory for analysis. If more than one biopsy is performed, then use separate instruments for each biopsy. Each biopsy should be placed in individual formalin containers. Treatment of anogenital warts by topical medications or cryotherapy is an acceptable study procedure. A biopsy of the identified lesion/lesions (e.g., morphology differs among identified lesions or more than one lesion is identified) must be obtained prior to administering treatment.

The investigator should provide a clinical impression of the lesion, which should include one of the following: condyloma acuminata, other HPV-related lesion (e.g., Bowenoid papulosis, Bowen's disease), or other non-HPV related lesions.

The location of all lesions that are being submitted for biopsy should be clearly identified on the study operative report form located in the administrative binder.

The location and anatomical area of each biopsied wart/lesion should be identified and noted (as per the lab kit requisition supplied by the SPONSOR and should also be recorded on the workbook/case report form).

1. To perform the biopsy, cleanse the biopsy area first with an antiseptic solution.

2. Using a 25-30 gauge needle and a syringe containing 0.5 to 1 mL of 1% lidocaine or lidocaine with epinephrine, infiltrate below the epidermis of the wart. Optionally, a topical anesthetic cream may be applied over the biopsy site prior to infiltration with lidocaine to decrease the pain associated with needle insertion.

3. Remove the wart tangentially with fine (iris) scissors or a scalpel blade to obtain the specimen.

4. A different set of instruments is to be used for each biopsy taken.

5. To promote hemostasis, apply gentle pressure. Monsel solution or 38% aluminum chloride may be used. For larger areas, a single interrupted suture may be used. Electrocauterization is to be avoided, but the decision is left to the discretion of the practitioner. Silver nitrate is to be avoided, as it is reported to be more caustic and painful to the subject.

6. Apply topical antibiotic ointment to the area to promote healing (optional).

7. Management of anogenital warts will be left to the discretion of the investigator. Excision of the wart is an acceptable study treatment. All excised tissue is to be submitted to the central laboratory for analysis.

8. During genital wart treatment, follow-up biopsies should be obtained if new HPV-related lesions of differing morphology, and/or differing location appear. A recurrence is defined as the reappearance within 2 months of a lesion of similar morphology in the same anatomical location after complete resolution of the initial lesion. Recurring lesions will not be biopsied. Otherwise, all new lesions will be biopsied.

The external genital lesion biopsies will be processed and read by a central laboratory chosen by the SPONSOR. These specimens will be processed at the central laboratory using study-specific guidelines. The central laboratory diagnosis will be used for management of subjects. However, this diagnosis will not be the diagnosis of record in the study. Rather all routine slides generated by the central laboratory will be sent to the Pathology Panel. The consensus diagnosis of this panel will represent the final diagnosis for study purposes. If the diagnosis of the Pathology Panel is worse than the diagnosis of central laboratory, then the investigator will be notified of the discrepancy in diagnoses.

External genital lesion specimens will also be sent to the SPONSOR for HPV analysis. HPV analysis will be performed on Thinsection microtomy specimens. Each biopsy specimen will be analyzed by HPV PCR, regardless of whether an HPV-related histologic diagnosis is made, for the purpose of determining the causal HPV type in the lesion.

If a subject has an external genital lesion biopsy taken, that subject may remain in the study.

3.2.5 Protocol Deviations

Protocol deviators are randomized subjects who do not meet either the inclusion or exclusion criteria at the start of the study and/or who do not follow the protocol correctly during the study. Deviation from the protocol procedures outlined in the protocol

requires consultation between the investigator and the sponsor and written documentation of the collaborative decision on patient management. See the Administrative Binder for a summary of deviations that require documentation in this study.

Table 3-3 pre-defines the most common types of protocol deviations. This is not an exhaustive list of protocol deviations. Please refer to the Administrative Binder for details.

Table 3-3

Description of Common Protocol Deviations

Common Protocol Deviations	Protocol References
Visit or procedure conducted outside of visit window.	Reference Study Flow Chart (Section 1.7)
Visit not done, or per protocol procedure not done at particular visit	Reference Study Procedures (Section 3.2)
Other protocol specific violation/deviation that would require a sponsor consultation and decision on patient management.	Reference Administrative Binder

3.2.6 Discontinuation/Withdrawal from Study

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject/patient has been discontinued/ withdrawn due to an adverse experience (telephone or FAX). When a subject/patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 3.4 SAFETY MEASUREMENTS - DETAILS.

If a subject must discontinue/withdraw after the Month 42 visit, the subject should be asked to return for a final "discontinuation visit" if it has been at least 4 months since the last study visit. The visit would consist of the same specimen collection and tests conducted at the last study visit and the subject would be formally discontinued from the study at the end of this visit. The discontinuation visit should not be done if it is medically contraindicated or if the subject refuses. If no discontinuation visit is performed, the subject should be formally discontinued from the study on the day the decision to discontinue is made.

All attempts should be made to contact a subject who is lost to follow-up (a certified letter must be sent at the final attempt). Subjects who are lost to follow-up should be formally discontinued from the study on the day of the last unsuccessful attempt at contact.

3.2.7 Subject Relocation

Given the duration of the study and the age of the study population, it can be expected that subjects may relocate during the study. The SPONSOR must be contacted for each temporary and permanent relocation as soon as the situation is known. Every effort should be made to adjust study visits around a subject's temporary absence (e.g., college breaks, summer vacation) so that the visits will be within the visit windows. Every effort should be made to have a relocated subject seen at another site participating in this study in order to keep the visits within the visit windows and to allow the subject to complete the study.

3.3 EFFICACY/IMMUNOGENICITY MEASUREMENTS

3.3.1 Immunogenicity Measurements

The 9-valent HPV competitive Luminex immunoassay (cLIA) and 9-valent HPV total IgG Luminex Immunoassay are the primary assays used for the primary objective of the study. Additional testing may be conducted on a subset of subjects using another HPV immunological assay (Pseudovirion-based Neutralization Assay, or PBNA) for supportive exploratory analyses.

3.3.1.1 Competitive Luminex Immunoassay (cLIA) - Anti-HPV Levels in Serum

The purpose of the 9-valent HPV cLIA is to detect antibodies to HPV VLPs types 6, 11, 16, 18, 31, 33, 45, 52, and 58, before and after vaccination with the 9-valent HPV L1 VLP vaccine. This is the primary assay used by the SPONSOR/Central Laboratory to evaluate the serological response to the vaccine, to measure HPV infection induced antibody, and to exclude subjects with evidence of a current or past HPV infection from the primary analysis.

Yeast-derived VLPs are coupled to a set of 9 distinct fluorescent Luminex microspheres. Antibody titers are determined in a competitive format in which known, HPV type-specific phycoerythrin (PE)-labeled, neutralizing monoclonal antibodies (mAbs) compete with the subject's serum antibodies for binding to type-specific conformationally sensitive, neutralizing epitopes on the VLPs. The fluorescent signals from the bound HPV-specific detection mAbs are inversely proportional to the subject's antibody levels to the neutralizing epitopes on the VLPs. Results for the assay are reported as a concentration of antibody in arbitrary milli-Merck Units per milliliter (mMU/mL).

The HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA is performed in a 96-well microtiter plate. A 12-point standard curve using reference serum from 9-valent HPV vaccine immunized Rhesus macaque monkeys, 4 controls, and 16 samples are added to the plate in duplicate. Samples are initially tested at dilutions of 1:4 and 1:40. The detection

antibodies followed by the VLP-microspheres for types 6, 11, 16, 18, 31, 33, 45, 52, and 58 are added to each well. The plates are sealed with foil covers and incubated for 15 to 25 hours. Following incubation, the plates are washed and then analyzed on a BioPlex (Luminex) instrument.

The high, medium, low, and negative controls used for this assay were collected from humans that were either HPV sero-negative, had low antibody titers from natural infection, or had medium to high antibody titers to HPV following vaccination.

The seropositivity cutoffs for HPV types are assessed using a panel of sera from subjects that are highly likely to be HPV naïve (children), and from subjects who are likely to be seropositive. Any sample with a cLIA titer lower than the cutoffs is considered serostatus negative. Serology cutoffs for the HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA will be determined. A memorandum with the serology cutoff values for each vaccine HPV type will be added to the study file before unblinding the study database.

3.3.1.2 Total IgG Luminex Immunoassay - Anti-HPV Levels in Serum

The purpose of the 9-valent HPV total IgG Luminex immunoassay (9-valent HPV IgG assay) is to measure antibody concentrations (titers) to HPV VLP 6, 11, 16, 18, 31, 33, 45, 52 and 58, determined in a multiplexed, direct binding format by measuring the amount of VLP-specific IgG bound to VLP-microspheres on the Luminex platform.

Yeast-derived VLPs are coupled to a set of 9 distinct fluorescent Luminex microspheres. Following incubation with human serum, fluorescent signal from an anti-human IgG detection antibody that binds directly to serum IgG and equally to each IgG subclass (1-4) is directly proportional to the individual's HPV type-specific anti-VLP IgG antibody levels.

A standard reference serum from Rhesus macaques that received 9-valent HPV vaccine is used to generate a 12 point standard curve starting at a 1:100 serum dilution followed by subsequent 3-fold dilutions, and to quantitate the levels of VLP-specific IgG antibodies. Titers to HPV16 are calibrated to the World Health Organization (WHO) serum standard for HPV16, and reported in International Units/milliliter (IU/mL). Titers to HPV 6, 11, 18, 31, 33, 45, 52 and 58 are cross-standardized to HPV16 and are reported in Antibody Units/milliliter (AbU/mL). The correlation of median fluorescent intensity (MFI) units to IU/mL or AbU/mL of VLP-specific IgG is made by interpolating the MFI data through a 4-parameter curve fitting algorithm.

The 9-valent HPV IgG assay is performed in a 96-well microtiter, filter plate. A 12-point standard reference serum, 4 controls and 32 samples are added to the plate in duplicate. Samples are tested after dilution in assay diluent consisting of phosphate buffered saline and 1% Triton X. To each well is added the VLP-microspheres for types 6, 11, 16, 18, 31, 33, 45, 52 and 58. The plates are covered with foil and incubated for 15 min. to 1 hour. The filter plates are washed and resuspended in buffer containing mouse anti-human IgG monoclonal antibody conjugated to phycoerytherin (PE). The plates are covered with foil and incubated for an additional 15 min. to 1 hour. Following the second incubation period, the plates are washed once and then analyzed on a BioPlex (Luminex) instrument.

3.3.1.3 Pseudovirion-based Neutralization Assay (PBNA)

The purpose of the HPV 16 and HPV 18 PBNA are to detect the presence of antibodies capable of inhibiting cellular uptake of HPV pseudovirions for HPV types 16 and 18 in serum after vaccination with the 9-valent HPV vaccine. This is assay is developed and executed by Deutsche Krebsforschungszentrum (DKFZ) laboratories, Heidelberg, Germany, on behalf of Merck Research Laboratories (MRL) to evaluate neutralizing antibody response to the HPV 16 and 18 components of the vaccines.

HPV 16 and 18 pseudovirions are produced at DKFZ laboratories by co-transfecting the 293TT human embryonic kidney cell line with an expression plasmid encoding the HPV L1 and L2 capsid genes and another encoding luciferase from the marine copepod *Gaussia princeps*. Pseudovirions of L1/L2 self-assemble and package the luciferase reporter plasmid within. Pseudovirions are incubated with HeLaT K4 cells and, when pseudovirions are able to enter cells, *Gaussia* luciferase is expressed and secreted to the cell culture supernatant. If neutralizing antibodies are present in the test sera, infection of cells by pseudovirions and subsequent expression of luciferase reporter is inhibited. The addition of luciferase substrate, coelenterazine, to the reaction results in luminescence when luciferase is present in the cell culture supernatant. This luminescence is measured in a plate reader.

The PBNA assay is performed in a 384-well format in clear, flat-bottom culture plates. Sera and controls are initially diluted 1:2.5 in neutralization cell culture medium and serially diluted 4-fold in a master plate from which nine identical assay plates are aliquoted to allow for triplicate measurements of neutralization for each: HPV16, HPV18 and BPV (bovine papillomavirus) pseudovirions. BPV PBNA assays are run as a control to verify that the test serum is not toxic to the cells, which can mimic neutralization. Pre-prepared serum assay plates are thawed and diluted pseudovirions are added, 15µl/well, such that the final dilutions of pseudovirions in each assay after addition of cells are: 1:20,000 for HPV16, 1:40,000 for HPV18 and 1:80,000 for BPV. Plates are incubated at room temperature for 1 hour. Human HeLaT K4 cells, 20 µl/well, are seeded onto the plates in neutralization cell culture medium at a density of 1500 cells/well and incubated at 37 ^{o}C and 5% CO_2 for 2 days. The triplicate HPV16, HPV18 and BPV PBNA assay plates are equilibrated to room temperature before addition of 1:100 diluted coelenterazine substrate buffer to each well of each plate, 20 µl/well, using FlexDrop automation, which synchronizes substrate addition to allow equal incubation times of all 9 plates in a batch. Luminescence is read by an Envision 2101 plate reader and data are stored as a text file. Serum neutralization titers are calculated by linear interpolation and defined as the reciprocal of the serum dilution that caused 50% reduction in luciferase reporter activity (EC_{50}) when compared to control wells (pseudovirions in the absence of serum and pseudovirions in the presence of a standard serum derived from HPV vaccine recipient).

This assay is currently designated to offer a secondary measurement, complementary to the 9-valent HPV cLIA and 9-valent HPV IgG assay.

3.3.2 PCR Assays - Detection of HPV in Swabs and Tissue Specimens

Gynecological and genitourinary swabs and all Thinsection microtomy biopsy specimens will be tested for detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. In addition to this testing, gynecological and genitourinary swabs and Thinsection microtomy biopsy specimens may tested for other HPV types.

HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be analyzed by type-specific multiplex (L1, E6, E7 gene detection) PCR assay (described in Section 3.3.2.1). HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be analyzed by the duplex (E6, E7 gene detection) PCR assay (using the preparation method described in Section 3.3.2.1).

3.3.2.1 Multiplex PCR Assays

The following procedures will be done for the detection of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in frozen swabs and Thinsection microtomy biopsy samples. Specimens are received and then prepared for multiplex PCR using a DNA purification method (Qiagen Technology Kit). Multiplex PCR (based on real-time fluorescent PCR) allows the simultaneous detection of 3 gene products (L1, E6, and E7) for a given HPV type in 1 reaction. The HPV type-specific primer pairs based on the published HPV L1, E6, and E7 sequences, are used to specifically amplify a portion of each gene simultaneously. The specific amplicons are detected in real-time by fluorescently-labeled oligonucleotide probes. The gene-specific oligonucleotide probes are each labeled with a different fluorescent label, and the fluorescent emission is captured during PCR cycling.

After analysis of the raw fluorescent data by the real time PCR instrument software, a threshold cycle (Ct), which represents the PCR cycle at which an increase in reporter fluorescence above a baseline signal can first be detected, is determined. Each gene-specific assay (i.e., gene-specific dye layer) is considered positive if the Ct is <45 cycles. A gene-specific assay is considered negative if the Ct = "No Ct". A sample is called positive when 2 or 3 genes are positive or when the same single gene scores positive on consecutive tests.

3.3.2.2 Preparation and Disposition of Thinsections of Biopsy Tissue

The following procedures will be performed at the SPONSOR-designated Central Laboratory. The procedures will be performed by an experienced, qualified histotechnologist according to the Central Laboratory's Standard Operating Procedure (SOP). The histotechnologist will assure that the microtome and work areas are clean and free of contaminants. All Thinsection microtomy for PCR will be performed at a time when all other routine work has been completed, so that potential contaminations can be minimized. Prior to sectioning each block, a new blade will be installed in the microtome. The blade will only be positioned so that it is at the left margin of the blade surface. Technicians sectioning study blocks will utilize “biologically clean” gloves while handling the blocks (new gloves for each block). First, the histotechnologist will face the block by removing two 4-micron sections from the face of the block. These sections will be discarded. Using sterile plastic forceps, the next two 4-micron paraffin

sections are collected and floated in a water bath for the preparation of 1 hematoxylin & eosin (H&E) slide (Slide 1, with 2 sections).

Nine additional, consecutive sections will then be cut to be used for Thinsection PCR. There will be 9 individual tubes (Tube 1, 2, 3, 4, 5, 6, 7, 8, 9), and one 4-micron section will be placed in each tube using a sterile disposable plastic forceps. The pair of sterile plastic forceps used is then discarded after placing the cut section in each tube. Each tube is then placed inside a plastic sleeve and sealed.

Two additional, consecutive 4-micron sections will then be cut and the 2 sections floated in the water bath for preparation of the second H&E slide both sections to be placed on one slide (Slide 2 with 2 sections each). All H&E slides (Slides 1 and 2) will have a histopathologic review by the central laboratory's pathologist.

Slides and tubes should be labeled with subject's allocation number. The specimen tubes are collated with the appropriate specimen requisition and prepared for shipping to the SPONSOR-designated Central Laboratory and then in turn, shipped on to MRL.

The microtome is cleaned in preparation for the next block and the process above is repeated. The microtome blade is replaced with a new blade and adjusted for each new biopsy block and the same procedure is to be followed. A new pair of clean gloves and a new pair of clean, disposable forceps will be used for each block being sectioned. The "used" blade may be retained for cutting non-PCR blocks. The total number of sections to be cut from each block is 13. A total of 2 slides and 9 tubes:

1. Slide 1 (H&E), with 2 sections each, stained.

2. Tubes 1, 2, 3, 4, 5, 6, 7, 8, 9 (HPV PCR Analysis), 1 section per tube.

3. Slide 2 (H&E), with 2 sections each, stained.

3.3.3 Responsibility of the HPV Vaccine Program Pathology Panel

The HPV Vaccine Program Pathology Panel will be responsible for providing the definitive pathologic diagnoses of cervical biopsies, vaginal biopsies, external genital lesion biopsies, endocervical curettage, and cervical definitive therapy specimens for study purposes (not for medical management). Cervical histology slides and slides from external genital lesion biopsies and vaginal lesion biopsies will be evaluated by HPV Vaccine Program Pathology Panel. The HPV Vaccine Program Pathology Panel will prepare reports on each tissue specimen. A separate guideline that details the HPV Vaccine Program Pathology Panel process has been approved by the HPV Vaccine Program Pathology Panel.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

Serious adverse experiences will be reported as described in Section 3.4.5.

Pregnancy and infant information will be reported as described in Section 3.4.4.

3.4.2 Recording Adverse Experiences

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

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

All adverse experiences will be collected from the time the consent form is signed through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, and such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

Serious adverse experiences occurring outside of that time period will be reported as described in Section 3.5.

3.4.3 Definition of an Overdose for This Protocol

No overdose should occur since no subject will be administered vaccinations of 9-valent HPV L1 VLP vaccine during this study.

3.4.4 Reporting of Pregnancy/Breastfeeding Events to the SPONSOR

Although not considered an adverse experience, it is the responsibility of the investigators or their designees to report any pregnancy in a subject (spontaneously reported to them or detected by urine or serum pregnancy test per protocol).

All randomized subjects who receive study vaccine, including discontinued subjects who agree to provide further information, must be followed to the completion/termination of the pregnancy. In addition, if the pregnancy continues to term, the outcome (health of the infant) must be reported.

Infant serious adverse experiences (SAEs) for all infants born to subjects who received study vaccine must be reported to the SPONSOR.

The reporting of pregnancy and infant SAE events must be reported within 24 hours to the SPONSOR either by electronic media or paper. Refer to Data Entry Guidelines (DEGs) for instructions for what information must be reported.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

3.4.5.1 Serious Adverse Experiences

Any serious adverse experience brought to the attention of an investigator who is a qualified physician at any time also must be reported immediately to one of the individuals listed on the sponsor contact information page (found in the administrative binder) if the event is either:

1. A death which resulted in the subject/patient discontinuing the study

or

2. A serious adverse experience that is considered by an investigator who is a qualified physician to be possibly, probably, or definitely vaccine related.

or

3. A serious adverse experience that is considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to a study procedure.

All subject/patients with serious adverse experiences must be followed up for outcome.

3.4.6 Evaluating Adverse Experiences

Refer to Table 3-4 for instructions in evaluating adverse experiences.

Table 3-4

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

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities) **Injection site redness or swelling from the day of vaccination through Day 4 post-vacc will be evaluated by maximum size.**
Seriousness	A serious adverse experience is any adverse experience occurring at any dose that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject/patient taking the product regardless of time to diagnosis);or	
	Is a cancer; or	
	Is an overdose (Whether accidental or intentional.) Any overdose whether or not associated with an adverse experience must be reported within 24 hours to one of the individuals on the Contact Information Page found in the Administrative Binder.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse experience cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse experience? The determination of the likelihood that the test vaccine caused the adverse experience will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet, that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse experience based upon the available information. **The following components are to be used to assess the relationship between the test vaccine and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse experience (AE):	
	Exposure	Is there evidence that the subject/patient was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g. diary), seroconversion or identification of vaccine virus in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine? Is the time of onset of the AE compatible with a vaccine-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject/patient reexposed to the test vaccine in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Study Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?
	The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements. **Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**	
	Definitely related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test vaccine or test vaccine class.
	Probably related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
	Probably not related	There is evidence of exposure to the test vaccine. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test vaccine. **OR** Temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable. **OR** There is another obvious cause of the AE.

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 DATA ANALYSIS

This section outlines the statistical analysis strategy and procedures for the study. If changes are made after the start of the study to the statistical analysis plan presented in the Data Analysis section of this protocol extension, the changes will be described in the Clinical Study Report for the study, as appropriate. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

3.5.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This extension of Protocol 002 will not be blinded, because all participants will have received 9-valent HPV L1 VLP vaccine. Freezes of the clinical database will be executed for each of the interim analyses at Months 72 and 96 and at end-of-study. Prior to each data freeze, the clinical data will be reviewed, cleaned, and screened to ensure accuracy and completeness following the SPONSOR's Global Development Processes (GDP) relating to Data Management. The data will be reviewed and errors will be corrected and protocol violations have been reviewed prior to freezing the clinical database for immunogenicity, safety, and effectiveness analyses.

The first analysis conducted under Protocol 002-20 is planned to take place at Month 72. During this interim analysis, safety, immunogenicity, and effectiveness data will be analyzed and feasibility of continuing the study through Month 126 will be assessed. If study continues beyond Month 72, additional analyses of safety, immunogenicity and effectiveness are planned to include data through Month 96 and Month 126.

3.5.2 Hypotheses/Estimation

There are no hypotheses for this long term follow-up study.

3.5.3 Analysis Endpoints

3.5.3.1 Immunogenicity Endpoints

Immunogenicity endpoints are GMTs and seropositivity rates to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58. A subject is considered seropositive for a given HPV type if he or she has a titer at or above the serostatus cutoff for that HPV type for the immunoassay considered. Serum samples are collected as indicated in flow chart in Section 1.7. Immunogenicity testing will be conducted at Months 66, 90 and 126.

3.5.3.2 Safety Endpoints

Safety endpoints are vaccine- or study procedure-related serious adverse experiences, deaths, and pregnancy- and infant-related outcomes.

3.5.3.3 Effectiveness Endpoints

Effectiveness endpoints are gender-specific. The effectiveness endpoint of primary interest is the incidence of subjects with at least one of the following endpoints (for the appropriate gender).

3.5.3.3.1 Female Endpoints

For females, the effectiveness endpoint of interest is the composite endpoint of persistent HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58 infection and HPV 6-, 11-, 16-, 18-, 31-, 33-, 45-, 52-, or 58-related CIN, AIS, VIN, VaIN, genital warts, and cervical/vaginal/vulvar cancer.

I. Persistent infection (with a duration of 6 months):

This endpoint is defined to have occurred if a subject who, after completion of the Month 7 visit, is positive for the same HPV type by the HPV 6/11/16/18/31/33/45/52/58 PCR assay to at least 1 common gene in 2 or more consecutive cervicovaginal/external genital swab, biopsy, or definitive therapy samples obtained at two or more consecutive visits 6 months (± 1 month) or longer.

Persistent infection is defined based on the protocol visit intervals. Scheduled visits for the collection of swabs are at 6-monthly intervals, so most cases of persistent infection will be based on consecutive specimens obtained 6 months apart; however, due to protocol-allowable deviations for scheduled visit intervals, the minimum length of time between samples for a subject to be counted as a case of persistent infection will be 4 months.

If a subject has 2 consecutive samples that are PCR positive to at least one common gene for the same HPV type and at least one of the samples is a biopsy or definitive therapy sample showing pathologic evidence of HPV disease, then the subject will be considered a case of persistent infection without regard to the length of time between the samples.

II. External Genital Warts, VIN, VaIN, and/or vulvar or vaginal cancer related to HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58:

A subject will be considered to have a case of external genital warts, VIN, VaIN, and/or vulvar or vaginal cancer related to HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58, if she has the following:

- On an individual biopsy or excised tissue, a consensus diagnosis by the HPV Vaccine Program Pathology Panel of condyloma acuminata (genital warts), VIN 1, VIN 2, VIN 3, VaIN 1, VaIN 2, VaIN 3, or vulvar cancer or vaginal cancer AND

- Detection of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58 by Thinsection PCR in an adjacent section from the same tissue block.

III. CIN, AIS, and/or cervical cancer related to HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58:

A subject will be considered to have a case of CIN, AIS, and/or cervical cancer related to HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58 if she has the following:

- On an individual biopsy, ECC, LEEP, or conization (cold knife/laser) specimen, a consensus diagnosis by the HPV Vaccine Program Pathology Panel of CIN 1, CIN 2, CIN 3, AIS, or cervical cancer, AND

- Detection of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58 by Thinsection PCR in an adjacent section from the same tissue block.

3.5.3.3.2 Male Endpoints

I. Persistent infection (with duration of 6 months):

This endpoint is defined to have occurred if a subject who, after completion of the Month 7 visit, is positive for the same HPV type by the HPV 6/11/16/18/31/33/45/52/58 PCR assay to at least 1 common gene in 2 or more consecutive anogenital swab or biopsy obtained at two or more consecutive visits 6 months (± 1 month) or longer.

Persistent infection is defined based on the protocol visit intervals. Scheduled visits for the collection of swabs are at 6-monthly intervals, so most cases of persistent infection will be based on consecutive specimens obtained 6 months apart; however, due to protocol-allowable deviations for scheduled visit intervals, the minimum length of time between samples for a subject to be counted as a case of persistent infection will be 4 months.

If a subject has 2 consecutive samples that are PCR positive to at least one common gene for the same HPV type and at least one of the samples is a biopsy or definitive therapy sample showing pathologic evidence of HPV disease, then the subject will be considered a case of persistent infection without regard to the length of time between the samples.

II. External genital warts, PIN, or penile/perineal/perianal cancer related to HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58:

A subject will be considered to have this endpoint if he has the following:

- Pathology panel consensus diagnosis of genital warts, PIN 1, PIN 2, PIN 3, penile, perineal, or perianal cancer, AND

- Detection of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58 DNA by Thinsection PCR in an adjacent section of the same tissue block.

The composite effectiveness endpoints for each gender include all of the gender-specific endpoints listed above. The incidence of each individual component will be summarized, as will the incidence of the composite endpoints for each gender. Endpoints related to non-vaccine types (i.e., HPV 35, 39, 51, 56, and 59), for the exploratory effectiveness analyses, are defined in the same way as the vaccine-type endpoints.

If a subject has experienced one or more of the components of the respective endpoint, he or she will be counted once in the summary of incidence rates of the composite endpoint, at the time of detection of the first endpoint for which the subject meets the case criteria. For example, if a subject has AIS related to HPV 16 and CIN related to HPV 18, she will be counted only once in the summary of the composite endpoint of HPV 6, 11, 16, 18, 31, 33, 45, 52, or 58 persistent infection, external genital warts, VIN, VaIN, AIS, or CIN. For summaries of individual components of the composite endpoint, a subject may be counted as a case at most once in each applicable category, but may appear in multiple sub-categories. In the example above, the subject would be counted as a case in a summary of HPV 16-related disease and also in a summary of HPV-18 related disease.

3.5.4 Analysis Populations

3.5.4.1 Immunogenicity Analysis Populations

The primary approach to the analysis of immunogenicity will be per-protocol, including subjects without major protocol violations who are seronegative to the respective HPV type pre-vaccination.

Per Protocol Immunogenicity (PPI) Population

The PPI population will serve as the primary population for the analysis of immune response to each of the 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58). To be included in this population, subjects must:

(1) Have received all 3 vaccinations with the correct dose of the correct clinical material, and each vaccination visit must occur within acceptable day ranges (See Table 3-5 for acceptable day ranges for vaccination visits).

(2) Be seronegative by cLIA to the appropriate HPV type at Day 1 (See Table 3-6 for acceptable day ranges for serum).

(3) Have no other protocol violations that could interfere with the evaluation of subject's immune response to the study vaccine. Specifically, at base study Day 1, satisfied the inclusion criterion 5 (i.e., ″ Subject must not yet have had coitarche

and does not plan on becoming sexually active during the Day 1 through Month 7 period.″) specified in Section 2.2 of the protocol of the base study (i.e., Protocol V503-002-00).

To be included in the PPI population for HPV 6 and 11, subjects must be seronegative by cLIA to both HPV 6 and 11 at Day 1. To be included in the PPI population for any other vaccine HPV type, subjects need to be seronegative by cLIA at Day 1 only for the HPV type being analyzed.

The final determination on protocol violations, and thereby the composition of the PPI population, will be made prior to the freezing of the database and will be documented in a separate memo.

Table 3-5

Acceptable Day Ranges for Vaccination Visits

Dose of 9-Valent HPV L1 VLP Vaccine Scheduled for Injection	Protocol Specified Visit Window	Day Range for Inclusion in Statistical Analysis (Relative to Day 1[†])
Dose 1	Day 1[†]	0
Dose 2	Month 2 ± 3 weeks	36 to 84
Dose 3	Month 6 ± 4 weeks	148 to 218
[†] Day 1 refers to the date when dose 1 of 9-valent HPV L1 VLP vaccine is injected. For post-Day 1 vaccinations, the day ranges for inclusion in the statistical analysis are wider than the protocol specified visit windows primarily to account for differences at the sites in counting months (e.g., 1 calendar month versus 30 days versus 4 weeks).		

Table 3-6

Acceptable Day Ranges for Collection of Serum Samples

Study Visit	Sample Type	Target Collection Day (Relative to Day 1[†])	Day Range for Inclusion in Statistical Analysis[†]
Day 1	**Serum**	**0**	–14 to 0 (Relative to Day 1)
Month 7	**Serum**	30 days post dose 3	21 to 49 post dose 3
Month 12	**Serum**	**365**	**274 to 547**
Month 24	**Serum**	**730**	**548 to 914**
Month 36	**Serum**	**1096**	**915 to 1552**
Month 66	**Serum**	**2009**	**1553 to 2374**
Month 90	**Serum**	**2739**	**2375 to 3287**
Month 126	**Serum**	**3835**	**3288 to 4384**
[†] Day 1 refers to the date when dose 1 of 9-valent HPV L1 VLP vaccine is injected. For Month 7, indicated target collection/day range is relative to date of injection of dose 3 of 9-valent HPV L1 VLP vaccine.			

3.5.4.2 Safety Analysis Populations

All subjects who received at least 1 study vaccination and have follow-up data will be included in the safety summaries.

3.5.4.3 Effectiveness Analysis Populations

Assessment of effectiveness will be conducted on two analysis populations: the per-protocol effectiveness (PPE) and the full analysis set (FAS) populations. The primary analysis will be conducted on the PPE population. The two analysis populations differ as described below with regard to compliance to vaccination regimen and potential HPV infection status at the time of vaccination of 9-valent HPV L1 VLP vaccine.

Per-Protocol Effectiveness (PPE)

The PPE analysis population is HPV type-specific. In analyses of endpoints related to a specific HPV type (e.g., HPV 16-related endpoints) the PPE population-eligible subjects include those who:

(1) received 3 doses of 9-valent HPV L1 VLP vaccine within 1 year; AND

(2) were seronegative by cLIA to the specific HPV type at the time of injection of dose 1 of 9-valent HPV L1 VLP vaccine (seronegative to both types 6 and 11 in analysis of HPV 6-related, and HPV 11-related endpoints); AND

(3) Have no other protocol violations that could interfere with the evaluation of the effectiveness of the study vaccine. Specifically, at base study Day 1, satisfied inclusion criterion 5 (i.e., ″ Subject must not yet have had coitarche and does not plan on becoming sexually active during the Day 1 through Month 7 period.″) specified in Section 2.2 of the protocol of the base study (i.e., Protocol V503-002-00).

Inclusion criterion 5, at base study, was intended to capture subjects who had not yet been infected with HPV through sexual intercourse and were therefore likely to be HPV-naïve during the period of vaccination with 9-valent HPV L1 VLP vaccine. The seronegativity condition is another criterion intended to capture subjects who were still HPV-naïve during the period of vaccination of 9-valent HPV L1 VLP vaccine

Note that a subject can be both PPE population-eligible for analyses of endpoints related to one HPV type (e.g., HPV 16-related endpoints) and PPE population-ineligible for analyses of endpoints related to another HPV type (e.g., HPV 18-related endpoints).

In analyses of endpoints related to any vaccine HPV type (e.g., HPV 6/11/16/18/31/33/45/52/58-related endpoints), the PPE population-eligible subjects include those who are PPE population-eligible for *any of* the HPV types 6, 11, 16, 18, 31, 33, 45, 52, or 58.

Only PPE population-eligible subjects who are at least 16 years of age and have at least one follow-up visit with PCR data will contribute to the PPE analyses.

The aforementioned definition of the PPE analysis population applies to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 only. There is no available serostatus information at the time of injection of dose 1 of 9-valent HPV L1 VLP vaccine with respect to non-vaccine HPV types (35, 39, 51, 56, and 59). In the absence of serostatus or DNA status with respect to non-vaccine HPV types at the time of injection of dose 1 of 9-valent HPV L1 VLP vaccine a PPE analysis population will not be defined for analyses of non-vaccine HPV type-related endpoints. Effectiveness analyses relating to non-vaccine HPV types will be conducted in the full analysis set and in addition in a population that satisfies all conditions but one of the PPE, namely the seronegativity condition (2)

Full Analysis Set (FAS)

The FAS analysis population is not HPV type-specific. The FAS population includes subjects who received at least 1 dose of 9-valent HPV L1 VLP vaccine and had at least 1 follow-up visit during the long-term follow-up study.

Only FAS population-eligible subjects who are at least 16 years of age and have at least one follow-up visit with PCR data will contribute to assessments of effectiveness in the FAS.

3.5.5 Statistical Methods

3.5.5.1 Statistical Methods for Immunogenicity Analyses

Immunogenicity summaries are planned to occur in Protocol 002-20 at three time points, to include follow-up data through Month 72, Month 96, and Month 126. Anti-HPV responses to each of the 9 vaccine HPV types will be summarized for both cLIA and IgG assay by gender and age at enrollment as GMTs and seropositivity rates, with associated 95 % confidence intervals, at each time point at which serology samples were collected, regardless of study visit windows.

In addition, exploratory analyses regarding the kinetics and persistence of antibody response may be conducted, with particular interest in the effect of age at first vaccination on duration of anti-HPV levels. Modeling techniques may be used to study the relationship between anti-HPV persistence and factors such as time since vaccination, age at vaccination, age at sexual debut, and GMT at 1 month post-dose 3.

3.5.5.2 Statistical Methods for Safety Analyses

Listings and narratives of subjects who experienced serious adverse experiences will be provided by vaccination group.

A summary of pregnancy outcomes will be provided. A summary of counts and percentages (relative to the total number infants/fetuses with known outcomes) of specific pregnancy outcomes will be provided.

3.5.5.3 Statistical Methods for Effectiveness Analyses

Subjects who meet the criteria to be considered cases of vaccine type HPV-related persistent infection and/or disease, but who have evidence of HPV exposure or infection (i.e., seropositivity to the respective HPV type(s) pre-vaccination or evidence of sexual activity prior to the completion of their vaccination series), or who do not complete their three doses of 9-valent HPV L1 VLP vaccine within one year, will not be considered breakthrough cases (i.e., vaccine failures). Such cases will be summarized separately in a manner similar to breakthrough cases, with all relevant factors such as baseline demographics and immunogenicity profiles over time characterized; however, these cases will not be included in the primary summary of effectiveness endpoints.

At the time of the interim analysis (Month 72), summaries of the incidence of HPV 6, 11, 16, 18-related persistent infection for a duration of ≥6 months (within ± 1 month windows) and cervical, vulvar, vaginal, perineal, perianal, and penile intraepithelial preinvasive and invasive disease, and external genital lesions will be provided, separately for males and females. Similar summaries of the incidence rates of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58-related persistent infection for a duration of ≥6 months (within ± 1 month windows) and disease will be provided to include follow-up data through Month 96 and Month 126.

The confidence intervals around the point estimate of the incidence rates per 100 person-years are exact Poisson distribution-based nominal 95% confidence intervals.

Summaries will be provided by gender. At each analysis time point, the cumulative incidence rate for effectiveness endpoints will be computed, along with the associated 95% confidence interval. In addition, exploratory analyses will be conducted to characterize subjects who become cases of persistent infection or disease endpoints in the long-term effectiveness follow-up period. Baseline demographic characteristics, pre-vaccination anti-HPV serology status, and post-vaccination immunogenicity profiles will be considered. Time-to-event plots will also be provided by gender if >5 cases are observed in the respective group(s).

Any comparisons of the incidence rates of effectiveness endpoints between Protocol V503-002 and Protocol V503-001 will be descriptive and no formal statistical comparisons will be made. Merck is undertaking other studies to evaluate the long-term effectiveness of 9-valent HPV L1 VLP vaccine.

Incidence rates of the same endpoints described above will be summarized for additional HPV types for which PCR testing is planned in this study (35, 39, 51, 56, and 59). These data, when available, will provide information related to incidence of non-vaccine type HPV in this population and potential cross-protection against these additional HPV types.

An additional analysis of persistent infection for a duration of 12 months (within ± 1 month windows) or more will be conducted.

3.5.5.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics and demographic variables have already been summarized in the base study. Additional summaries in this extension study are planned as below. Baseline characteristics and demographic variables will be summarized using descriptive statistics or categorical tables. No statistical hypothesis tests will be performed on these characteristics.

Subject Accounting

Reasons for subjects excluded from the PPI population and the PPE population will be summarized and displayed in subject accounting tables.

Subject Characteristics

At interim analyses and end of study we will also report the percentage of subjects who are 16 years of age or above. Pap test results, STIs and sexual history will also be summarized.

3.5.6 Multiplicity

Since there is no hypothesis test for the Protocol 002-20 extension, multiplicity considerations are not relevant.

3.5.7 Sample Size and Power Calculations

The sample size for this long-term follow-up study is fixed by the number of Protocol 002 study participants who are eligible and willing to participate in the extension. There is no formal hypothesis that will be tested this long-term follow-up study. Approximately 2600 subjects 9 to 15 years of age were enrolled in Protocol V503-002. At the end of the base study, approximately 97% of the boys and girls had completed the study.

3.5.8 Subgroup Analyses and Effect of Baseline Factors

Immunogenicity summaries will be available by age groups and by gender.

3.5.9 Interim Analyses

Interim analyses will be conducted at Month 72 and Month 96 to assess the feasibility of obtaining 10 full years of follow-up. The decision to continue with the effectiveness component of the study will depend on the ability to collect sufficient effectiveness data through Months 72 and 96, and anticipated through the remainder of the study. At the first interim analysis, the percent of subjects (relative to the total number of subjects who received 3 injections of 9-valent HPV L1 VLP vaccine) who received 3 injections of 9-valent HPV L1 VLP vaccine, reached age 16, and had no further follow-up with effectiveness data after reaching age 16 will be estimated. If this proportion is greater than or equal to 80%, the effectiveness component of the study will be terminated from Month 78 onwards. Under this scenario, subjects will continue to be evaluated for

immunogenicity and safety. At the second interim analysis, this percentage up to and including data to Month 96 will be estimated. If it is greater than or equal to 80%, the effectiveness component of the study will be terminated from Month 102 and onwards. After each interim analysis, summaries of the incidence of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58-related persistent infection and cervical, vulvar, vaginal, perineal, perianal, and penile intraepithelial preinvasive and invasive disease, and external genital lesions will be provided, separately for males and females.

3.5.10 Compliance (Medication Adherence)

V503-002-20 participants will not receive injections of 9-valent HPV L1 VLP vaccine during the long term follow-up study. Therefore, measurement of compliance to vaccine dosing regimen does not apply to the long term follow-up study.

3.6 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.7 BIOLOGICAL SPECIMENS

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

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

All specimens will be labeled with preprinted computer-generated labels provided by the SPONSOR and/or by the SPONSOR's Central Laboratory. Labels can only be affixed to dry surfaces. However, the labels can be used on polypropylene or polyethylene and will survive freezing and thawing.

Information regarding biological specimens and sample labeling for this protocol will be provided by the SPONSOR/Central Laboratory.

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

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

For All Studies

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

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

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

For Studies Conducted Under the U.S. IND

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

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

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

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

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

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

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

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

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

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

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study, provide all data, and upon completion or termination of the clinical study submit any

other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

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

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

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

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

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

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

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

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

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

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

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

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, http://clinicaltrials.gov/. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

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

4.6 PUBLICATIONS

As this study is part of a multicenter trial, publications derived from this study should include input from the investigator(s) and SPONSOR personnel. Such input should be reflected in publication authorship, and whenever possible, preliminary agreement regarding the strategy for order of authors' names should be established before conducting the study. Subsequent to the multicenter publication, or 24 months after completion of the study, whichever comes first, an investigator and/or his/her colleagues may publish the results for their study site independently. However, the SPONSOR does not recommend separate publication of individual study site results due to scientific concerns.

The SPONSOR must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication guidelines.

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6. APPENDICES

There are no appendices.

7. ATTACHMENTS

Merck Code of Conduct for Clinical Trials

Mandatory Regimen for Triage: Investigator Aids for Colposcopy and Definitive Therapy