| | |
|---|---|
| **Official Protocol Title:** | A Phase III Open-label Safety and Immunogenicity Study of GARDASIL™9 Administered to 9- to 26-Year-Old Females and Males in Vietnam |
| **NCT number:** | NCT03546842 |
| **Document Date:** | 19-DEC-2017 |

# Title Page

**THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.**

**Protocol Title:** A Phase III Open-label Safety and Immunogenicity Study of GARDASIL™9 Administered to 9- to 26-Year-Old Females and Males in Vietnam

**Protocol Number: 017-01**

**Compound Number: V503**

**Sponsor Name and Legal Registered Address:**

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

**Regulatory Agency Identifying Number(s):**

**IND NUMBER:** Not Applicable

**EudraCT NUMBER:** 2017-001205-33

**Approval Date: 19-Dec-2017**

**Sponsor Signatory**

Typed Name: Date
Title:

**Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).**

**Investigator Signatory**

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

# PROTOCOL AMENDMENT SUMMARY OF CHANGES

**Amendment** 01

**Overall Rationale for the Amendment:**

Sections and text pertaining to Future Biomedical Research samples have been removed in response to a request by the applicable ethics committee. Text regarding pregnancies has been revised in order to clarify that outcomes for pregnancies is applicable only to those participants who received any study vaccine.

**Summary of Changes Table:**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title | ~~9-Valent HPV/ 9vH vaccine~~ GARDASIL™9<br>Safety~~, Tolerability~~ and Immunogenicity | Brand name replaced generic designation in the title<br>The term "tolerability" has been removed as "safety" is a more generic term (see next row) |
| Throughout | The word ~~tolerability~~ has been removed<br>(eg, "safety and tolerability" now reads simply "safety") | The term "tolerability" has been removed as "safety" is a more generic term to use for assessing adverse events (AEs) to include injection-site AEs, systemic AEs, and vaccine-related serious AEs (SAEs) |
| Overall Design | ~~Multi~~ single-site | The study is to be conducted at a single site |
| 2.<br>Schedule of Activities (SoA) | Removed text regarding informed consent for and collection of blood samples for Future Biomedical Research | Future Biomedical Research samples will no longer be collected in this study |
| 4.<br>Objectives/Hypotheses and Endpoints | "3" had been added after the word "Dose" in the endpoint for the primary objective, so that it now reads "Dose 3" | Correcting of inadvertent typographical omission in original protocol document |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1<br>Overall Design | "in vaccinated subjects" added to last sentence about pregnancies, so that it now reads "Pregnancies and any associated AEs in vaccinated subjects will be followed to outcome" | To clarify that outcomes for pregnancies is applicable only to those participants who received any study vaccine |
| 5.4.2<br>Future Biomedical Research | The entire section and associated text has been removed | Sections and text pertaining to Future Biomedical Research samples have been removed in response to a request by the applicable ethics committee |
| 6.1<br>Inclusion Criteria | In inclusion criterion 8, the following text has been removed:<br>~~The participant (or, for minor participants, the parent/legal guardian and participant) may also provide consent/assent for Future Biomedical Research. However, the participant may participate in the main study without participating in Future Biomedical Research.~~ | To account for the removal of Future Biomedical Research blood sample collection from this study |
| 8.3<br>Lost to Follow Up | The following last/third bullet/text has been removed:<br>~~Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the pre-specified statistical data handling and analysis guidelines~~ | For clarification the text was removed because the first statement is not always the case. The subject may be considered lost to follow up earlier than their scheduled last visit if the site is unsuccessful at contacting the subject after repeated attempts. |
| 9.<br>Study Assessments and Proceedures | The maximum amount of blood collected from each participant has been changed from 20 mL to 14 mL | To account for the removal of Future Biomedical Research blood sample collection from this study |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.1.1.2<br>Consent/Assent and Collection of Specimens for Future Biomedical Research | The entire section and associated text has been removed | Sections and text pertaining to Future Biomedical Research samples have been removed in response to a request by the applicable ethics committee |
| 9.2.1.<br>Serum for Anti-HPV Antibody Testing | Amount of blood needed for anti-HPV specimen has been changed from 10 mL to 7 mL<br>Minimum amount of serum to be aliquoted has been changed from 3.0 mL to 2.0 mL<br>The additional amount of serum ("retention serum" was changed from 1.5 mL to approximately 0.8 mL<br>The following bulleted text has been removed:<br>~~Serum may also be used during the clinical trial, for further HPV immunologic testing in addition to tests specified in the protocol.~~<br>and<br>~~After the end of study (final report of study results), additional testing outside that specified in the protocol may be conducted on leftover samples~~ | Correction of the amounts of blood and serum needed, as well as removal of text regarding alternative uses of the samples |
| 9.3.1<br>Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information | The following text has been removed:<br>~~In addition, SAEs (regardless of causality), cancer, overdose, pregnancy, exposure during breast feeding, and infant SAEs are reportable for the entire study period~~ | This text has been removed in order that the text is now more consistent with standard template text |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table 2<br>Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events | The following text has been added to the row pertaining to Pregnancy/Lactation Exposure:<br>"(if the participant received at least 1 vaccine dose and became pregnant)" | To clarify that outcomes for pregnancies is applicable only to those participants who received any study vaccine |
| 9.3.3<br>Follow-up of AE, SAE and Other Reportable Safety Event Information | The following text has been added:<br>"(if the participant received at least 1 vaccine dose)" | To clarify that outcomes for pregnancies is applicable only to those participants who received any study vaccine |
| 9.3.5<br>Disease-Related Events and/or Disease-Related Outcomes not Qualifying as AEs or SAEs | Section added, with the following text:<br>"Not Applicable" | This section has been included in order that the document structure is now more consistent with standard template text |
| 9.3.6<br>Pregnancy and Exposure During Breastfeeding | Section number revised from 9.3.5 to 9.3.6<br>The following text has been added:<br>"(if the participant received at least 1 vaccine dose)" | To account for the added section<br>To clarify that outcomes for pregnancies is applicable only to those participants who received any study vaccine |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.5.2<br>Pregnancy Testing | The following text has moved from Section 9.3.6 (Pregnancy and Exposure During Breastfeeding) to Section 9.5.2 (Pregnancy Testing):<br>Management of pregnant participants will be as follows. All female participants undergo pregnancy testing based on urine or serum analyses for β-hCG at each study visit (Section 2: SoA). Participants found to be pregnant at Day 1 are not eligible to participate in the study (Section 6.2: exclusion criterion 14). Female participants 16 years and older enrolled in the study are instructed to use effective contraception through Month 7 (Section 6.1: inclusion criterion 7). Participants who inadvertently become pregnant before receiving all 3 doses of vaccine do not receive additional doses until ≥4 weeks after resolution of pregnancy and normalization of β hCG levels as described in Table 3 ~~(Section 9.5.2)~~. Breastfeeding is not a contraindication to enrollment or to receiving study vaccinations. Pregnancy and breastfeeding in study participants and infant SAEs for all infants born to participants who received the study vaccine or who were breastfed during the study must be reported must be reported. | To be more consistent with standard template text organization |
| 10.5.1<br>Immunogenicity Analysis Population | Removal of the following text regarding determination of protocol deviations:<br>~~and will be documented in a separate memo~~ | To be more consistent with recently revised Sponsor processes concerning protocol deviations |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Appendix 2<br><br>Collection and Management of Specimens for Future Biomedical Research | Entire appendix and associated text has been removed | Sections and text pertaining to Future Biomedical Research samples have been removed in response to a request by the applicable ethics committee |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore have not been summarized |

# Table of Contents

## LIST OF TABLES

## LIST OF FIGURES

## 1. Synopsis

**Protocol Title:**

A Phase III Open-label Safety and Immunogenicity Study of GARDASIL™9 Administered to 9- to 26-Year-Old Females and Males in Vietnam

**Short Title:**

Immunogenicity and safety of GARDASIL™9 in Vietnam, 9-26 year-olds

**Objectives/Hypotheses and Endpoints:**

In 9- to 26-year-old female and male participants:

| Objective/Hypothesis | Endpoint |
|---|---|
| Primary | |
| • Objective: To demonstrate that the 9-valent human papillomavirus (9vHPV) vaccine is immunogenic.<br>• Hypothesis: 9vHPV vaccine induces acceptable anti-human papillomavirus (HPV) 6, 11, 16, 18, 31, 33, 45, 52, and 58 seroconversion at 4 weeks post Dose 3. The statistical criterion for acceptable anti-HPV seroconversion requires the lower limit of the 95% confidence interval (CI) of the percent of participants who seroconverted to be greater than 90% for each HPV type. | • Seroconversion, defined as a participant who was anti-HPV seronegative at Day 1 and became seropositive at 4 weeks post Dose 3. |
| Secondary | |
| • Objective: To evaluate the safety of 9vHPV vaccine. | • Proportion of participants experiencing solicited injection-site adverse events (AEs).<br>• Proportion of participants experiencing solicited systemic AEs.<br>• Proportion of participants experiencing vaccine-related serious AEs (SAEs). |
| • Objective: To summarize geometric mean titers (GMTs) at Day 1 and at 4 weeks post Dose 3 of 9vHPV vaccine. | • GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Day 1 and 4 weeks post Dose 3. |

**Overall Design:**

| | |
|---|---|
| Study Phase | III |
| Clinical Indication | Prevention of cervical, vulvar, vaginal, and anal cancers and related precancers, external genital lesions, Pap test abnormalities, and persistent infection caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. |
| Population | Healthy females and males between the ages of 9 and 26 years will be enrolled in this study. |
| Study Type | Interventional |
| Type of Design | Single group, single-site |
| Type of Control | No control |
| Study Blinding | Unblinded Open-label |
| Estimated Duration of Study | The Sponsor estimates that the study will require approximately 11 months from the time the first participant signs the informed consent/assent until the last participant's last study-related phone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last serology assay result. |

**Number of Participants:**

Approximately 200 participants will be enrolled.

**Treatment Groups and Duration:**

| | |
|---|---|
| Treatment Groups | All participants should receive 3 doses of 9vHPV vaccine administered at Day 1, Month 2, and Month 6. |
| Duration of Participation | Each participant will participate in the study for approximately 7 months, from the time the participant signs the informed consent form through the final contact. Each participant will be receiving 3 doses of study vaccination intramuscularly and will be followed up to Month 7. |

A list of abbreviations used in this document can be found in Section 12.4 (Appendix 4: Abbreviations).

## 2. Schedule of Activities (SoA)

| **Study Visit Number** | **1** | **2** | **3** | **4** | **Comments (Protocol Section Reference)** |
|---|---|---|---|---|---|
| **Study Visit Time Point** | **Day 1** | **Month 2** | **Month 6** | **Month 7** | |
| **Study Visit Scheduled Day (Window)** | | **2 Months After Day 1 (±3 Weeks)** | **6 Months After Day 1 (±4 Weeks)** | **3 to 7 Weeks After Month 6 Visit** | To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days. |
| Informed Consent/Assent | X | | | | Consent/assent must be obtained before any study procedures. (9.1.1.1)<br>If date of Day 1 visit is later than consent date, the interval between date of consent and date of Day 1 visit should be ≤14 days. If this interval is ≥15 days, then participant must be re-consented. |
| Assign Screening Number | X | | | | (9.1.6) |
| Inclusion/Exclusion Criteria | X | | | | (6.1, 6.2, 9.1.2) |
| Participant Identification Card | X | | | | (9.1.3) |
| Medical History/New Medical History | X | X | X | X | At Day 1, medical history for 1 year prior to Day 1 is collected. After Day 1, new conditions not already recorded as medical history or adverse events are collected. (9.1.4) |
| Lifetime/New Gynecological/Genitourinary History | X | X | X | X | Participants age 16-26 years only. At Day 1, lifetime gynecological/genitourinary history is collected. After Day 1, new conditions not already recorded as gynecological/genitourinary history or adverse events are collected. (9.1.4) |
| Prior/Concomitant Medication and Non-study Vaccination Review | X | X | X | X | (9.1.5) |
| Perform Physical Examination (Optional) | X | | | | Optional, per investigator's discretion; perform if needed to assess inclusion/exclusion criteria |

| **Study Visit Number** | **1** | **2** | **3** | **4** | **Comments (Protocol Section Reference)** |
|---|---|---|---|---|---|
| **Study Visit Time Point** | **Day 1** | **Month 2** | **Month 6** | **Month 7** | |
| **Study Visit Scheduled Day (Window)** | | **2 Months After Day 1 (±3 Weeks)** | **6 Months After Day 1 (±4 Weeks)** | **3 to 7 Weeks After Month 6 Visit** | To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days. |
| Pregnancy Testing, Serum or Urine (all females) | X | X | X | X | The serum pregnancy test or urine pregnancy test must be sensitive to 25 mIU/ML β-hCG and performed prior to vaccination. Results should be negative prior to vaccination. Pregnancy testing is required for all female participants. (9.5.2) |
| Serum for Anti-Human Papillomavirus (Anti-HPV) Antibody Testing (Including Retention Serum) | X | | | X | On Day 1, serum for anti-HPV measurements must be collected before vaccination. (9.2) |
| Optional Sexually Transmitted Infections (STI) Testing (Local Laboratory, if Clinically Indicated) | X | X | X | X | Optional, per investigator's discretion, if needed to evaluate eligibility criteria or new medical conditions. (9.1.13.2) |
| Vital Signs Prior to Vaccination | X | X | X | | Weight and height are to be measured at Day 1 only. Body temperature is to be taken prior to each vaccination. Participants with fever (defined as an oral temperature of ≥100.0°F [≥37.8°C]) will have the vaccination delayed until fever is resolved. (9.1.13.1) |
| Assign Treatment/Randomization Number | X | | | | At Day 1, allocation to study vaccine should not occur until all screening procedures have been completed (all items above in this table); although allocation is performed by non-random assignment, assigned numbers are referred to as "treatment/randomization numbers". (9.1.7) |
| Study Vaccine Administration | X | X | X | | Day 1 visit (and all procedures) must be done within 14 days of informed consent (screening). The first study vaccination may be administered only after the treatment/randomization number for the participant has been obtained. (9.1.8, 9.10.1) |

| **Study Visit Number** | **1** | **2** | **3** | **4** | **Comments (Protocol Section Reference)** |
|---|---|---|---|---|---|
| **Study Visit Time Point** | **Day 1** | **Month 2** | **Month 6** | **Month 7** | |
| **Study Visit Scheduled Day (Window)** | | **2 Months After Day 1 (±3 Weeks)** | **6 Months After Day 1 (±4 Weeks)** | **3 to 7 Weeks After Month 6 Visit** | To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days. |
| 30-minute Post-Vaccination Observation Period | X | X | X | | Observe participants for 30 minutes after each vaccination for immediate untoward effects. (9.5.3) |
| Provide Vaccination Report Card (VRC) to Participant and Review Instructions | X | X | X | | (9.5.1) |
| Review Adverse Events/Safety Follow-Up | X | X | X | X | (9.3) |

β-hCG=beta human chorionic gonadotropin; VRC=vaccination report card.

# 3. Introduction

## 3.1 Study Rationale

A local immunogenicity and safety study is generally required for vaccine registration in Vietnam. For instance, an immunogenicity and safety study of the quadrivalent human papillomavirus HPV (qHPV) (Types 6, 11, 16, 18) vaccine previously conducted in Vietnam demonstrated that the vaccine was immunogenic and well tolerated [Neuzil, K. M., et al 2011]. The study supported the licensure of the qHPV vaccine in Vietnam. Similarly, Protocol V503-017 is designed to evaluate the immunogenicity and safety of the 9-valent human papillomavirus (9vHPV) vaccine[1] and support licensure of the vaccine in Vietnam.

The V503 clinical program has been conducted in males and females 9 to 26 years of age [Pitisuttithum, P., et al 2015] [McKeage, K. 2016]. This study is designed to assess the safety and immunogenicity of the 9vHPV vaccine in male and female participants 9 to 26 years of age.

## 3.2 Background

Refer to the Investigator's Brochure and approved labeling for detailed background information on V503 (9vHPV vaccine).

Human papillomavirus (HPV) is the causative agent of nearly all cervical cancer cases, as well as a substantial proportion of anal, vulvar, vaginal, penile, and oropharyngeal cancers [Forman, D., et al 2012]; thus, HPV is responsible for approximately 5% of the global cancer burden [Parkin, D. Maxwell and Bray, Freddie 2006].

The 9vHPV vaccine was developed to cover 7 cancer-causing HPV types (HPV 16, 18, 31, 33, 45, 52, and 58) that are together responsible for approximately 90% of cervical cancers and HPV-related vulvar, vaginal, and anal cancers and 2 HPV types (HPV 6 and 11) that are responsible for 90% of genital warts worldwide [Serrano, B., et al 2015] [Alemany, L., et al 2015] [Garland, S. M., et al 2009]. In a clinical study (Protocol V503-001), the 9vHPV vaccine prevented infection and disease due to the 9vHPV vaccine types in young women 16 to 26 years of age [Joura, E. A., et al 2015]. In two separate Phase 3 clinical studies (Protocols V503-002 and V503-003), antibody responses to HPV 6/11/16/18/31/33/45/52/58 in girls and boys aged 9 to 15 years and in young men 16 to 26 years of age were non-inferior to those among young women aged 16 to 26 years following 9vHPV vaccination, thereby supporting the bridging of efficacy findings with 9vHPV vaccine from young women to girls, boys, and young men [Van Damme, P., et al 2015] [Castellsague, X., et al 2015]. Key aspects of the 9vHPV vaccine development program are summarized in published literature [Pitisuttithum, P., et al 2015] [McKeage, K. 2016]. The 9vHPV vaccine was licensed in the

[1] The 9-valent human papillomavirus (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle vaccine, also known as V503, will hereafter be referred to as 9vHPV vaccine in this protocol.

United States in 2014; in Canada, the European Union, and Australia in 2015; and in other countries in 2015-2017 under the name GARDASIL™9 (Merck & Co., Inc., Kenilworth, New Jersey, USA).[2] As of August 2017, the 9vHPV vaccine was approved in over 60 countries.

The 9vHPV vaccine formulated with amorphous aluminium hydroxyphosphate sulfate (AAHS) consists of highly purified virus-like particles (VLPs) of the L1 capsid proteins from HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. Like for GARDASIL™,[3] 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 are comprised 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, highly purified, and then adsorbed onto AAHS without the addition of preservative. After preparation, the monovalent bulk adsorbed products are mixed to create the 9vHPV vaccine with the desired concentrations of each monovalent L1 VLP. The 9vHPV vaccine is not a live virus vaccine. It is not capable of causing viral infection.

### 3.2.1 Pharmaceutical and Therapeutic Background

The 9vHPV vaccine is comprised of VLPs of the 4 HPV types (HPV 6, 11, 16, and 18) contained in the qHPV vaccine GARDASIL™, plus the VLPs of 5 additional oncogenic HPV types (HPV 31, 33, 45, 52, and 58). The 9vHPV vaccine is intended to prevent cervical, vulvar, vaginal, and anal cancers and related precancers, and anogenital warts caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. It is generally accepted that HPV VLP vaccines elicit protection by generating antibody responses to the HPV types covered by the vaccine [Stanley, M., et al 2012].

## 3.3 Benefit/Risk Assessment

As of August 2017, the 9vHPV vaccine has been licensed in over 60 countries to prevent cervical, vulvar, vaginal, and anal cancers and precancers and anogenital warts caused by HPV types covered by the 9vHPV vaccine. The United States Food and Drug Administration and the European Medicines Agency have both determined that the benefits of the 9vHPV vaccine outweigh the risks [Center for Drug Evaluation and Research 2014] [European Medicines Agency 2016].

---

[2] GARDASIL™9 (human papillomavirus 9-valent vaccine recombinant) is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

[3] GARDASIL™ (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine] is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, USA. GARDASIL™ is also known as SILGARD® in some countries. SILGARD® is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

It cannot be guaranteed that participants in clinical studies will directly benefit from the study vaccine during participation in this study, as clinical studies are designed to provide information about the safety and effectiveness of an investigational vaccine.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying Investigator's Brochure and informed consent documents.

## 4. Objectives/Hypotheses and Endpoints

In 9- to 26-year-old female and male participants:

| Objective/Hypothesis | Endpoint |
|---|---|
| **Primary** | |
| • Objective: To demonstrate that the 9vHPV vaccine is immunogenic<br>• Hypothesis: 9vHPV vaccine induces acceptable anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 seroconversion at 4 weeks post Dose 3. The statistical criterion for acceptable anti-HPV seroconversion requires the lower limit of the 95% confidence interval (CI) of the percent of participants who seroconverted to be greater than 90% for each HPV type. | • Seroconversion, defined as a participant who was anti-HPV seronegative at Day 1 and became seropositive at 4 weeks post Dose 3. |
| **Secondary** | |
| • Objective: To evaluate the safety of 9vHPV vaccine. | • Proportion of participants experiencing solicited injection-site adverse events (AEs).<br>• Proportion of participants experiencing solicited systemic AEs.<br>• Proportion of participants experiencing vaccine-related serious AEs (SAEs). |
| • Objective: To summarize geometric mean titers (GMTs) at Day 1 and at 4 weeks post Dose 3 of 9vHPV vaccine. | • GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Day1 and 4 weeks post Dose 3. |

# 5. Study Design

## 5.1 Overall Design

This is a non-randomized, single-site, open-label study of the 9vHPV vaccine in 9- to 26-year-old females and males to be conducted in conformance with Good Clinical Practice (GCP).

A total of approximately 200 participants will be enrolled (see Section 5.2). Participants will receive a centrally generated "treatment/randomization number"; however, as all participants will receive the same open-label study vaccine regimen, and no actual randomization will occur. At the time of enrollment, participants must meet all inclusion criteria and must not meet any exclusion criteria.

Collection of medical history and vital signs will be conducted at Day 1 for all participants. Physical examination at Day 1 is optional and will be conducted, per investigator's discretion, if needed to assess inclusion/exclusion criteria.

Study vaccine will be administered under open-label conditions at the following time points: Day 1, Month 2, and Month 6.

Serum samples will be obtained at Day 1 and Month 7 for measurement of anti-HPV antibodies for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Safety will be monitored from Day 1 until Month 7; a vaccination report card (VRC) will be provided to each participant for recording AE information.

A pregnancy test will be performed on all female participants at Day 1, Month 2, Month 6, and Month 7 visits. Any female participant with a positive pregnancy test at Day 1 will not be vaccinated and will not be allowed to participate in the study. Female participants with a positive pregnancy test after Day 1 will not be vaccinated until after pregnancy outcome. Pregnant participants who receive less than 3 vaccinations during the study will be offered the possibility to complete the vaccination course. Pregnancies and any associated AEs in vaccinated subjects will be followed to outcome.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Study SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

### 5.1.1 Study Diagram

The study design is depicted in Figure 1.

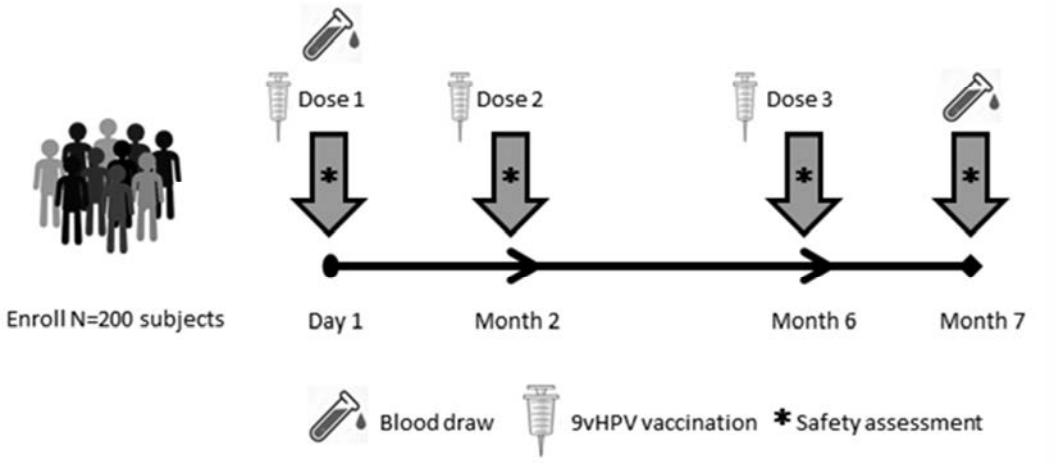


Figure 1 Design of the V503-017 Study

## 5.2 Number of Participants

Approximately 200 participants will be enrolled. Enrollment will be stratified by age and gender (see Sections 7.3 and 7.3.1). Age stratification will include the following age strata, in a 1:1 ratio: 9 to 15 years and 16 to 26 years. Gender stratification will include a female:male ratio of 2:1.

Additionally, enrollment limits will be applied in the 9 to 15 years age group to ensure ≥30% enrollment into each of the following 2 age subgroups (with a minimum number of female and male participants in each age subgroup): 9 to 12 years and 13 to 15 years (at least 20 female and 10 male participants in each age subgroup). Enrollment will be managed by use of an interactive response technology (IRT) system.

## 5.3 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent/assent form. The overall study ends when the last participant completes the last study-related phone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last serology assay result.

### 5.3.1 Clinical Criteria for Early Study Termination

There are no pre-specified criteria for terminating the study early.

## 5.4 Scientific Rationale for Study Design

The purpose of this trial is to fulfill the requirement for licensure in Vietnam to conduct an immunogenicity and safety study of the 9vHPV vaccine within Vietnam. All participants will receive 3 doses of 9vHPV vaccine at Day 1, Month 2, and Month 6. Each participant is expected to participate in the trial for approximately 7 months.

### 5.4.1 Rationale for Endpoints

#### 5.4.1.1 Immunogenicity Endpoints

Serum will be collected at Day 1 (before the first study vaccination) and at Month 7 (approximately 4 weeks post Dose 3) for analysis of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses, by competitive Luminex immunoassay (cLIA), to support the primary and secondary objectives of the study.

Seroconversion as defined in Section 10.4.1 is the primary study immunogenicity endpoint. Seroconversion at 4 weeks post Dose 3 is a standard immunogenicity endpoint in the qHPV and 9vHPV vaccine clinical programs and is an appropriate measure of immune response to HPV vaccination in a single arm study with no control arm.

GMTs at 4 weeks post Dose 3 will be calculated for each HPV type as part of assessments of the secondary immunogenicity objective. Summarization of GMTs is also the standard immune response assessment in qHPV and 9vHPV vaccine clinical programs.

#### 5.4.1.2 Safety Endpoints

The safety endpoints evaluated in this study were selected based on the product's safety profile demonstrated in previous studies and feedback received from regulatory agencies during product development. A list of the safety endpoints to evaluate safety in the study population is provided in Section 10.4.2.

## 5.5 Justification for Dose

The efficacy of the 9vHPV vaccine was established in young women 16-26 years of age based on a dosing regimen of 0, 2, 6 months [Joura, E. A., et al 2015]. Efficacy results were extended to girls and boys 9-15 years of age and young men 16-26 years of age who received 3 doses at 0, 2, 6 months based on the demonstration of noninferior HPV antibody responses compared with young women who received 3 doses at 0, 2, 6 months [Van Damme, P., et al 2015] [Castellsague, X., et al 2015]. This dosing regimen is similar to that previously developed for the qHPV vaccine [Schiller, J. T., et al 2012].

The dose formulation of 9vHPV vaccine (including dose of antigen and amount of adjuvant) was determined based on immunogenicity and safety results of Phase II studies [Pitisuttithum, P., et al 2015] [Luxembourg, A., et al 2015].

## 6. Study Population

Healthy female and male participants between the ages of 9 and 26 years (inclusive) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

### 6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

**Type of Participant and Disease Characteristics**

1. Is a healthy individual who meets all enrollment criteria defined in this section.

**Demographics and General Medical History**

2. Is female or male between the ages of 9 years and 0 days and 26 years and 364 days on the day of enrollment.
3. Is judged to be in good physical health on the basis of medical history, physical examination, and laboratory results.
4. (*Participants 9 to 15 years of age only*) Has not yet had coitarche and does not plan on becoming sexually active during the vaccination period (Day 1 through Month 7).
5. (*Participants 16 to 26 years of age only*) Has never had Pap testing (cervical or anal) or has had only normal Pap test results.
6. (*Participants 16 to 26 years of age only*) Has a lifetime history of 0 to 4 male and/or female sexual partners at the time of enrollment. Male or female partner is defined as someone with whom the participant has had penile penetrative sexual intercourse or someone who has contacted, either by penetrative (with fingers or other objects) or non-penetrative means, the participant's genitalia during sexual activity.

**Female participants**:

7. (*Female participants 16 to 26 years of age only*) Has not had sex with males or has had sex with males and used effective contraception with no failures (an example of a failure is a male condom that ruptures during sexual intercourse) since the first day of the participant's last menstrual period through Day 1. Effective contraception is defined as a marketed, approved contraceptive product that the participant has used per the manufacturer's instructions with every act of sexual intercourse. The participant understands and agrees that during the Day 1 through Month 7 period, she should not have sexual intercourse with males without effective contraception, and that the use of the rhythm method, withdrawal, and emergency contraception are not acceptable methods per the protocol.

**Informed Consent/Assent**

8. Participant (*or, for minor participants, the parent/legal guardian and participant*) fully understands study procedures, alternative treatments available, and the risks involved with the study, and voluntarily agrees to participate by giving written informed consent/assent.

**General**

9. Agrees to provide study personnel with a primary telephone number as well as an alternate form of contact, if available, for follow-up purposes.

## 6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1. Has a known allergy to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]). For the purpose of this exclusion criterion, an allergy to vaccine components is defined as an allergic reaction that met the criteria for SAEs as defined in Section 9.3.
2. Has a history of severe allergic reaction (eg, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention.
3. Has thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
4. Is concurrently enrolled in clinical studies of investigational agents.
5. Is currently immunocompromised or has been diagnosed as having a congenital or acquired immunodeficiency, human immunodeficiency virus (HIV) infection, lymphoma, leukemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, or other autoimmune condition.
6. Has had a splenectomy.
7. Has had a fever (defined as an oral temperature of ≥100.0°F or ≥37.8°C) within the 24-hour period prior to the Day 1 vaccination (if the participant meets this exclusion criterion, the Day 1 visit may be rescheduled for a time when this criterion is not met).
8. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might confound the results of the study, or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate.
9. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug abuse or dependence. Alcohol abusers are defined as those who drink despite recurrent social, interpersonal, and/or legal problems as a result of alcohol use.

10. Has a history of a positive test for HPV.
11. (*Male participants 16 to 26 years of age only*) Has a history of HPV-related external genital lesions (eg, condyloma acuminata) or HPV-related anal lesions (eg, condyloma acuminata, or anal intraepithelial neoplasia) or anal cancer.
12. (*Female participants 16 to 26 years of age only*) Has a history of an abnormal cervical biopsy result (showing cervical intraepithelial neoplasia or worse).
13. (*Female participants 16 to 26 years of age only*) Has a history of HPV-related external genital lesions (eg, condyloma acuminata, or vulvar intraepithelial neoplasia) or external genital cancer, HPV-related vaginal lesions (eg, condyloma acuminata, or vaginal intraepithelial neoplasia) or vaginal cancer, or HPV-related anal lesions (eg, condyloma acuminata, or anal intraepithelial neoplasia) or anal cancer.
14. (*Female participants only*) Is pregnant as determined by a serum pregnancy test or urine pregnancy test that is sensitive to 25 mIU/mL beta human chorionic gonadotropin (β-hCG).
15. (*Female participants only*) Is expecting to donate eggs during Day 1 through Month 7 of the study.

**Prior/Concomitant Therapy**

16. Is receiving or has received in the year prior to enrollment the following immunosuppressive therapies: radiation therapy, cyclophosphamide, azathioprine, methotrexate, any chemotherapy, cyclosporin, leflunomide (Arava™), tumor necrosis factor (TNF)-α antagonists, monoclonal antibody therapies (including rituximab [Rituxan™]), intravenous gamma globulin (IVIG), antilymphocyte sera, or other therapy known to interfere with the immune response. With regard to systemic corticosteroids, a participant will be excluded if he/she is currently receiving steroid therapy, has recently (defined as within 2 weeks of enrollment) received such therapy, or has received 2 or more courses of high-dose corticosteroids (orally or parenterally) lasting at least 1 week in duration in the year prior to enrollment. Participants using inhaled, ophthalmic, topical steroids, or intra-articular / soft tissue injection are considered eligible for the study.
17. Has received any immune globulin product (including RhoGAM™ [Ortho-Clinical Diagnostics]) or blood-derived product within the 3 months prior to the Day 1 vaccination, or plans to receive any such product during Day 1 through Month 7 of the study.
18. Has received inactivated or recombinant vaccines within 14 days prior to the Day 1 vaccination or has received live vaccines within 21 days prior to the Day 1 vaccination.
19. Has received a marketed HPV vaccine, or has participated in an HPV vaccine clinical study and has received either active agent or placebo.

**General**

20. Is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.
21. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this study.

## 6.3 Lifestyle Restrictions

### 6.3.1 Meals and Dietary Restrictions

There are no dietary restrictions for participants participating in the study.

### 6.3.2 Caffeine Alcohol, and Tobacco Restrictions

There are no caffeine, alcohol, or tobacco restrictions for participants participating in the study.

### 6.3.3 Activity

There are no activity restrictions for participants participating in the study.

## 6.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the data entry guidelines.

## 6.5 Participant Replacement Strategy

A participant who discontinues study vaccination or withdraws from the study will not be replaced.

## 6.6 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 (eg, 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.

## 7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment. Participants will receive open-label single-dose vials, each vial containing 1 dose of study vaccine; no kitting will be required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

### 7.1 Treatments Administered

The vaccine to be used in this study is outlined below in Table 1.

Table 1 Study Vaccine

| | |
|---|---|
| **Study Vaccine Name:** | 9vHPV vaccine (9-valent human papillomavirus vaccine)<br>Also known as V503 |
| **Dosage Formulation:** | Sterile suspension for intramuscular injection |
| **Unit Dose Strength:** | 0.5 mL |
| **Dosage Level:** | 1 dose on each of 3 occasions: Day 1, Month 2, Month 6<br>Amount per unit dose:<br>HPV Type: 6 11 16 18 31 33 45 52 58<br>Amount (µg): 30 40 60 40 20 20 20 20 20<br>Amorphous aluminum hydroxyphosphate sulfate (500 µg)<br>Excipients: sodium chloride (9.56 mg), L-histidine (0.78 mg), polysorbate 80 (50 µg), sodium borate (35 µg), water for injection (quantum satis) |
| **Route of Administration:** | Intramuscular injection |
| **Sourcing:** | Provided by the Sponsor (manufactured by the Sponsor) |

All supplies indicated in Table 2 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 9.1.8 for details regarding administration of the study treatment.

### 7.2 Dose Modification

Not Applicable

## 7.3 Method of Treatment Assignment

Participants participating in this study will be allocated by non-random assignment.

### 7.3.1 Stratification

Treatment allocation will be stratified according to the following factors:

1. Age: 1:1 allocation between 9 to 15 and 16 to 26 year-old age strata.
   Within 9 to 15 year-old stratum: enrollment will be monitored to ensure ≥30% enrollment in the 9 to 12 year-old range and ≥30% enrollment in the 13 to 15 year-old age range.
2. Gender: 2:1 allocation between females and males within each of the 9 to 15 and 16 to 26 year-old age strata.

Therefore, it is expected that the study will enroll 200 participants in the following strata:

- Approximately 33 male participants, 9 to 15 years of age (at least 10 participants 9 to 12 years of age and at least 10 participants 13 to 15 years of age)
- Approximately 67 female participants 9 to 15 years of age (at least 20 participants, 9 to 12 years of age and at least 20 participants, 13 to 15 years of age
- Approximately 33 male participants 16 to 26 years of age
- Approximately 67 female participants 16 to 26 years of age

## 7.4 Blinding

This is an open-label study; therefore, the Sponsor, investigator and participant will know the identity of the study vaccine administered.

## 7.5 Preparation/Handling/Storage/Accountability

### 7.5.1 Dose Preparation

Processes for preparation and administration of the study vaccine are described in Section 9.1.8 (ie, Sections 9.1.8.1 and 9.1.8.2).

The rationale for selection of doses to be used in this study is provided in Section 5.5 (Justification for Dose). There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

### 7.5.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance

with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

### 7.6 Treatment Compliance

Interruptions from the protocol specified vaccination schedule (ie, administration of 3 doses at scheduled time points; Section 9.1.8) for reasons not defined per protocol require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

### 7.7 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

See the exclusion criteria for specific restrictions for prior and concomitant medications at Day 1 (Section 6.2) and prerequisites for other vaccination visits (Section 9.10.1).

If possible, participants should not receive “special medications” (corticosteroids, immunosuppressives, immune globulins, and blood products) from 3 days prior to Day 1 through Month 7, nonstudy inactive or recombinant vaccines for 14 days prior to each study vaccination through 14 days after each study vaccination, or nonstudy live vaccines for 21 days prior to each study vaccination through 14 days after each study vaccination.

Participants may receive allergen desensitization therapy and tuberculin skin testing while participating in the study.

Use of prior and concomitant medications/vaccination should be recorded as described in Section 9.1.5.

### 7.7.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

## 7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

## 7.9 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor and/or designee are not blinded. Study treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

# 8. Discontinuation/Withdrawal Criteria

## 8.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the third vaccination will still continue to participate in the study as specified in Section 2 (SoA) and Section 9.10.2 (Discontinued Participants Continuing to be Monitored in the Study). Whenever possible, when a participant discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation except for serum collection for HPV testing. The final visit assessments can be done via a phone call and the VRC.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 (Discontinuation and Withdrawal).

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.

For participants who are discontinued from study treatment but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Participants may be allowed to begin study treatment again if deemed medically appropriate, with consultation from the Clinical Director.

## 8.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 9.1.9 (Discontinuation and Withdrawal). The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 8.3 (Lost to Follow Up).

## 8.3 Lost to Follow Up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

# 9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The Investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant to assess the primary study objective over the duration of the study, including any extra assessments that may be required, will not exceed 14 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 9.1 Administrative and General Procedures

### 9.1.1 Informed Consent/Assent

The investigator or qualified designee must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study-. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent/assent is in place.

#### 9.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the participant before participation in the study.

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

Specifics about a study and the study population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements. The assent, as applicable will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

### 9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or medically qualified designee to ensure that the participant qualifies for the study.

### 9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

### 9.1.4 Medical History

At the Day 1 visit, the participant's medical history for the year prior to Day 1 will be collected. For participants in the 16- to 26-year-old women's group, lifetime gynecological history will also be collected at the Day 1 visit. For participants in the 16- to 26-year-old men's group, lifetime genitourinary history will also be collected at the Day 1 visit.

After the Day 1 visit, any new medical history that has not been previously documented (either as adverse experiences or as medical history conditions) will be collected. For participants in the 16- to 26-year-old women's group, new gynecologic history will be collected. For participants in the 16- to 26-year-old men's group, new genitourinary history will be collected.

Other documentation, such as demographics, sexual history, pregnancy history, and contraceptive use, will be collected in the data collection system, as discussed in the electronic case report form (eCRF) entry guidelines.

### 9.1.5 Prior and Concomitant Medications Review

#### 9.1.5.1 Prior Medications

Prior and concomitant use of medicines and nonstudy vaccines should be documented in the data collection system in the following manner:

1. "Special medications" (corticosteroids, immunosuppressives, immune globulins, and blood products) from 3 days prior to Day 1 through Month 7.
2. "Other medications" from 3 days prior to each study vaccination through 14 days after each study vaccination
3. "Nonstudy inactive or recombinant vaccines" for 14 days prior to each study vaccination through 14 days after each study vaccination

4. "Non-study live vaccines" for 21 days prior to each study vaccination through 14 days after each study vaccination.

#### 9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study as outlined above.

### 9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to treatment allocation. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

### 9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Treatment allocation will occur centrally using an IRT system. All prevaccination (screening) data must be collected and all study procedures must be completed before the participant is assigned a treatment/ randomization number and vaccine administration.

Day 1 (and all Day 1 procedures) must occur within 14 days after informed consent (screening). Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

### 9.1.8 Treatment Administration

Vaccine will be administered at the study sites by the investigator and/or study staff.

The first dose of study vaccine will be administered on Day 1, which should be the day of allocation. The second and third (final) doses of study vaccine will be administered subsequently, at time points 2 and 6 months, respectively, after the first dose.

Participants should not be enrolled or vaccinated if protocol requirements are not met. At Day 1, vaccine should be administered after the blood draw for HPV testing (see Section 9.2.1 for procedures related to blood draw). Pregnant participants should not be vaccinated (see Section 9.5.2 for management of study visits and study vaccinations for pregnant participants). Section 9.10.1 provides additional information on other prerequisites for vaccination visits.

#### 9.1.8.1 Preparation of Study Vaccine for Administration

This study vaccine must be used as supplied (no dilution before administration). Prior to administration, mix the contents of the vial thoroughly by rolling the vial between the palms of both hands for 30 seconds. Withdraw a 0.5-mL dose from the vial, which contains approximately 0.75 mL of study vaccine. The study vaccine should be a whitish, semi-translucent suspension when thoroughly mixed. If the appearance is otherwise, do not administer and contact the Sponsor immediately.

#### 9.1.8.2 Study Vaccine Administration

Study vaccine will be administered at Day 1, Month 2, and Month 6. At each vaccination visit, participants will receive 9vHPV vaccine as a 0.5-mL intramuscular injection. The deltoid muscle of the nondominant arm is the preferred site of vaccination.

Study vaccinations should not be administered in the buttocks area. If the female participant has an implanted contraceptive (eg, NORPLANT™) at the time of the study vaccination, avoid administering the study vaccination in the arm with the implanted contraceptive. If female participants have received injectable contraceptives (eg, DEPO PROVERA™) or implanted contraceptives (eg, NORPLANT™) in both arms in the past 9 months, the injection may be given in the thigh rather than in an arm. Injections should not be given within 2 cm of a tattoo, scar, or skin deformation.

Injections should be administered at a 90° angle into the muscle tissue using a needle long enough to ensure intramuscular deposition of study vaccine. The study vaccine should be administered in the deltoid muscle using preferably a 1.0-mL syringe (the largest allowable size is a 3.0-mL syringe) with the following needle length and gauge specifications:

- 1-inch needle, 22 to 23 gauge for participants weighing <200 pounds (<90.9 kg)
- 1½-inch needle, 22 to 23 gauge for participants weighing ≥200 pounds (≥90.9 kg)
- 1½ -inch needle, 22 to 23 gauge for thigh injections

All participants will be observed for at least 30 minutes after each study vaccination for any untoward effects, including allergic reactions. This observation period will be documented in the participant's study chart.

#### 9.1.8.3 Timing of Dose Administration

Vaccination will be administered at the following time points: Day 1, Month 2, and Month 6.

Acceptable day ranges for vaccination visits are as follows:

- Dose 1: Day 1 (±0 days)
- Dose 2: Month 2 (±3 weeks)
- Dose 3: Month 6 (±4 weeks)

The Day 1 visit is defined as the day that the first study vaccination is given (ie, date when Dose 1 of 9vHPV vaccine is injected).

The visit windows described here are for site scheduling purposes. The visit windows used for exclusion from the statistical analyses are provided in Section 10.5.1.

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 (eg, 1 calendar month versus 30 days versus 4 weeks).

To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days.

### 9.1.9 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the vaccination regimen should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit (exception: serum collection should not be done if the participant has not received all 3 scheduled doses of study vaccine) should be performed (at the time of withdrawal). Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3.

### 9.1.10 Participant Blinding/Unblinding

This is an open label study; there is no blinding for this study.

### 9.1.11 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical study that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

Critical Equipment for this study includes:

- Refrigerator equipped with an appropriate temperature monitoring device to ensure the temperature is maintained at 2°C to 8°C for storage of study vaccine supplies
- Non frost-free freezer with an appropriate temperature monitoring device to ensure serum samples are stored at -20°C or colder until shipped to the Central Laboratory
- Centrifuge for processing of blood samples

### 9.1.12 Other Assessments

#### 9.1.12.1 Physical Examination and Vital Signs Prior to Study Vaccination

A physical examination at Day 1 is optional. It will be conducted, per investigator's discretion, if needed to determine whether the subject meets enrollment criteria for the study. Physical examination details will be documented in the subject's chart and any medical condition will be documented in the data collection system.

Oral temperature, height, weight will be taken before study vaccine is administered at Day 1.

Oral temperature will also be taken before study vaccine is administered at Month 2, and Month 6 visits). If the participant has a fever (defined as an oral temperature of ≥100.0°F or ≥37.8°C) within the 24-hour period prior to receiving a study vaccination, the participant should not receive the study vaccine, and the vaccination visit should be rescheduled until after the fever has resolved.

#### 9.1.12.2 Optional Testing for Sexually Transmitted Infections (STIs)

Local laboratory testing to screen for sexually transmitted infections (STIs), including HPV testing (cervical and/or anal); Pap test and/or HPV polymerase chain reaction, chlamydia, gonorrhea, herpes simplex virus, syphilis, hepatitis B, and HIV may be performed on any participant at any visit if deemed necessary by the investigator. Any participant who tests positive for an STI will not be discontinued from the trial and may participate in all study procedures. These participants will be referred for appropriate counseling and treatment outside of the context of the protocol.

## 9.2 Efficacy Assessments

### 9.2.1 Serum for Anti-HPV Antibody Testing

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual.

Each participant will have serum collected for anti-HPV measurements at scheduled time points (Section 2: SoA). For collection of the serum samples, the study sites must adhere to the procedures described in the protocol, must follow instructions provided by the Sponsor-designated Central Laboratory, and must use the materials provided by the Sponsor-designated Central Laboratory. 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.

The following are the step-by-step procedures for collection of study specimens, a description of supplies needed, and the guidelines for handling specimens:

- For each visit that requires a serum specimen for anti-HPV measurements, a 7-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 2.0 mL of serum should be aliquoted to a vial provided by the Sponsor-designated Central Laboratory.
- An additional approximately 0.8 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.
- After the serum has been processed, transfer the vials to the freezer (-20 °C or lower) without delay.

- All serum samples are kept in the freezer until they shipped on dry ice as instructed by the Sponsor (see Administrative Binder).
    - If the samples thaw, contact the Sponsor.
    - Thawed serum samples require written documentation, including details such as treatment/randomization 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).
- "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.
- "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.

### 9.2.2 Immunogenicity Measurements

The 9-valent HPV competitive Luminex immunoassay (HPV-9 cLIA) is used for the primary and secondary objectives of the study.

The purpose of the HPV-9 cLIA assay is to quantify the antibodies specific to the neutralizing epitopes of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This assay is used by the Testing Laboratory to evaluate the serological response before and after vaccination with the 9vHPV vaccine and to measure HPV infection-induced antibodies for sero-epidemiology studies.

HPV virus-like particles (VLPs) derived from yeast for each of the 9HPV types are coupled to one of 9 distinct fluorescent Luminex MagPlex® magnetic microspheres. Each microsphere has its own distinct fluorescent dye that can be recognized by excitation with an infrared laser, allowing for the measurement of antibodies against multiple HPV types from a single test of a human serum sample. HPV type-specific neutralizing monoclonal antibodies conjugated with phycoerythrin (PE-mAb conjugate) compete with the antibodies in the serum sample for binding to the neutralizing epitopes of the VLPs coupled to the microspheres. After incubation with PE-mAb conjugate and sample serum, the microspheres are washed and the fluorescent signal from the PE-mAb conjugate is read. The fluorescence signal is inversely proportional to the HPV antibody concentration of the serum sample tested. Antibody concentrations are derived from a standard curve, which is generated using a Reference Standard made from a pool of serum from individuals immunized against the nine HPV types. A standard curve for each HPV type is calculated using a weighted 4-

parameter logistic curve fit. Antibody concentration results are expressed as milliMerck Units/mL (mMU/mL).

The high, medium, low, and negative controls used for this assay were collected from humans who were either HPV-seronegative, had low antibody titers from natural infection, or had medium-to-high antibody titers to the 9 HPV types following vaccination.

## 9.3 Adverse Events (AE), Serious Adverse Events (SAE) and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Section 12.2 (Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

### 9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of allocation/randomization through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is either:

1. A death that occurs prior to the participant completing the study, but outside the time period specified in the previous paragraph.
2. An SAE is an AE that is considered by an investigator who is a qualified physician to be vaccine related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 2.

Table 2 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

| **Type of Event** | | **Reporting Time Period:**<br>**Consent to Randomization/ Allocation** | **Reporting Time Period:**<br>**Randomization/ Allocation through Protocol-Specified Follow-up Period** | **Reporting Time Period:**<br>**After the Protocol Specified Follow-up Period** | | **Timeframe to Report Event and Follow-up Information to SPONSOR:** |
|---|---|---|---|---|---|---|
| **Non-Serious Adverse Event (NSAE)** | | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Not required | | Per data entry guidelines |
| **Serious Adverse Event (SAE)** | | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion | Report all | Report if:<br>- drug/vaccine related.<br>- any death until participant completion of study<br>(Follow ongoing to outcome) | | Within 24 hours of learning of event |
| **Pregnancy/Lactation Exposure** | | Report if:<br>- due to intervention<br>- causes exclusion | Report all | Previously reported – Follow to completion/termination; report outcome (if the participant received at least 1 vaccine dose and became pregnant) | | Within 24 hours of learning of event |
| **Cancer** | | Report if:<br>- due to intervention<br>- causes exclusion | Report all | Not required | | Within 5 calendar days of learning of event |
| **Overdose** | | - | Report all | Not required | | Within 5 calendar days of learning of event |

### 9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

A VRC will be used by the participant to document any AEs.

### 9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy (if the participant received at least 1 vaccine dose) and exposure during breastfeeding, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Section 12.2 (Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

### 9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### 9.3.5 Disease-Related Events and/or Disease-Related Outcomes not Qualifying as AEs or SAEs

Not Applicable

### 9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the trial are reportable to the Sponsor. All reported pregnancies (in participants who received at least 1 vaccine dose) must be followed to the completion/termination of the pregnancy.

## 9.4 Treatment of Overdose

In this study, an overdose is defined as a participant receiving >3 doses (0.5 mL each dose), or receiving ≥0.75 mL of 9vHPV vaccine in any one dose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

## 9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below.

Planned time points for all safety assessments are provided in the SoA.

### 9.5.1 Patient Reported Outcome

Adverse events will be documented using a validated VRC.

All participants will receive a VRC at the Day 1, Month 2, and Month 6 study vaccination visits. Using the VRC, the participant or the parent/guardian of the participant will be asked to record the participant's oral temperature in the evening after each study vaccination and daily for 4 days after each study vaccination for the purpose of identifying febrile events. Also, beginning after each study vaccination and for a total of 15 days including the day of vaccination, the participant will be asked to record injection-site and systemic AEs, concomitant medications, and concomitant vaccinations by means of the VRC.

Serious AEs, cancers and overdoses, pregnancy information, lactation information, and infant SAEs will also be collected for the entire duration of the study as described in Section 9.3. In addition, new medical conditions not present at baseline and not reported as an adverse experience will be collected throughout the study.

### 9.5.2 Pregnancy Testing

All female participants will have a serum or urine pregnancy test (sensitive to 25 mIU/mL β-hCG performed at each vaccination visit (ie, Day 1, Month 2, or Month 6) and at Month 7 per the manufacturer's instructions. All materials used for serum and/or urine pregnancy testing will be provided by the study sites.

The pregnancy test results must be obtained prior to each study vaccination (on the day the participant is vaccinated). Any participant found to be pregnant at Day 1 will not be allocated and will not participate in the study. For randomized participants who become pregnant after receiving one or two study vaccinations, study visits and vaccinations will be paused until resolution of the pregnancy (eg, term, elective termination, spontaneous abortion). Study visits and study vaccination in pregnancy participants will be handled as described in Table 3.

Table 3 Guidelines for Pregnant Participants: Managing Study Visits and Study Vaccinations

| **Time When Pregnancy is Detected** | **Action** |
|---|---|
| Day 1 *(before first vaccination)* | Do not enroll. |
| Between Day 1 and Month 2<br><br>*(After study vaccine dose 1 and before study vaccine Dose 2 was administered)* | • No scheduled visits until resolution of the pregnancy (eg, term, elective termination, spontaneous abortion).<br>• The Month 2 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels.<br>• The Month 6 study vaccination should be administered 4 months after the Month 2 study vaccination.<br>• The Month 7 visit should be conducted 1 month after the Month 6 study vaccination. |
| Between Month 2 and Month 6<br><br>*(After study vaccine dose 2 and before study vaccine Dose 3 was administered)* | • No scheduled visits until resolution of the pregnancy (eg, term, elective termination, spontaneous abortion).<br>• The Month 6 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels.<br>• The Month 7 visit should be conducted 1 month after the Month 6 study vaccination. |
| After Month 6<br><br>*(After study vaccine Dose 3 was administered)* | • Continue with scheduled study visits during the pregnancy.<br>• Safety follow-up will be conducted after resolution of the pregnancy (eg, term, elective termination, spontaneous abortion). |

β-hCG=beta human chorionic gonadotropin.

Management of pregnant participants will be as follows. All female participants undergo pregnancy testing based on urine or serum analyses for β-hCG at each study visit (Section 2: SoA). Participants found to be pregnant at Day 1 are not eligible to participate in the study (Section 6.2: exclusion criterion 14). Female participants 16 years and older enrolled in the study are instructed to use effective contraception through Month 7 (Section 6.1: inclusion criterion 7). Participants who inadvertently become pregnant before receiving all 3 doses of vaccine do not receive additional doses until ≥4 weeks after resolution of pregnancy and normalization of β-hCG levels as described in Table 3. Breastfeeding is not a contraindication to enrollment or to receiving study vaccinations.

Pregnancy and breastfeeding in study participants and infant SAEs for all infants born to participants who received the study vaccine or who were breastfed during the study must be reported.

### 9.5.3 Post-vaccination Observation Period (30 minutes)

All participants will be observed for at least 30 minutes after each study vaccination for any untoward effects, including allergic reactions. This observation period will be documented in the participant's study chart.

### 9.5.4 Clinical Laboratory Assessments

Refer to Section 12.3 (Appendix 3: Clinical Laboratory Tests) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- All protocol-required laboratory assessments, as defined in Section 2 (SoA), must be conducted in accordance with the manufacturer's specifications.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents.
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 15 days after the last dose of study treatment, repeat assessments may be performed as determined by the investigator.

## 9.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

## 9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

### 9.8 Biomarkers

Biomarkers are not evaluated in this study.

### 9.9 Visit Requirements

Visit requirements are outlined in Section 2 (SoA). Specific procedure-related details are provided above in Section 9 (Study Assessments and Procedures).

#### 9.9.1 Prerequisites for Vaccination Visits

This section summarizes prerequisites for visits with study vaccinations and specimen collection. 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.

See the inclusion/exclusion criteria for specific restrictions at Day 1. For visits with study vaccinations, study personnel should verify by questioning the participant and/or by examination that:

1. The participant has not had a fever (defined as an oral temperature of ≥100.0°F or ≥37.8°C) within the 24-hour period prior to any study vaccination visit.
2. The participant has not received any systemic (oral or parenteral) corticosteroids in the 2 weeks prior to the Month 2 and Month 6 study vaccination visits.
3. The participant has not received a nonstudy inactive or recombinant vaccine within 14 days prior to any study vaccination visit or a nonstudy live vaccine within 21 days prior to any study vaccination visit.
4. The participant is not pregnant as confirmed by a serum or urine pregnancy test.

If the participant does not meet the requirements listed above, the study visit (including specimen collection and study vaccination) should be rescheduled.

#### 9.9.2 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study vaccinations but continue in the study may attend study visits per the study flow chart (SoA table). However, serum will not be collected at the Month 7 study visit from participants who did not complete the 3-dose vaccination regimen.

## 10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to the final database lock, changes are made to the primary hypothesis, or the statistical methods related to those hypothesis, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental Statistical Analysis Plan and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

## 10.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this study. Full details are provided in the following sections.

| | |
|---|---|
| Study Design Overview | A Phase III open-label, safety, and immunogenicity study of a 9vHPV vaccine administered to 9- to 26-Year-Old Females and Males in Vietnam |
| Treatment Assignment | Single-arm, open-label, 9vHPV vaccine administration with 1:1 allocation ratio among 9- to 15- and 16- to 26-year-old participants. The study will recruit females and males, with 2:1 enrollment ratio within each age group. |
| Analysis Populations | Immunogenicity: Per-Protocol Immunogenicity (PPI) |
| | Safety: All Participants as Treated (APaT) |
| Primary Endpoint | Percent of participants who seroconverted to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post Dose 3. |
| Key Secondary Endpoints | Immunogenicity: GMTs of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post Dose 3. |
| | Safety: Number (and proportion) of participants with the following: vaccine-related SAEs and any SAE (occurring at any time during the study); injection-site AEs, systemic AEs, and discontinuations due to an AE within Day 1 to Day 15 following receipt of 9vHPV vaccination; and, oral temperatures within Day 1 to Day 5 following receipt of 9vHPV vaccination. |
| Statistical Methods for Key Immunogenicity Analysis | The primary immunogenicity hypothesis will be addressed by calculating point and 95% CI estimates of percent seroconversion based on the exact binomial method of Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934]. |
| | The secondary immunogenicity objective will be addressed by calculating point and 95% CI estimates of GMTs based on the t-distribution. |
| Statistical Methods for Key Safety Analyses | Safety assessments will be descriptive in nature and will include calculation of proportions of participants with adverse events. |
| Interim Analyses | No interim analyses are planned for this study. |
| Multiplicity | No multiplicity adjustment is planned as successful demonstration of the primary immunogenicity hypothesis requires the lower limit of the 95% CI of percent seroconversion be >90% of all 9 HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. |

| | |
|---|---|
| Sample Size and Power | The planned sample size of 200 participants to be vaccinated with 9vHPV vaccine provides ~97% power at an overall 1-sided Type I error equal to 0.025 to establish that the 9vHPV vaccine induces among participants >90% seroconversion to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post Dose 3. |

## 10.2 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 study is being conducted as a non-randomized, open-label study (ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned).

The Clinical Biostatistics department will generate the allocation schedules for study treatment assignment. Treatment allocation will be implemented via an IRT.

## 10.3 Hypotheses/Estimation

Objectives and hypothesis of the study are stated in Section 4.

## 10.4 Analysis Endpoints

### 10.4.1 Immunogenicity Endpoints

The primary immunogenicity endpoints are the seroconversion percentages to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 by 4 weeks post Dose 3. Seroconversion is defined as changing a participant's serostatus from seronegative at Day 1 to seropositive by 4 weeks post Dose 3. A participant with anti-HPV cLIA titer at or above the serostatus cutoff for a given HPV type is considered seropositive for that HPV type.

The secondary immunogenicity endpoints are GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post Dose 3.

### 10.4.2 Safety Endpoints

The safety endpoints are the number (and proportions) of participants who reported injection-site AEs, systemic AEs, and discontinuations due to an AE within Day 1 to Day 15 following receipt of 9vHPV vaccination. In addition, SAEs occurring at any time during the study and oral temperatures (reported Day 1 to Day 5 following any vaccination) will be summarized.

### 10.4.3 Derivations of Immunogenicity Endpoints

In numerical calculation of HPV type-specific GMTs, anti-HPV titer results reported as "less than [lower limit of quantification (LLOQ)]" or "<[LLOQ]", where [LLOQ] corresponds to the lower limit of quantitation of the cLIA assay for the relevant HPV type, will be replaced by a numerical number equal to half of LLOQ of the relevant HPV type.

## 10.5 Analysis Populations

### 10.5.1 Immunogenicity Analysis Population

The PPI population will serve as the primary population for the analysis of immune response to each of the HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in this study. The PPI population is HPV type-specific and consists of all allocated participants who:

1. Were seronegative to the appropriate HPV type at Day 1;
2. Have received all 3 vaccinations with the correct dose of 9vHPV vaccine within acceptable day ranges around the planned vaccination visits as shown in Table 4;
3. Have provided serum sample within 21 to 49 days post Dose 3;
4. Have no protocol deviations that could interfere with the evaluation of participant's immune response to 9vHPV vaccination. At Day 1, participants 9 to 15 years of age must satisfy inclusion criterion 4 (ie, "Has not yet had coitarche and does not plan on becoming sexually active during the vaccination period (Day 1 through Month 7)" as specified in Section 6.1.

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

The final determination of protocol deviations that could interfere with the evaluation of participant's immune response to 9vHPV vaccination, and thereby the composition of the PPI population, will be made prior to the final database lock.

Details on the approach to handling missing data are provided in Section 10.6 (Statistical Methods).

Table 4 Acceptable Day Ranges for Vaccination Visits

| Dose of 9vHPV vaccine Scheduled for Injection | Protocol Specified Visit Window | Day Range for Inclusion in Statistical Analysis (Relative to Day 1[a]) |
|---|---|---|
| Dose 1 | Day 1[a] | 0 |
| Dose 2 | Month 2 ±3 weeks | 36 to 84 |
| Dose 3 | Month 6 ±4 weeks | 148 to 218 |

[a] Day 1 refers to the date when Dose 1 of 9vHPV 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 (eg, 1 calendar month versus 30 days versus 4 weeks).

### 10.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety in this study. The APaT population consists of all allocated participants who received at least one dose of 9vHPV vaccine and have provided safety data at any time during the study.

## 10.6 Statistical Methods

Statistical analyses of safety described in Section 10.6.2. Immunogenicity results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 10.8 (Multiplicity).

### 10.6.1 Statistical Methods for Immunogenicity Analyses

A summary of the analysis strategy for key primary and secondary immunogenicity endpoints is shown in Table 5.

The primary immunogenicity hypothesis will be addressed by calculating point and 95% CI estimates of percent seroconversion, to be derived from the point and 95% CI estimates of the proportion of participants who seroconverted (ie, point estimate and 95% CI of proportion × 100%). Specifically, for each HPV type:

- The point estimate of proportion of participants who seroconverted to a particular HPV type is the ratio of the number of PPI-eligible participants for that particular HPV type who seroconverted to the relevant HPV type over the total number PPI-eligible participants for that particular HPV type who had evaluable Month 7 serology result based on serum sample collected within 21 to 49 days post Dose 3.
- The corresponding 95% CI estimate of proportion will be derived based on exact binomial calculations.
- The statistical criterion for acceptable anti-HPV seroconversion requires the lower limit of the 95% CI of the percent of participants who seroconverted to be greater than 90% for each HPV type.

The secondary immunogenicity objective will be addressed by calculating point and 95% CI estimates of GMTs. For each HPV type:

- The point estimate of GMT will be calculated by taking the anti-natural-logarithm of the arithmetic mean of the natural-logarithm-transformed anti-HPV titers.
- The two-sided 95% CI estimate of GMT will be calculated by taking the anti-natural-logarithm of the two-sided 95% CI estimate of the mean of the natural-logarithm-transformed anti-HPV titers based on the t-distribution.

Table 5 Analysis Strategy for Key Immunogenicity Endpoints

| Endpoint | Primary vs. Supportive Approach | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| Primary Hypothesis | | | | |
| Percent seroconversion | Primary | Point and 95% CI estimation of binomial proportion based on Clopper-Pearson (exact) method | PPI | Observed data only |
| Secondary Objective | | | | |
| GMTs | Primary | Point and 95% CI estimation of means based on t-distribution | PPI | Observed data only |
| CI=confidence interval; GMT=geometric mean titer; PPI=Per-Protocol Immunogenicity. | | | | |

### 10.6.2 Statistical Methods for Safety Analyses

Safety will be assessed by clinical review of all safety data collected after each vaccination.

Since this study is a single-arm study with no comparator arm, safety assessments will be descriptive in nature and will include calculation of proportions of participants with any AEs, injection-site AEs, systemic AEs, SAEs, vaccine-related SAEs, and discontinuations due to an AE within Day 1 to Day 15 following receipt of 9vHPV vaccination; in addition, 95% CI values for AEs will be provided for SAEs, injection site AEs, systemic AEs, and vaccine-related systemic AEs. Oral temperatures recorded on the VRC will be summarized.

## 10.7 Interim Analyses

No interim analyses are planned for this study.

## 10.8 Multiplicity

The criterion for successful demonstration of the primary immunogenicity hypothesis requires demonstration of the lower limit of the 95% CI of the percent of participants who seroconverted to be greater than 90% for each (ie, all) HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The corresponding tests of hypothesis for each of these HPV types will be conducted at 1-sided Type I error level of 0.025 (see Section 10.9; Sample size and Power Calculations). No multiplicity adjustment is required on the 0.025 1-sided Type I error level since success is required for all of the 9 HPV types being tested.

## 10.9 Sample Size and Power Calculations

### 10.9.1 Sample Size and Power for Immunogenicity Analysis

This study will enroll 200 participants to be vaccinated with 9vHPV vaccine and has approximately 97% power at an overall one-sided 2.5% alpha-level (ie, 1-sided Type I error equal to 0.025) to establish that the 9vHPV vaccine induces among participants >90% seroconversion to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post Dose 3. The overall study power corresponding to the sample size of 200 participants is based on the following assumptions: 1) approximately 24% to 34% of participants enrolled will be ineligible for the per-protocol analysis of seroconversion to the 9 HPV types; and 2) the underlying true seroconversion across the 9 HPV types is ≥98% (see Table 6). The power calculation was based on the exact binomial method of Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934] and was done using PASS 2008. The minimum criterion for success for each HPV type is that the lower limit of the 95% CI of percent seroconversion be >90%. Given the number of participants eligible for the per-protocol analysis expected from this study, this may occur when the point estimate of percent seroconversion observed during the study is >96% in each of the 9 HPV types. The numbers of seroconversions across the 9 HPV types relative to the expected number of participants eligible for the per-protocol analysis that will yield a point estimate of seroconversion >96% are shown in Table 6.

Table 6 Power for Testing the Primary Immunogenicity Hypothesis

| HPV Type | Participants Enrolled (N) | Expected to be Observed in the Study | | | Assessment of Power for Testing $H_0$: $P = P_0$ versus $H_a$: $P > P_0$ | | | | | Minimum Number of Seroconversions Needed to Attain a Point Estimate of Percent Seroconversion >96%[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Type I Error (α) | | | |
| | | Exclusions from PPI Analysis[a] | Evaluable for PPI Analysis (n) | Percent Sero-conversion[a] | $P_0$[b] | $P_E$[b] | Target | Expected Actual | Power | |
| 6 | 200 | 34% | 132 | 98.3% | 0.90 | 0.98 | 0.025 | 0.018 | 0.9826 | 127 |
| 11 | | 34% | 132 | 99.7% | | 0.99 | | 0.018 | 0.9996 | 127 |
| 16 | | 30% | 140 | 100% | | 0.99 | | 0.011 | 0.9994 | 135 |
| 18 | | 27% | 146 | 99.2% | | 0.99 | | 0.018 | 0.9999 | 140 |
| 31 | | 25% | 150 | 99.0% | | 0.99 | | 0.014 | 0.9999 | 144 |
| 33 | | 26% | 148 | 99.1% | | 0.99 | | 0.016 | 0.9999 | 142 |
| 45 | | 24% | 152 | 98.4% | | 0.98 | | 0.012 | 0.9881 | 146 |
| 52 | | 32% | 137 | 99.4% | | 0.99 | | 0.013 | 0.9995 | 132 |
| 58 | | 31% | 139 | 99.4% | | 0.99 | | 0.012 | 0.9995 | 134 |
| | | | | | | | | Overall Study Power: | 0.9687 | |

[a] Historical data from the Asian cohort (Korean and Taiwanese) of the V503-001 study.
[b] For each HPV type, the null hypothesis that the seroconversion proportion is 0.90 ($P=P_0$) is being tested against the alternative hypothesis that the seroconversion proportion is greater than 0.90 ($P>P_0$). In the calculation of power corresponding to the expected number of participants evaluable for the PPI analysis, a proportion of seroconversion that is expected ($P_E$) to be observed during the study is required. The values of $P_E$ used in the calculation of power are obtained from the historical percent seroconversion observed from the Asian cohort of the V503-001 study.
[c] Assuming the number of participants contributing to the PPI analysis is equal to (n), a point estimate of percent seroconversion >96% will yield a corresponding lower limit of 95% CI of percent seroconversion >90%.
CI=confidence interval; PPI=Per-Protocol Immunogenicity.

### 10.9.2 Sample Size and Power for Safety Analyses

The probability of observing a specific AE in this study depends on the number of vaccinated participants with safety follow-up and the underlying incidence of that specific AE in the study population. In seven clinical studies in the 9vHPV program, 356 of 15,778 (2.3%) individuals who were administered 9vHPV vaccine and had safety follow-up reported a SAE; 7 (0.04%) reported at least one SAE determined to be vaccine related [Moreira, E. D., et al 2016]. Assuming that all 200 participants enrolled in this study will have safety follow-up, then there is a 99% chance of observing at least one SAE; and 7.7% chance of observing at least one vaccine related SAE, on at least one of the 200 participants. If no vaccine-related SAEs are observed among the 200 participants, this study will provide 97.5% confidence that the underlying percentage of participants with vaccine-related SAE is <1.8% (1 in every 56 participants) among 9vHPV vaccinated participants. This is based on calculation of a 1-sided 97.5% upper confidence limit of a binomial proportion using the exact binomial method of Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

## 10.10 Subgroup Analyses

To determine whether immune response to 9vHPV vaccination is consistent across various subgroups, the percent seroconversion and Month 7 GMTs (with corresponding nominal 95% CIs) will be estimated and Forest plots will be produced for the age subgroups of 9 to 15 years old; 16 to 26 years old.

The consistency of immune response to 9vHPV vaccination will be assessed descriptively via summary statistics by category for the classification variables listed above.

Analysis of immune response to 9vHPV vaccination by gender is not required because in previous studies of the 9vHPV vaccine (Protocols V503-002 and V503-003 [Van Damme, P., et al 2015] [Castellsague, X., et al 2015]), HPV antibody response was similar between genders.

## 10.11 Compliance (Medication Adherence)

Compliance in this study is defined as receipt of all 3 doses of 9vHPV vaccine. To summarize compliance, the numbers of participants who receive each vaccination will be tabulated. For each of vaccination doses 2 and 3, histograms of the time (in days) of administration of the vaccine relative to the target vaccination visit will be provided.

## 10.12 Extent of Exposure

Each study participant is planned to be administered 0.5 mL of 9vHPV vaccine at each of 3 vaccination visits (Day 1, Month 2, and Month 6). Thus, each participant is expected to be administered a total of 1.5 mL of 9vHPV vaccine over a 6 months duration.

## 11. References


| | | |
|---|---|---|
| [Alemany, L., et al 2015] | Alemany L, Saunier M, Alvarado-Cabrero I, Quiros B, Salmeron J, Shin HR, et al. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. Int J Cancer. 2015 Jan 1;136(1):98-107. | 0409ZR |
| [Castellsague, X., et al 2015] | Castellsague X, Giuliano AR, Goldstone S, Guevara A, Mogensen O, Palefsky JM, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine. 2015 Nov 27;33(48):6892-901. | 04FD2G |
| [Center for Drug Evaluation and Research 2014] | Center for Drug Evaluation and Research (CDER). Summary basis for regulatory action - Gardasil 9 [Internet]. Maryland: Department of Health and Human Services, Food and Drug Administration; 2014. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM428239.pdf . | 04LNXC |
| [Clopper, C. J. and Pearson, E. S. 1934] | Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13. | 03Q0LW |
| [European Medicines Agency 2016] | European Medicines Agency. Gardasil 9 - Human papillomavirus 9-valent vaccine (recombinant, adsorbed) (EMA/192711/2016) [Internet]. London: European Medicines Agency; 2016. 4 p. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003852/WC500189114.pdf . | 04LNX8 |
| [Forman, D., et al 2012] | Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. Vaccine 2012;305:F12-F23. | 04BBPB |
| [Garland, S. M., et al 2009] | Garland SM, Steben M, Sings HL, James M, Lu S, Railkar R, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect Dis 2009;199:805-14. | 03RMDR |

| | | |
|---|---|---|
| [Joura, E. A., et al 2015] | Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015 Feb 19;372(8):711-23. | 044RDM |
| [Luxembourg, A., et al 2015] | Luxembourg A, Brown D, Bouchard C, Giuliano AR, Iversen OE, Joura EA, et al. Phase II studies to select the formulation of a multivalent HPV L1 virus-like particle (VLP) vaccine. Hum Vaccin Immunother. 2015;11(6):1313-22. | 04LPSP |
| [McKeage, K. 2016] | McKeage K, Lyseng-Williamson KA. 9-Valent human papillomavirus recombinant vaccine (Gardasil 9): a guide to its use in the EU. Drugs Ther Perspect. 2016 Aug 20;32:414-421. | 04LMFS |
| [Moreira, E. D., et al 2016] | Moreira ED Jr, Block SL, Ferris D, Giuliano AR, Iversen OE, Joura EA, et al. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. Pediatrics. 2016 Aug;138(2). pii: e20154387. | 04HBHT |
| [Neuzil, K. M., et al 2011] | Neuzil KM, Canh DG, Thiem VD, Janmohamed A, Huong VM, Tang Y, et al. Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized noninferiority trial. JAMA 2011;305(14):1424-31. | 03RKFN |
| [Parkin, D. Maxwell and Bray, Freddie 2006] | Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine 2006;24(Suppl 3):S11-S25. | 03QZ7V |
| [Pitisuttithum, P., et al 2015] | Pitisuttithum P, Velicer C, Luxembourg A. 9-Valent HPV vaccine for cancers, pre-cancers and genital warts related to HPV. Expert Rev Vaccines. 2015 Sep 14:1-15. | 047XK8 |
| [Schiller, J. T., et al 2012] | Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;305:F123-F138. | 03RTYW |
| [Serrano, B., et al 2015] | Serrano B, de Sanjose S, Tous S, Quiros B, Munoz N, Bosch X, et al. Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. Eur J Cancer. 2015 Sep;51(13):1732-41. | 04F4S3 |

| | | |
|---|---|---|
| [Stanley, M., et al 2012] | Stanley M, Pinto LA, Trimble C. Human papillomavirus vaccines - immune responses. Vaccine. 2012 Nov 20;30 Suppl 5:F83-7. | 04LNWV |
| [Van Damme, P., et al 2015] | Van Damme P, Olsson SE, Block S, Castellsague X, Gray GE, Herrera T, et al. Immunogenicity and Safety of a 9-Valent HPV Vaccine. Pediatrics. 2015 Jul;136(1):e28-39. | 04885H |

# 12. Appendices

## 12.1 Appendix 1: Study Governance Considerations

## Merck Code of Conduct for Clinical Trials

**Merck***
**Code of Conduct for Clinical Trials**

**I. Introduction**

**A. Purpose**

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

**B. Scope**

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

**II. Scientific Issues**

**A. Trial Conduct**

**1. Trial Design**

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants must meet protocol entry criteria to be enrolled in the trial.

**2. Site Selection**

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

**3. Site Monitoring/Scientific Integrity**

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

**B. Publication and Authorship**

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

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

**III. Participant Protection**

**A. IRB/IEC review**

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck will approve the participant informed consent form.

**B. Safety**

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

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

**C. Confidentiality**

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

**D. Genomic Research**

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

**IV. Financial Considerations**

**A. Payments to Investigators**

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

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

**B. Clinical Research Funding**

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

**C. Funding for Travel and Other Requests**

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

**V. Investigator Commitment**

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

### Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

### Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### Confidentiality of Data

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 (IRB/IEC) 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.

### Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of

verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

**Confidentiality of IRB/IEC Information**

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

**Publication Policy**

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

**Compliance with Study Registration and Results Posting Requirements**

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies 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 obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

**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 (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other 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 MSD, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

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

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority 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.

**Data Quality Assurance**

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any

regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or regulatory authority as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

**Source Documents**

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

**Study and Site Closure**

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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

## 12.2 Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

**Definition of AE**

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.<br>• NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication.<br>• For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."<br>• Any new cancer or progression of existing cancer. |

| **Events NOT Meeting the AE Definition** |
|---|
| ● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.<br>● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.<br>● Refer to section 9.3.5 for protocol specific exceptions |

**Definition of SAE**

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

| **A SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>● 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history. |
| **d. Results in persistent or significant disability/incapacity**<br>● The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |

| **A SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **e. Is a congenital anomaly/birth defect**<br>● in offspring of participant taking the product regardless of time to diagnosis |
| **f. Other important medical events:**<br>● Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.<br>Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

**Additional Events Reported**

| **Additional Events which require reporting** |
|---|
| ● In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.<br>● Is a cancer;<br>● Is associated with an overdose. |

**Recording AE and SAE**

| **AE and SAE Recording** |
|---|
| ● When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.<br>● The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination.<br>● It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.<br>● There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.<br>● The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. |

**Assessment of Intensity**

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. (for pediatric studies, awareness of symptoms, but easily tolerated)
  - Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. (for pediatric studies, definitely acting like something is wrong)
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities). **Injection site redness or swelling from the day of vaccination through Day 5 post-vaccination will be evaluated by maximum size**.

**Assessment of Causality**

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event 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 product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? 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
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product 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); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug 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 Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very

important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

**Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor**

**AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool**

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

| **SAE Reporting to the Sponsor via Paper CRF** |
| --- |
| ● If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.<br>● In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.<br>● Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.<br>● Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent). |

## 12.3 Appendix 3: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 6.1 and 6.2 of the protocol.

Table 7 Protocol-Required Safety Laboratory Assessments

| Laboratory Test | Study Visits Performed |
|---|---|
| Serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test (for all female participants at all vaccination visits) | Day 1<br>Month 2<br>Month 6<br>Month 7 |

The serum pregnancy test or urine pregnancy test must be sensitive to 25 mIU/ML β-hCG and performed prior to vaccination. Results should be negative prior to vaccination. Pregnancy testing is required for all female participants.

Any female participant with a positive pregnancy test at Day 1 will not be vaccinated and will not be allowed to participate in the study. Female participants with a positive pregnancy test after Day 1 will not be vaccinated until after pregnancy outcome.

Investigators must document their review of each laboratory safety report.

## 12.4 Appendix 4: Abbreviations

| | |
|---|---|
| 9vHPV | 9-valent human papillomavirus |
| AAHS | amorphous aluminium hydroxyphosphate sulfate |
| AE | adverse event |
| APaT | All Participants as Treated |
| β-hCG | β-hCG=beta human chorionic gonadotropin |
| CI | confidence interval |
| cLIA | competitive Luminex immunoassay |
| CRF | case report form |
| DNA | deoxyribonucleic acid |
| eCRF | electronic case report form |
| GCP | Good Clinical Practice |
| GMT | geometric mean titer |
| HIV | human immunodeficiency virus |
| HPV | human papillomavirus |
| HPV-9 cLIA | 9-valent HPV competitive Luminex immunoassay |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| LLOQ | lower limit of quantification |
| PPI | Per-Protocol Immunogenicity |
| qHPV | quadrivalent human papillomavirus HPV |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SoA | schedule of activities |
| STI | sexually transmitted infection |
| SUSAR | suspected unexpected serious adverse reactions |
| V503 | 9vHPV vaccine |
| VLP | virus-like particle |
| VRC | Vaccination Report Card |