Official Protocol Title:	A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity and Safety of 9-Valent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine (V503) in Chinese females 9 to 45 Years of Age
NCT number:	NCT03903562
Document Date:	09-Jan-2023

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

This protocol amendment is applicable only to China.

Protocol Title: A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity and Safety of 9-Valent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine (V503) in Chinese females 9 to 45 Years of Age

Protocol Number: 024-02

Compound Number: V503

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND NUMBER: To Be Determined

EudraCT NUMBER: Not Applicable

Approval Date: 09 January 2023

Sponsor Signatory

Typed Name:
Title:

Date

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:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
V503-024-02	09-JAN-2023	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
V503-024-01	12-MAR-2020	To extend the visit window of Dose 3 vaccination.
V503-024-00	14-SEP-2018	Original version

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment [02]

Overall Rationale for the Amendment:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1 Appendix 1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity and Safety of 9-Valent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine (V503) in Chinese females 9 to 45 Years of Age

Short Title:

Immunobridging study of 9vHPV vaccine in Chinese females 9 to 45 years of age

Objectives/Hypotheses and Endpoints:

This study consists of two stages, i.e. Stage I and II. The study period of Stage I is from Day 1 through Visit 10 (1 month post Dose 3) and Stage II is post Visit 10 up to Visit 15.

Stage I in females 9 to 45 years of age (Day 1 to Visit 10):

Objective/Hypothesis	Endpoint
Primary	
• Objective: To demonstrate that administration of the 9-valent human papillomavirus (9vHPV) vaccine induces non-inferior geometric mean titers (GMTs) for serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 in females 9 to 19 years of age compared to females 20 to 26 years of age. Hypothesis (H1): 9vHPV vaccine induces non-inferior immune responses in females 9 to 19 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-	• Competitive Luminex Immunoassay (cLIA) antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

sided 97.5% confidence interval of GMT ratio (females 9 to 19 years of age vs. females 20 to 26 years of age) be greater than 0.67 for each HPV type.) • Objective: To demonstrate that administration of the 9vHPV vaccine induces non-inferior seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in females 27 to 45 years of age compared to females 20 to 26 years of age. Hypothesis (H2): 9vHPV vaccine induces non-inferior immune responses in females 27 to 45 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by the seroconversion percentages to each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval for the difference (females 27 to 45 years of age minus females 20 to 26 years of age) in seroconversion percentages be greater than -5% for each HPV type.)	• cLIA antibody seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
Secondary	
• Objective: To demonstrate that administration of the 9vHPV vaccine induces non-inferior seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in females 9 to 19 years of age compared to females 20 to 26 years of age.	• cLIA antibody seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Hypothesis (H3): 9vHPV vaccine induces non-inferior immune responses in females 9 to 19 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by the seroconversion percentages to each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval for the difference (females 9 to 19 years of age minus females 20 to 26 years of age) in seroconversion percentages be greater than -5% for each HPV type.)	
• Objective: To demonstrate that administration of the 9vHPV vaccine induces non-inferior GMTs for serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 in females 9 to 15 years of age compared to females 20 to 26 years of age. Hypothesis (H4): 9vHPV vaccine induces non-inferior immune responses in females 9 to 15 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-	• cLIA antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

sided 97.5% confidence interval of GMT ratio (females 9 to 15 years of age vs. females 20 to 26 years of age) be greater than 0.67 for each HPV type.)	
• Objective: To summarize immune responses induced by the 9vHPV vaccine in females 9 to 15 years of age as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA seroconversion percentages.	• cLIA antibody seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
• Objective: To summarize immune responses induced by the 9vHPV vaccine in females 27 to 45 years of age as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs.	• cLIA antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
• Objective: To summarize immune responses induced by the 9vHPV vaccine using the HPV total IgG Luminex immunoassay (IgG LIA) in females 9 to 19 years of age, 20 to 26 years of age, and 27 to 45 years of age.	• IgG LIA antibody titer and seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
• Objective: To evaluate the safety of the 9vHPV vaccine in females 9 to 19 years of age, 20 to 26 years of age, and 27 to 45 years of age based on the proportions of participants experiencing solicited injection-site adverse events (AEs), solicited systemic AEs, and serious AEs.	• Participant experiencing solicited injection-site AEs. • Participant experiencing solicited systemic AEs. • Participant experiencing serious AEs.

Stage II in females 9 to 19 years of age (post Visit 10 to Visit 15):

Objective/Hypothesis	Endpoint
Primary	
• Objective: To evaluate persistence of immune responses induced by the 9vHPV vaccine in females 9 to 19 years of age.	• cLIA antibody titer and seropositivity to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. • IgG LIA antibody titer and seropositivity to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
Secondary	
• Objective: To evaluate the safety of the 9vHPV vaccine in females 9 to 19 years of age based on the proportion of participants experiencing serious AEs.	• Participant experiencing serious AEs.

Overall Design:

Study Phase	Phase 3
Clinical Indication	Prevention of cervical, vulvar, vaginal, and anal cancers and related precancers, anogenital lesions, Pap test abnormalities, and persistent infection caused by human papillomavirus (HPV) 6, 11, 16, 18, 31, 33, 45, 52, and 58.
Population	Healthy Chinese females 9-45 years of age will be enrolled in this study.
Study Type	Interventional
Type of Design	Multi-site, Single-arm
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 66 months from the time the first participant signs the informed consent/assent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 1990 participants will be enrolled in the Stage I as described in Section 9.9.

Participants 9 to 19 years of age who are enrolled in the Stage I and have received 3 doses of study vaccination will be eligible for participation into the Stage II.

Treatment Groups and Duration:

Treatment Groups	All enrolled participants will intramuscularly receive a 3-dose regimen of 9vHPV vaccine (V503) at Visit 1, Visit 4, and Visit 8.
Duration of Participation	A subset of 25 girls 9 to 15 years of age enrolled in Stage I will receive 2 doses of 9vHPV vaccine and be evaluated for safety from 1st dose through Day 15 following 2nd dose by a Data Monitoring Committee (DMC). If safety evaluation is favorable, the 25 girls evaluated for safety will receive a 3rd dose and enrollment of the rest of the participants 9 to 15 years of age will be initiated; participants 9 to 15 years of age will receive 3 doses of 9vHPV vaccine and will be followed up to 1 month post Dose 3 (Visit 10) during Stage I. Participants 16 to 45 years of age will be receiving 3 doses of 9vHPV vaccine and will be followed up to Visit 10 during Stage I. After Visit 10, only participants 9 to 19 years of age who have received 3 doses of study vaccination will be eligible for participation into Stage II and will be followed up to Visit 15.

Study Governance:

Study Governance Committees

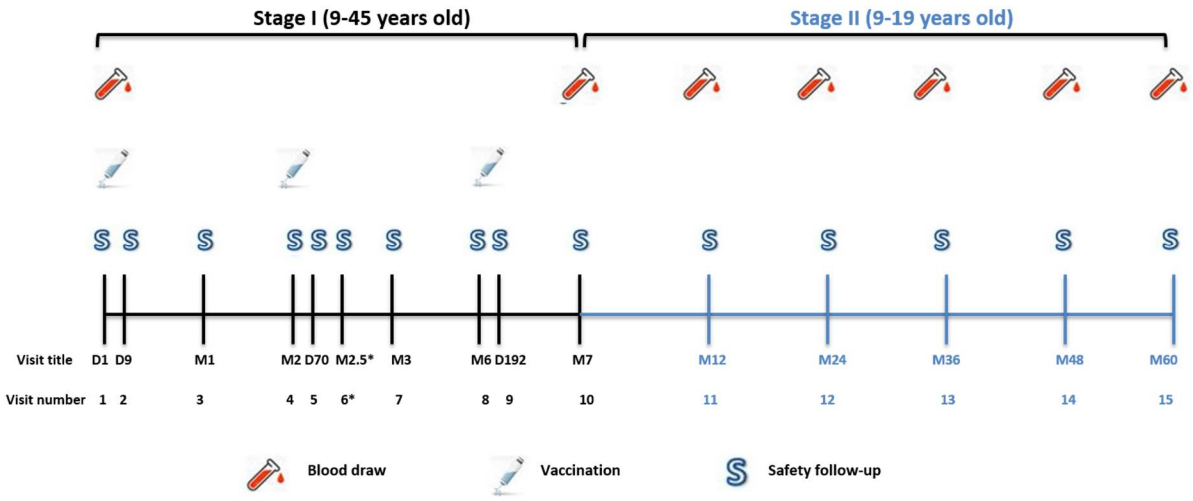
Committee	**Included in this study?**
Steering Committee	N
Executive Oversight Committee	Y
Data Monitoring Committee	Y
Clinical Adjudication Committee	N

Study governance considerations are outlined in Appendix 1.

A list of abbreviations used in this document can be found in Appendix 5.

1.2 Schema

The study design is depicted in Figure 1.



*: Visit 6 (Month 2.5) is only applicable to the first 25 participants enrolled in the 9-15 years old group who will be evaluated for safety from 1st dose through Day 15 following 2nd dose by the Data Monitoring Committee (DMC). If safety evaluation is favorable, the 25 girls evaluated for safety will receive the 3rd dose and enrollment of the rest of participants 9 to 15 years of age will be initiated.

Figure 1 Study Diagram

1.3 Schedule of Activities (SoA)

Study Period	Stage I (Participants 9-45 years of age)										Stage II (Participants 9-19 years of age)					Notes
Visit Number/Title	**Visit 1 Day 1**	**Visit 2 Day 9**	**Visit 3 Month 1**	**Visit 4 Month 2**	**Visit 5 Day 70**	**Visit 6 Month 2.5***	**Visit 7 Month 3**	**Visit 8 Month 6**	**Visit 9 Day 192**	**Visit 10 Month 7**	**Visit 11 Month 12**	**Visit 12 Month 24**	**Visit 13 Month 36**	**Visit 14 Month 48**	**Visit 15 Month 60**	
Scheduled Day	**1**	**9**	**32**	**62**	**70**	**77**	**93**	**184**	**8 days post Visit 8**	**31 days post Visit 8**	**183 days post Visit 8**	**548 days post Visit 8**	**913 days post Visit 8**	**1278 days post Visit 8**	**1643 days post Visit 8**	
Scheduling Windows	**± 0 day**	**8 to 14 days after Dose 1**	**31 to 38 days after Dose 1**	**40 to 82 days after Dose 1**	**8 to 14 days after Dose 2**	**15 to 17 days after Dose 2**	**31 to 38 days after Dose 2**	**155 to 364 days after Dose 1**	**8 to 14 days after Dose 3**	**21 to 49 days after Dose 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Administrative and General Procedures																
Informed Consent/ Assent	X															The interval between the date of consent/assent and the date of the Day 1 visit should be no more than 14 days apart. If the interval is 15 days or longer, then the participant must be re-consented.
Provide Participant Identification Card	X															
Assign Screening Number	X															
Review Inclusion/ Exclusion Criteria	X															

Study Period	Stage I (Participants 9-45 years of age)										Stage II (Participants 9-19 years of age)					Notes
Visit Number/Title	**Visit 1 Day 1**	**Visit 2 Day 9**	**Visit 3 Month 1**	**Visit 4 Month 2**	**Visit 5 Day 70**	**Visit 6 Month 2.5***	**Visit 7 Month 3**	**Visit 8 Month 6**	**Visit 9 Day 192**	**Visit 10 Month 7**	**Visit 11 Month 12**	**Visit 12 Month 24**	**Visit 13 Month 36**	**Visit 14 Month 48**	**Visit 15 Month 60**	
Scheduled Day	**1**	**9**	**32**	**62**	**70**	**77**	**93**	**184**	**8 days post Visit 8**	**31 days post Visit 8**	**183 days post Visit 8**	**548 days post Visit 8**	**913 days post Visit 8**	**1278 days post Visit 8**	**1643 days post Visit 8**	
Scheduling Windows	**± 0 day**	**8 to 14 days after Dose 1**	**31 to 38 days after Dose 1**	**40 to 82 days after Dose 1**	**8 to 14 days after Dose 2**	**15 to 17 days after Dose 2**	**31 to 38 days after Dose 2**	**155 to 364 days after Dose 1**	**8 to 14 days after Dose 3**	**21 to 49 days after Dose 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Review Medical History	X															At Day 1, any medical history for 5 years prior to Day 1 and lifetime major medical history prior to Day 1 is to be collected for all participants. For participants who have had sexual intercourse, the lifetime gynecologic history is to be collected at Day 1.
Record Medications and Non-study Vaccinations	X		X	X		X	X	X		X						
Physical Examination	X					X										Height and weight are only to be measured at Day 1.
Urine or Serum Pregnancy Testing in Participant of Childbearing Potential	X			X				X								The pregnancy testing must be sensitive to 25 mIU/mL β-hCG. Results should be negative prior to each vaccination.

Study Period	Stage I (Participants 9-45 years of age)										Stage II (Participants 9-19 years of age)					Notes
Visit Number/Title	**Visit 1 Day 1**	**Visit 2 Day 9**	**Visit 3 Month 1**	**Visit 4 Month 2**	**Visit 5 Day 70**	**Visit 6 Month 2.5***	**Visit 7 Month 3**	**Visit 8 Month 6**	**Visit 9 Day 192**	**Visit 10 Month 7**	**Visit 11 Month 12**	**Visit 12 Month 24**	**Visit 13 Month 36**	**Visit 14 Month 48**	**Visit 15 Month 60**	
Scheduled Day	**1**	**9**	**32**	**62**	**70**	**77**	**93**	**184**	**8 days post Visit 8**	**31 days post Visit 8**	**183 days post Visit 8**	**548 days post Visit 8**	**913 days post Visit 8**	**1278 days post Visit 8**	**1643 days post Visit 8**	
Scheduling Windows	**± 0 day**	**8 to 14 days after Dose 1**	**31 to 38 days after Dose 1**	**40 to 82 days after Dose 1**	**8 to 14 days after Dose 2**	**15 to 17 days after Dose 2**	**31 to 38 days after Dose 2**	**155 to 364 days after Dose 1**	**8 to 14 days after Dose 3**	**21 to 49 days after Dose 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Axillary Temperature and Blood Pressure Prior to Study Vaccination	X			X				X								Axillary temperature and blood pressure are taken prior to each vaccination. If the participant has a fever (defined as an axillary temperature ≥37.1°C) within the 24-hour period prior to vaccination, the vaccination should be rescheduled after the fever has resolved.
Assign Treatment/ Randomization Number	X															The treatment/ randomization number will be assigned by an interactive response technology (IRT) system.
Study Vaccine Administration	X			X				X								All the study-related procedures for Day 1 visit except informed consent/assent, screening number assignment, participant identification card, should be performed on the same day as and prior to the first vaccination. All 3 doses should be administered within 1 year. The interval between Dose 2 and Dose 3 should be at least 3 months.

Study Period	Stage I (Participants 9-45 years of age)										Stage II (Participants 9-19 years of age)					Notes
Visit Number/Title	**Visit 1 Day 1**	**Visit 2 Day 9**	**Visit 3 Month 1**	**Visit 4 Month 2**	**Visit 5 Day 70**	**Visit 6 Month 2.5***	**Visit 7 Month 3**	**Visit 8 Month 6**	**Visit 9 Day 192**	**Visit 10 Month 7**	**Visit 11 Month 12**	**Visit 12 Month 24**	**Visit 13 Month 36**	**Visit 14 Month 48**	**Visit 15 Month 60**	
Scheduled Day	**1**	**9**	**32**	**62**	**70**	**77**	**93**	**184**	**8 days post Visit 8**	**31 days post Visit 8**	**183 days post Visit 8**	**548 days post Visit 8**	**913 days post Visit 8**	**1278 days post Visit 8**	**1643 days post Visit 8**	
Scheduling Windows	**± 0 day**	**8 to 14 days after Dose 1**	**31 to 38 days after Dose 1**	**40 to 82 days after Dose 1**	**8 to 14 days after Dose 2**	**15 to 17 days after Dose 2**	**31 to 38 days after Dose 2**	**155 to 364 days after Dose 1**	**8 to 14 days after Dose 3**	**21 to 49 days after Dose 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Immunogenicity Procedures																
Blood Collection	X									X	X	X	X	X	X	The blood sample collected at Day 1 for anti-HPV antibody measurements must be collected before vaccination.
Safety Procedures																
30-minute Post-Vaccination Observation	X			X				X								
Provide Vaccination Report Card (VRC)	X			X				X								

Study Period	Stage I (Participants 9-45 years of age)										Stage II (Participants 9-19 years of age)					Notes
Visit Number/Title	**Visit 1 Day 1**	**Visit 2 Day 9**	**Visit 3 Month 1**	**Visit 4 Month 2**	**Visit 5 Day 70**	**Visit 6 Month 2.5***	**Visit 7 Month 3**	**Visit 8 Month 6**	**Visit 9 Day 192**	**Visit 10 Month 7**	**Visit 11 Month 12**	**Visit 12 Month 24**	**Visit 13 Month 36**	**Visit 14 Month 48**	**Visit 15 Month 60**	
Scheduled Day	**1**	**9**	**32**	**62**	**70**	**77**	**93**	**184**	**8 days post Visit 8**	**31 days post Visit 8**	**183 days post Visit 8**	**548 days post Visit 8**	**913 days post Visit 8**	**1278 days post Visit 8**	**1643 days post Visit 8**	
Scheduling Windows	**± 0 day**	**8 to 14 days after Dose 1**	**31 to 38 days after Dose 1**	**40 to 82 days after Dose 1**	**8 to 14 days after Dose 2**	**15 to 17 days after Dose 2**	**31 to 38 days after Dose 2**	**155 to 364 days after Dose 1**	**8 to 14 days after Dose 3**	**21 to 49 days after Dose 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Review and Collect VRC data		X	X		X	X	X		X	X						Telephone contacts are to be done around every week between Visit 2 and Visit 3, Visit 5 and Visit 7 (telephone contacts are done after Visit 6 for the first 25 participants in the 9-15 years old group), Visit 9 and Visit 10 to remind the participants to record the VRC and answer any questions related to VRC.
Collect New Medical Conditions			X	X			X	X		X	X	X	X	X	X	After Day 1, any new medical conditions not already recorded as medical history or adverse events are collected.
Clinical Follow-up for Safety	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Review and follow AEs, SAEs and other reportable safety events. See Section 8.4.1 for time period and frequency of safety events reporting during the study.

*: Visit 6 (Month 2.5) is only applicable to a subset of participants aged 9-15 years (N=25) who will be evaluated for safety from the 1st dose through Day 15 following the 2nd dose by the Data Monitoring Committee (DMC). If the safety is favorable, this subset of participant will receive the 3rd dose and enrollment of the rest of participants in the 9-15 years old group will be initiated.

2. Introduction

2.1 Study Rationale

Human papillomavirus (HPV) infection is a sexually transmitted disease. The incidence of HPV infection peaks soon after the onset of sexual activity. Adolescents are at risk of HPV infection immediately after sexual debut. In a survey covering approximately 22,300 girls and young women aged 15 to 24 years in China, it is reported that 97.2% of young women had their sexual debut after 17 years of age [Guo, W., et al 2012]. Therefore, virginal adolescents 17 years of age or younger represent a population at risk of HPV exposure in China who would benefit the most from prophylactic HPV vaccination. The prevalence of HPV infection peaked in the adolescent group ≤20 years old (38.18%) according to the study including 961,029 HPV tests during 2011-2015 in southeastern China [Chen, X., et al 2017]. In addition, Chinese mid-adult women also remain at risk of HPV infections and related diseases in their sexual lives. Bimodal distribution of HPV prevalence was observed in Chinese women with the second peak among rural women aged 35-39 years and urban women aged 40-44 years [Zhao, F. H., et al 2012].

Based on the clinical data of global studies, 9vHPV vaccine was approved in China in April 2018 for the prevention against infections, precancerous or dysplastic lesions and cervical, vulvar, vaginal and anal cancers caused by vaccine HPV types in women 16 to 26 years of age. According to the post-marketing requirement of local regulatory authority, the efficacy, immunogenicity, and safety of the 9vHPV vaccine should be evaluated in Chinese women.

In this phase 3 study, the immunogenicity and safety of the 9vHPV vaccine will be evaluated in Chinese females 9 to 45 years of age. This study consists of Stage I and Stage II. The dual-primary objectives of Stage I are to demonstrate that immune responses induced by the 9vHPV vaccine in females 9 to 19 years of age and females 27 to 45 years of age are non-inferior to those in females 20 to 26 years of age. The immunogenicity data of Stage I will be submitted to local regulatory authority as soon as possible to support the extension of indication for females 9 to 15 years of age and females 27 to 45 years of age.

In the Stage II, female participants 9 to 19 years of age will continue to be followed to evaluate persistence of immune responses to the 9vHPV vaccine in this population.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

V503 (9vHPV vaccine) is a prophylactic 9-valent HPV (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine that is comprised of VLPs of the 4 HPV types (type 6, 11, 16, and 18) represented in the quadrivalent HPV (types 6, 11, 16, and 18) vaccine (qHPV vaccine,

Gardasil®[1]), plus the VLPs of 5 additional oncogenic HPV types (type 31, 33, 45, 52, and 58). This vaccine offers the potential of significant prophylactic cancer coverage in addition to that already provided by qHPV vaccine, with an increase in overall cervical cancer coverage from approximately 70% to 90% worldwide. Based on Chinese data, overall cervical cancer coverage will be increased from 69% to 92% by the 9vHPV vaccine [Serrano, B., et al 2014]. This is in addition to the potential of coverage for genital warts provided by VLPs of HPV Types 6 and 11.

2.3 Benefit/Risk Assessment

As of March 2018, 9vHPV vaccine has been licensed in more than 70 countries worldwide to prevent cervical, vulvar, vaginal, and anal cancers and precancers and anogenital warts caused by HPV types covered by the vaccine. The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have both determined that the benefits of the 9vHPV vaccine outweigh the risks [Center for Drug Evaluation and Research 2014] [European Medicines Agency 2016].

The risk benefit was deemed acceptable for 16-26 years old women by local regulatory authority as the 9vHPV vaccine has been approved for this age group in China based on global efficacy data. For 9-15 years old and 27-45 years old women, local clinical data are required to support the indication of these age groups in China.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and Informed Consent documents.

3. Objectives/Hypotheses and Endpoints

This study consists of two stages (Stage I and II). The study period of Stage I is from Day 1 through Visit 10 (1 month post Dose 3) and Stage II is post Visit 10 up to Visit 15.

[1]Gardasil® [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A. Gardasil® is also known as SILGARD™ in some countries. SILGARD™ is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A. Gardasil® will be hereafter referred to as the qHPV vaccine or V501.

3.1 Stage I in females 9 to 45 years of age (Day 1 to Visit 10)

Objective/Hypothesis	Endpoint
Primary	
• Objective: To demonstrate that administration of the 9-valent human papillomavirus (9vHPV) vaccine induces non-inferior geometric mean titers (GMTs) for serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 in females 9 to 19 years of age compared to females 20 to 26 years of age. Hypothesis (H1): 9vHPV vaccine induces non-inferior immune responses in females 9 to 19 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval of GMT ratio (females 9 to 19 years of age vs. females 20 to 26 years of age) be greater than 0.67 for each HPV type.)	• Competitive Luminex Immunoassay (cLIA) antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Objective/Hypothesis	Endpoint
• Objective: To demonstrate that administration of the 9vHPV vaccine induces non-inferior seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in females 27 to 45 years of age compared to females 20 to 26 years of age. Hypothesis (H2): 9vHPV vaccine induces non-inferior immune responses in females 27 to 45 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by the seroconversion percentages to each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval for the difference (females 27 to 45 years of age minus females 20 to 26 years of age) in seroconversion percentages be greater than -5% for each HPV type.)	• cLIA antibody seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Objective/Hypothesis	Endpoint
Secondary	
• Objective: To demonstrate that administration of the 9vHPV vaccine induces non-inferior seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in females 9 to 19 years of age compared to females 20 to 26 years of age. Hypothesis (H3): 9vHPV vaccine induces non-inferior immune responses in females 9 to 19 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by the seroconversion percentages to each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval for the difference (females 9 to 19 years of age minus females 20 to 26 years of age) in seroconversion percentages be greater than -5% for each HPV type.)	• cLIA antibody seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Objective/Hypothesis	Endpoint
• Objective: To demonstrate that administration of the 9vHPV vaccine induces non-inferior GMTs for serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 in females 9 to 15 years of age compared to females 20 to 26 years of age. Hypothesis (H4): 9vHPV vaccine induces non-inferior immune responses in females 9 to 15 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval of GMT ratio (females 9 to 15 years of age vs. females 20 to 26 years of age) be greater than 0.67 for each HPV type.)	• cLIA antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
• Objective: To summarize immune responses induced by the 9vHPV vaccine in females 9 to 15 years of age as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA seroconversion percentages.	• cLIA antibody seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
• Objective: To summarize immune responses induced by the 9vHPV vaccine in females 27 to 45 years of age as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs.	• cLIA antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
• Objective: To summarize immune responses induced by the 9vHPV vaccine using the HPV total IgG Luminex immunoassay (IgG LIA) in females 9 to 19 years of age, 20 to 26 years of age, and 27 to 45 years of age.	• IgG LIA antibody titer and seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Objective/Hypothesis	Endpoint
• Objective: To evaluate the safety of the 9vHPV vaccine in females 9 to 19 years of age, 20 to 26 years of age, and 27 to 45 years of age based on the proportions of participants experiencing solicited injection-site adverse events (AEs), solicited systemic AEs, and serious AEs.	• Participant experiencing solicited injection-site AEs. • Participant experiencing solicited systemic AEs. • Participant experiencing serious AEs.
Exploratory	
• Objective: To summarize of immune responses to the 9vHPV vaccine using the pseudovirion-based neutralization assay (PBNA) in females 9 to 19 years of age, 20 to 26 years of age, and 27 to 45 years of age.	• PBNA antibody titer and seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

3.2 Stage II in females 9 to 19 years of age (post Visit 10 to Visit 15)

Objective/Hypothesis	Endpoint
Primary	
• Objective: To evaluate persistence of immune responses induced by the 9vHPV vaccine in females 9 to 19 years of age.	• cLIA antibody titer and seropositivity to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. • IgG LIA antibody titer and seropositivity to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
Secondary	
• Objective: To evaluate the safety of the 9vHPV vaccine in females 9 to 19 years of age based on the proportion of participants experiencing serious AEs.	• Participant experiencing serious AEs.
Exploratory	
• Objective: To summarize persistence of immune responses to the 9vHPV vaccine using PBNA in females 9 to 19 years of age.	• PBNA antibody titer and seropositivity to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

4. Study Design

4.1 Overall Design

This is a non-randomized, multi-site, open-label study to investigate the immunogenicity and safety of the 9vHPV vaccine in healthy Chinese females 9 to 45 years of age to be conducted in conformance with Good Clinical Practices.

The study consists of Stage I (Day 1 to Visit 10) and Stage II (post Visit 10 to Visit 15). The dual-primary objectives of Stage I are to demonstrate that immune responses induced by the 9vHPV vaccine in females 9 to 19 years of age and 27 to 45 years of age are non-inferior to those in females 20 to 26 years of age. The results of immunobridging analyses of Stage I will be submitted to local regulatory authority as soon as possible to extend the indication of 9vHPV vaccine to Chinese females 9 to 15 years of age and 27 to 45 years of age.

The objective of Stage II is to assess the immune persistence following 9vHPV vaccination in females 9 to 19 years of age. The data of immune persistence will be submitted to local regulatory authority after the data are available.

4.1.1 Stage I

Approximately 1990 female participants 9 to 45 years of age who meet eligibility will be enrolled in the study. Enrollment of participants will be stratified based on the following age strata: 9-19 years old (N=690), 20-26 years old (N=650), and 27-45 years old (N=650). Within each 9-19 years old group and 27-45 years old group, enrollment will be further stratified by the pre-defined age subgroups as described in Section 6.3.1.1.

For participants 9-15 years of age, a sequential enrollment will be applied. The 1st step is to enroll 25 participants 9-15 years of age and the safety data after Dose 1 through Day 15 post Dose 2 will be reviewed by a Data Monitoring Committee (DMC). If the safety data are judged to be acceptable in the opinion of the DMC, then the 25 participants 9 to 15 years of age enrolled initially will received a 3rd dose at Visit 8, and the enrollment will be initiated to the rest of participants 9-15 years of age. All participants 9 to 15 years of age enrolled in the 2nd step of enrollment will receive one dose of 9vHPV vaccine at Visit 1, Visit 4, and Visit 8, respectively.

The enrollment of participants 16 to 45 years of age will be initiated at the same time as that of the first 25 participants 9-15 years of age. Safety review by the DMC is not necessary for participants 16 to 45 years of age. All enrolled participants 16 to 45 years of age will receive one dose of 9vHPV vaccine at Visit 1, Visit 4, and Visit 8, respectively.

Medical history and vital signs will be collected at Day 1 for all participants. Physical examination will be conducted at Day 1 for all participants, and at Visit 6 for the 25 participants initially enrolled in the 9-15 years old group for whom the safety will be reviewed by the DMC.

Serum samples will be obtained from each participant at Day 1 prior to vaccination and 1 month post Dose 3 (Visit 10) for measurement of anti-HPV antibodies for HPV 6, 11, 16, 18,

31, 33, 45, 52, and 58 by cLIA and IgG LIA. However, only serum samples from a subset of participants will be tested by PBNA (N=600 in total, i.e. 200 participants randomly selected from each age group) as an exploratory objective of this study.

The safety will be monitored for all participants from Day 1 through Visit 10. Vaccination Report Card (VRC) will be provided to each participant after vaccination for recording AE information within 30 days (Days 1-31) after study vaccination including the day of vaccination. Serious adverse events (SAEs), cancers, overdoses, pregnancy events, lactation events, and SAEs of infants born to participant who received the study vaccine or who were breastfed during the vaccination period will be collected during the entire period of Stage I.

As participants 20-45 years of age will not enter into Stage II, the last study visit for these participants will be the Visit 10.

4.1.2 Stage II

Participants who are enrolled in the 9 to 19 years age group and have completed 3 doses of study vaccination during Stage I will be eligible for participation into Stage II and followed up to Visit 15. Therefore, the last study visit for participants 9-19 years of age who will not enter into Stage II will be the Visit 10.

Serum samples will be obtained at the time points of Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15. All the serum samples will be tested by cLIA and IgG LIA for measurement of anti-HPV antibodies for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. As an exploratory objective, PBNA will be performed on serum samples collected from the same subset of participants in the 9-19 years old group selected for PBNA testing during Stage I.

SAEs, cancers, overdoses, pregnancy events, lactation events, and infant SAEs will be collected during the entire period of Stage II.

For the purposes of analysis and results reporting, the primary outcome of each stage will be defined as the Sponsor’s receipt of the last serological data in each stage.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Schedule of Activities (SoA), Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This phase 3 study is to fulfill the post-marketing requirement of local regulatory authority to evaluate the immunogenicity and safety of the 9vHPV vaccine in Chinese females. The main purpose of this study is to demonstrate that immune responses to the 9vHPV vaccine in females 9 to 19 years of age and females 27 to 45 years of age are non-inferior to those in females 20 to 26 years of age. Persistence of immunogenicity of the vaccine will be evaluated up to Visit 15 in females 9 to 19 years of age in this study.

As participants who are seropositive to the vaccine HPV types at baseline will not be included in the final analyses of immunogenicity (see Section 9.5.1 for definitions of

immunogenicity analysis populations), the baseline seropositivity rates in the study population were estimated based on previous local and global HPV studies and were considered as one of the assumptions for sample size calculation (see Section 9.9.1).

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

Competitive Luminex immunoassay (cLIA) is the primary assay to assess the immunogenicity in the qHPV and 9vHPV vaccine programs. In Stage I, serum samples will be collected at Day 1 and 1 month post Dose 3 (Visit 10) for analysis of antibody responses to 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58) by cLIA to support the primary and secondary objectives of the study.

As described in Section 9.4.1, the primary immunogenicity endpoints are cLIA antibody titer (for H1) and seroconversion (for H2) to each of 9 HPV types at 1 month post Dose 3. The secondary immunogenicity endpoints are cLIA antibody seroconversion (for H3) and titer (for H4) to each of 9 HPV types at 1 month post Dose 3.

Antibody titer is the primary endpoint for 9-19 years old group and antibody seroconversion is the primary endpoint for 27-45 years old group, which is consistent with regulatory precedent for HPV vaccine licensure in China.

Non-inferiority margins used in this study are consistent with prior HPV vaccine studies.

HPV total IgG Luminex immunoassay (IgG LIA) will be used as a secondary measurement to evaluate the immunogenicity of the 9vHPV vaccine. IgG LIA antibody titer and seroconversion to 9 vaccine HPV types at 1 month post Dose 3 will be summarized.

The detailed description of these two immunoassays are provided in Section 8.2.2.

Pseudovirion-based neutralization assay (PBNA) which is developed by the National Institutes for Food and Drug Control (NIFDC, Beijing, China) will be used as an exploratory measurement to characterize the immune responses induced by the 9vHPV vaccine in a subset of participants.

In Stage II, serum samples will be collected at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15 to evaluate the persistence of immune responses. Anti-HPV antibody titer and seropositivity at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15 measured by cLIA and IgG LIA will be summarized. The exploratory endpoints for persistence of immune responses include PBNA antibody titer and seropositivity at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15 in a subset of participants.

4.2.1.2 Safety Endpoints

The safety endpoints used in this study are selected based on the product's safety profile demonstrated in prior clinical studies with the 9vHPV vaccine, and meet the vaccine clinical requirements in China.

A list of the safety endpoints to evaluate the safety of the 9vHPV vaccine in the study population is provided in Section 8.3.1 and 9.4.2.

4.3 Justification for Dose

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 [Luxembourg, A., et al 2015] [Pitisuttithum, P., et al 2015].

The efficacy of the 9vHPV vaccine was established in a clinical trial in young women 16 to 26 years of age based on a dosing regimen of 0, 2, 6 months [Joura, E. A., et al 2015].

The formulation and regimen of 9vHPV vaccine are identical to those used in prior global studies, and the licensed 9vHPV vaccine in China.

4.4 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 telephone 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 assay results (eg, serum, swab, and biopsy) or participant data from the last study-related telephone call or visit.

4.4.1 Clinical Criteria for Early Study Termination

Enrollment and vaccination of girls 9 to 15 years of age may be terminated if the DMC determines that the safety profile of the 9vHPV vaccine assessed in 25 girls 9 to 15 years of age after Dose 2 is not acceptable.

5. Study Population

Healthy Chinese females aged 9 and 45 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.

5.1 Inclusion Criteria

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

5.1.1 Stage I

Type of Participant and Disease Characteristics

1. Only healthy participants are to be enrolled. A participant is judged to be in good physical health on the basis of medical history and physical examination.

Demographics

2. Participant is female between the ages of 9 years and 0 days and 45 years and 364 days on the day of Day 1 vaccination.

3. Participant is eligible to participate, if at least one of the following conditions applies:

   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 2

   OR

   b.) A WOCBP has not had sex with males or has had sex with males and used effective contraception as defined in Appendix 2 since the first day of participant's last menstrual period through Day 1. And the participant understands and agrees that during the Day 1 through 1 month post Dose 3 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.

4. Participant has a lifetime history of 0 to 4 male and/or female sexual partners at the time of enrollment. Male partner is defined as someone with whom the participant has penile penetrative sexual intercourse. Female partner is defined as someone who has contacted, either by penetrative (with fingers or other objects) or non-penetrative means, the participant's genitalia during sexual activity.

Informed Consent/Assent

5. *(Participants 9-17 years of age only)* Participant's legally acceptable representative provides written informed consent for the study. Participant provides written informed assent for the study.

6. *(Participants 18-45 years of age only)* Participant provides written informed consent for the study.

General

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

5.1.2 Stage II

1. Participant is enrolled in the Stage I.

2. Participant is 9 to 19 years of age at the enrollment in the Stage I.

3. Participant has completed 3 doses of study vaccination.

5.2 Exclusion Criteria

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

The following exclusion criteria are only required for Stage I.

No exclusion criteria are applicable for Stage II.

Medical Conditions

1. Participant has 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 serious adverse event defined in Appendix 3.

2. Participant has a history of severe allergic reaction (e.g. swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention.

3. Participant with known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

4. Participant has a fever (defined as an axillary temperature ≥37.1°C) within 24 hours 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).

5. Participant has any history of abnormal Pap test showing squamous intraepithelial lesion (SIL) or atypical squamous cells – undetermined significance (ASC-US), atypical squamous cells – cannot exclude HSIL (ASC-H), atypical glandular cells, or biopsy showing cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ or cervical cancer.

6. Participant has a history of external genital wart, vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), vulvar cancer or vaginal cancer.

7. Participant has a history of a positive test for HPV.

8. Participant is currently immunocompromised or has been diagnosed as having congenital or acquired immunodeficiency, human immunodeficiency virus (HIV) infection, lymphoma, leukemia, systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), inflammatory bowel disease, or other autoimmune condition.

9. Participant has a history of splenectomy.

10. Participant 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.

11. Participant has donated blood within 1 week prior to the Day 1 vaccination, or intends to donate during Day 1 through 1 month post Dose 3 of the study (if the participant meets this exclusion criterion, the Day 1 visit may be rescheduled for a time when this criterion is not met).

12. Participant is expecting to donate eggs during Day 1 through 1 month post Dose 3 of the study.

13. Female participant of childbearing potential as defined in Appendix 2 is pregnant as determined by a urine or serum pregnancy testing that is sensitive to 25 mIU/mL beta human chorionic gonadotropin (β-hCG).

Prior/Concomitant Therapy

14. Participant is receiving or has received in the year prior to Day 1 vaccination the following immunosuppressive therapies: radiation therapy, cyclophosphamide, azathioprine, methotrexate, any chemotherapy, cyclosporin, leflunomide (Arava™), 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 she is currently receiving steroid therapy, has recently (defined as within 2 weeks of Day 1 vaccination) received such therapy, or has received 2 or more courses of corticosteroids (orally or parenterally) lasting at least 1 week in duration in the year prior to Day 1 vaccination. Participants using inhaled, nasal or topical corticosteroids are considered eligible for the study.

15. Participant who has received immune globulin product (including RhoGAM™ [Ortho-clinical Diagnostics]) or blood-derived product other than IVIG within 6 months prior to Day 1 vaccination, or plans to receive any such product during Day 1 through 1 month post Dose 3 of the study.

16. Participant has received a marketed HPV vaccine, or has participated in an HPV vaccine clinical trial and has received either active agent or placebo.

17. Participant has received inactivated or recombinant vaccines within 14 days prior to Day 1 vaccination or has received live vaccines within 21 days prior to 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).

Prior/Concurrent Clinical Study Experience

18. Participant is concurrently enrolled in clinical studies of interventional agents.

Diagnostic Assessments

Not Applicable.

Other Exclusions

19. Participant is unlikely to adhere to the study procedures, keep appointments, or is planning to permanently relocate from the area prior to the completion of the study or to leave for an extended period of time when study visits would need to be scheduled.

20. Participant 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 or alcohol 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.

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.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently entered in the study. 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 (AEs) or serious adverse events (SAEs) meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

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

6. 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. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Treatments Administered

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

Table 1 Study Treatment

Study Treatment Name	**Dose Formulation**	**Unit Dose Strength(s)**	**Dosage Level(s)**	**Route of Administration**	**Vaccination Regimen**	**Use**	**IMP/NIMP**	**Sourcing**
9vHPV vaccine, also known as V503	Liquid in vial	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/20 mcg per dose	0.5 mL per dose	Intramuscular injection	Day 1, Month 2, and Month 6*	Experimental	IMP	Provided centrally by the Sponsor
Definition Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed. *: For the first 25 participants enrolled in the 9-15 years old group, the safety from 1st dose through Day 15 following 2nd dose will be evaluated by a DMC. If the safety is favorable, this subset of participant will receive the 3rd dose and enrollment of the rest of participants in the 9-15 years old group will be initiated.								

All supplies indicated in Table 1 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 where possible.

Refer to Section 8.1.11 for details regarding administration of the study treatment.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 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 (if applicable) 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.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

Participants participating in this study will be allocated by nonrandom assignment.

6.3.1.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

Age: Enrollment of participants will be stratified into three age strata. A total of 1990 participants will be enrolled, with 690 participants 9 to 19 years of age, 650 participants 20 to 26 years of age and 650 participants 27 to 45 years of age.

- Within 9-19 years old stratum, approximately 2:1 allocation will be applied based on two age subgroups: 9-15 years old and 16-19 years old.
- Within 27-45 years old stratum, approximately 1:1 allocation will be applied based on two age subgroups: 27-35 years old and 36-45 years old.

6.3.2 Blinding

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

6.4 Treatment Compliance

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

6.5 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 treatment 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 restriction for prior and concomitant medications at Day 1 (Section 5.2) and prerequisites for other vaccination visits (Section 8.10.1).

The participant should not receive systemic corticosteroids, immunosuppressive therapies, immune globulin or blood-derived products during Day 1 through 1 month post Dose 3 (Visit 10) of the study, non-study inactivated or recombinant vaccines within 14 days prior to or 14

days after any dose of study vaccination, non-study live vaccines within 21 days prior to or 14 days after any dose of 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 documented as described in Section 8.1.5.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

Not Applicable.

6.7 Treatment After the End of the Study

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

6.8 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.

7. Discontinuation of Study Treatment and Participant Withdrawal

7.1 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 vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.10.2.

Participants may discontinue study treatment at any time for any reason or be discontinued 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 8.1.12.

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.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study treatment.

For participants who are discontinued from study treatment but continue to be monitored in the study, see Section 1.3 and Section 8.10.2 for those procedures to be completed at each specified visit.

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

7.2 Participant 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 8.1.12. 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 7.3.

7.3 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, telephone 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.

- 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 prespecified statistical data handling and analysis guidelines.

8. 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 study-related medical decisions must be made by an investigator who is a qualified physician.
- 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 total maximum amount of blood collected from each participant for the immunogenicity objectives over the duration of Stage I, including any extra assessments that may be required, will not exceed approximately 20 mL.

The total maximum amount of blood collected from each participant for the immunogenicity objectives over the duration of Stage II, including any extra assessments that may be required, will not exceed approximately 50 mL.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) 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 medically qualified designee must ensure the appropriate consent/assent is in place.

8.1.1.1 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 Institutional Review Board/Independent Ethics Committee's (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.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 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.

8.1.4 Medical History

At the Day 1 visit, the participant's medical history for 5 years prior to Day 1 and lifetime major medical history prior to Day 1 will be collected. The major medical history is defined as a medical condition in which emergency room visit, hospitalization and/or surgery were needed. For the participants who have had sexual intercourse prior to Day 1, lifetime gynecologic history will be collected at the Day 1 visit.

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

See the exclusion criteria for specific restrictions for prior and concomitant medications at Day 1 (Section 5.2). Prior and concomitant use of medicines and non-study vaccines will be reviewed at the specified study visits of Stage I (see Section 1.3) and should be documented in the data collection system by the investigator or qualified designee in the following manner:

- "Special medications" (corticosteroids, immunosuppressive therapies, immune globulins, and blood-derived products) from the year prior to Day 1 through Visit 10.
- "Other medications" from 3 days prior to each study vaccination through 14 days after each study vaccination.
- "Non-study inactivated or recombinant vaccines" from 14 days prior to each study vaccination through 14 days after each study vaccination.
- "Non-study live vaccines" from 21 days prior to each study vaccination through 14 days after each study vaccination.

8.1.5.2 Concomitant Medications

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

For the specific case where a participant mistakenly receives a non-study HPV vaccine at any time during the study, the non-study HPV vaccine should be documented in the data collection system.

8.1.6 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.

8.1.7 Physical Examinations

A physical examination will be conducted at Day 1 for all participants, and at Visit 6 (Month 2.5) for the first 25 participants enrolled in the 9-15 years old group, for whom the safety will be reviewed by the DMC. Height and weight will only be measured at Day 1.

Physical examination details will be documented in the participant's study chart and any medical condition will be documented in the data collection system. Height and weight will be documented in the data collection system.

8.1.8 Axillary Temperature and Blood Pressure Prior to Study Vaccination

Axillary temperature and blood pressure will be taken before study vaccination at Visit 1, Visit 4, and Visit 8.

If the participant has a fever (defined as an axillary temperature of ≥37.1°C) within the 24-hour period prior to vaccination, the vaccination should be rescheduled after the fever has resolved.

Axillary temperature will be documented in the data collection system and blood pressure will be documented in the participant's study chart.

8.1.9 Pregnancy Testing Prior to Study Vaccination

All female participants of childbearing potential will have a urine or serum pregnancy testing at each vaccination visit (i.e. Visit 1, Visit 4, Visit 8) (see Section 10.2 - Appendix 2).

The pregnancy testing results must be obtained prior to each study vaccination (on the day the participant is vaccinated). Any participant found to be pregnant at the Day 1 visit will not be allocated and will not participate in the study.

Management of study visits and study vaccination for enrolled participants who become pregnant after the Day 1 visit is summarized in Table 10 (see Section 10.2 - Appendix 2).

8.1.10 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Although treatment is allocated by non-random assignment, the numbers assigned are called "treatment/randomization numbers" in the protocol. The treatment allocation will occur centrally using an interactive response technology (IRT) system. 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.

8.1.11 Treatment Administration

Study vaccine(s) should be prepared and administered by appropriately qualified members of the study personnel (e.g. physician, nurse, physicians' assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state country and intuitional guidance.

Study vaccine should not be used for any purpose other than that stated in the protocol.

The first dose of study vaccine will be administered at Day 1 (Visit 1), which should be the day of allocation. The second and third (final) doses of study vaccine will be administered subsequently at Visit 4 and Visit 8, respectively. All 3 doses should be administered within 1 year as shown in the SoA (Section 1.3).

All the study-related procedures for Day 1 visit except informed consent/assent, baseline number assignment, participant identification card, should be performed on the same day as and prior to the first study vaccination.

The interval between the date of consent and the date of the Day 1 visit should be no more than 14 days apart. If the interval is 15 days or longer, then the participant must be re-consented.

Participants should not be enrolled or vaccinated if protocol requirements are not met. At Day 1, study vaccine should be administered after the blood draw for anti-HPV antibody testing (see Section 8.2.1). Section 8.10.1 provides additional information on other prerequisites for vaccination visits.

8.1.11.1 Preparation of Study Vaccine for Administration

The study vaccine may be removed from the refrigerator and allowed to sit at room temperature for no longer than 15 minutes prior to administration.

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. After mixing, the study vaccine will appear as a

whitish, semi-translucent suspension. If the appearance is otherwise, do not administer and contact the Sponsor immediately.

8.1.11.2 Study Vaccine Administration

At each vaccination visit, participants will receive study vaccine as a 0.5-mL intramuscular injection. The deltoid muscle of the nondominant arm is the preferred site of vaccination.

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 with the following needle length and gauge specifications: 1-inch needle, 22 to 23 gauge, for participants weighing < 90 kg; 1½-inch needle, 22 to 23 gauge, for participants weighing ≥ 90 kg. If the injection is given in the thigh, a 1½ -inch needle, 22 to 23 gauge should be used.

Study vaccination should not be administered in the buttocks area. Injections should not be given within 2 cm of a tattoo, scar, or skin deformation.

All participants will be observed for at least 30 minutes after each vaccination. This observation period will be documented for any immediate reaction with particular attention to any evidence of allergic phenomena.

8.1.11.3 Timing of Dose Administration

Study vaccine will be administered at Visit 1, Visit 4, and Visit 8, as shown in the SoA (See Section 1.3).

Acceptable day ranges for vaccination visits are as follows:

- Dose 1: Day 1 (±0 days)
- Dose 2: 40 to 82 days after Dose 1
- Dose 3: 155 to 364 days after Dose 1 (The interval between Dose 2 and Dose 3 should be at least 3 months.)

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

8.1.12 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 (Visit 10 is the final visit for Stage I, and Visit 15 is the final visit for Stage II) (exception for Stage I: serum collection should not be done at the final visit if the participant has not received all 3 doses of study vaccine) should be performed (at

the time of withdrawal). Any AEs which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

The final visit assessment for participant withdraws from the study can be done via a phone call.

8.1.13 Participant Blinding/Unblinding

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

8.1.14 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or 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 vaccines.
- 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 Sponsor-designated Central Laboratory.
- Centrifuge for processing of blood samples.

8.2 Immunogenicity Assessments

8.2.1 Serum for Anti-HPV Antibody Testing

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

An approximate 10-mL blood sample will be collected from each participant at the scheduled time points (see Section 1.3) and serum will be separated for anti-HPV antibody measurements.

8.2.2 Immunogenicity Measurements

The 9-valent HPV competitive Luminex immunoassay (HPV-9 cLIA) will be 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).

In this study, the 9-valent HPV total IgG Luminex immunoassay (HPV-9 IgG LIA) will be used as a secondary measurement, complementary to the cLIA.

Yeast-derived VLPs are coupled to a set of 9 distinct fluorescent Luminex microspheres. Antibody concentrations are determined in a multiplexed, direct binding format by measuring the amount of VLP-specific IgG bound to VLP-microspheres on the Luminex platform. Following incubation with human serum, fluorescent signal from an anti-human IgG detection antibody that binds directly to serum IgG and equally to each IgG subclass (1-4) is directly measured on the Luminex or Bioplex instrument. The fluorescent signal from the IgG-bound fluorescent detection antibody is proportional to the individual's HPV type-specific anti-VLP IgG antibody levels. Results for the assay are reported as concentration of antibody in mMU/mL.

cLIA and IgG LIA will be performed at the Sponsor-designated Central Laboratory in China.

PBNA developed by NIFDC (Beijing, China) will be used in the exploratory analysis to characterize the immune responses to the 9 types of HPV vaccine following study vaccination. PBNA is an assay that functionally measures the full spectra of neutralizing antibodies to HPV. HPV pseudovirions are produced by co-transfecting the 293TT or 293FT human embryonic kidney cell line with an expression plasmid encoding the HPV L1 and L2

capsid genes and another encoding reporter gene. Pseudovirions of L1/L2 self-assemble and package a reporter plasmid within. Pseudovirions are incubated with 293TT or 293FT cell and when pseudovirions enter cells, report gene will be expressed. If neutralizing antibodies are present in the test sera, infection of cells by pseudovirions and subsequent expression of reporter gene is inhibited. The serum neutralization titers are defined as the 50% maximal inhibitory concentration (IC_{50}).

Serum samples collected from a subset of participants will be tested by PBNA as described in Section 4.1 at NIFDC.

All the immunoassays listed above will be used for immunogenicity analyses through Stage I and II.

8.3 Safety Assessments

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.

8.3.1 Vaccination Report Card and Patient Reported Outcome

All participants will receive a VRC at each study vaccination visit (Visit 1, Visit 4, and Visit 8).

Using the VRC, participant or participant's legally acceptable representative will be asked to record the following safety information: axillary temperature in the evening after each study vaccination and daily, at the same time of day whenever possible, for 7 days after each study vaccination; solicited injection-site AEs (injection-site redness, swelling, induration, and pain) from Day 1 through Day 8 after each study vaccination; any AEs from Day 1 through Day 31 after each study vaccination. Participant or participant's legally acceptable representative will be asked to record concomitant medications and concomitant vaccinations for 15 days following each study vaccination on VRC. Medications taken by participants due to AEs during Day 16 through Day 31 after each study vaccination will also be collected on VRC.

VRCs will be returned for review on Day 9 (i.e. Visit 2, Visit 5, and Visit 9) and Day 32 (i.e. Visit 3, Visit 7, and Visit 10) after each study vaccination, respectively. The first 25 participants enrolled in the 9-15 years old group will have an additional VRC return visit (Visit 6) to collect the safety data through Day 15 following the 2nd dose.

Except Visit 10 (1 month post Dose 3) at which visit blood samples will be collected, the purpose of other VRC return visits is to review the VRCs, so out of windows will not be considered as protocol deviation for Visit 2, Visit 3, Visit 5, Visit 6, Visit 7, and Visit 9. However, Visit 10 sample collection out of windows will be considered as a protocol deviation.

Telephone contacts will be done around every week between Visit 2 and Visit 3, Visit 5 and Visit 7 (telephone contacts will be done after Visit 6 for the first 25 participants in the 9-15 years old group), Visit 9 and Visit 10 until the VRCs are returned to remind the participants to record the VRC and answer any questions related to VRC.

SAEs, cancers, overdoses, pregnancy events, lactation events, and infant SAEs will be collected during the entire study period as instructed in the Section 8.4.

In addition, new medical conditions will be collected after the Day 1 visit throughout the end of study. At the specified visits, participants will be questioned regarding any new medical conditions that occurred since the last scheduled visit. The new medical conditions are any medical events which occur after entry into the study and have not been reported as an adverse event (i.e., events that occur outside of the period of 31 days after each vaccination and are not reported as SAEs). A condition reported as medical history at Day 1 is not reportable as new medical condition. However, a medical condition which has been reported as medical history at Day 1 but aggravates during the study and is not reported as an AE or SAE should be reported as new medical condition. Unlike AE, relationship to study vaccine will not be evaluated for new medical conditions.

8.3.2 Post-vaccination Observation Period (30 minutes)

All participants will be observed for at least 30 minutes after each study vaccination for any immediate untoward effects with particular attention to any evidence of allergic phenomena. This observation period will be documented in the participant's study chart.

8.3.3 Clinical Safety Laboratory Assessments

- There are no protocol specified laboratory assessments in this study.
- If laboratory values from nonprotocol 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).

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or 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 10.3 - Appendix 3.

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 and any designees are responsible for detecting, 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 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 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 30 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 30 days thereafter, all AEs, SAEs and other reportable safety events must be reported by the investigator.

SAEs (regardless of causality) at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor. Other reportable safety events (cancer, pregnancy, breastfeeding exposure, and overdose) at any time outside of the time period specified in the previous paragraph should also be reported to the Sponsor. In addition, SAEs of infants born to participants who received the study vaccine or who were breastfed during the study are reportable for the entire study period.

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 time frames as indicated in Table 2.

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

Type of Event	Time Period			Time Frame to Report Event and Follow-up Information to SPONSOR:
	Consent to Randomization/ Allocation	**Randomization/ Allocation through Protocol-Specified Follow-up Period**	**After the Protocol Specified Follow-up Period**	
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - 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: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report all	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Report all	Within 24 hours of learning of event
Event of Clinical Interest	There are no ECIs for this study			Not applicable
Cancer	Report if: - due to intervention - causes exclusion	Report all	Report all	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Report all	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

A VRC will be used by the participant to document any AEs within 30 days (Days 1-31) following each study vaccination.

8.4.3 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 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Section 10.3 - Appendix 3. Both Sponsor's criteria (Section 10.3 - Appendix 3) and CFDA (China Food and Drug Administration)'s criteria (Section 10.4 - Appendix 4) will be applied to assess the intensity/toxicity of adverse events by investigator.

8.4.4 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 AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable to this study.

8.4.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study 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. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal

death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

All participants of childbearing potential will undergo a urine or serum pregnancy testing prior to each study vaccination (see Section 1.3, Section 10.2 - Appendix 2). Participants found to be pregnant at Day 1 are not eligible to participate in the study (Section 5.2). 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 10 (Section 10.2 - Appendix 2). Breastfeeding is not a contraindication to enrollment or to receiving study vaccinations. Pregnancy and breastfeeding in study participants and SAEs of infants born to participants who received the study vaccine or who were breastfed within the protocol pre-defined period must be reported as described in Section 8.4.1.

8.4.7 Events of Clinical Interest (ECIs)

There are no ECIs for this study.

8.5 Treatment of Overdose

In this study, an overdose is defined as a participant receiving >1 dose of study vaccine in a 24-hour period or >3 doses of study vaccine throughout the study.

Sponsor does not recommend specific treatment for an overdose.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided above in Section 8.

8.10.1 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 inclusion/exclusion criteria for specific restrictions at Day 1 (see Section 5.1.1 and Section 5.2). At the Dose 2 and Dose 3 study vaccination visits (Visit 4 and Visit 8), study personnel should verify by questioning the participant and/or by examination that:

1. The participant has not had a fever (defined as an axillary temperature of ≥37.1°C) within the 24-hour period prior to the Dose 2 or Dose 3 study vaccination visit.

2. The participant has not received any systemic (oral or parenteral) corticosteroids within 2 weeks prior to the Dose 2 or Dose 3 study vaccination visit.

3. The participant has not received a non-study inactivated or recombinant vaccine within 14 days prior to the Dose 2 or Dose 3 study vaccination visit or a non-study live vaccine within 21 days prior to the Dose 2 or Dose 3 study vaccination visit.

4. The participant of childbearing potential is not pregnant as determined by a urine or serum pregnancy testing (see Section 10.2 - Appendix 2).

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

8.10.2 Discontinued Participants Continuing to be Monitored in the Study

During Stage I, participants who discontinue study vaccinations but continue in the study may attend study visits per the SoA (Section 1.3). However, serum samples will not be collected at Visit 10 from participants who did not complete the 3-dose regimen of study vaccination.

Participants 9 to 19 years of age who did not complete the 3-dose regimen of study vaccine will not be eligible for participation into Stage II (see Section 5.1.2 for Inclusion Criteria of Stage II).

9. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes made to primary (H1/H2) and/or secondary (H3/H4) hypotheses, or the statistical methods related to those hypotheses, 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 (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity and Safety of a 9-Valent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine (V503) in Chinese females 9 to 45 Years of Age
Treatment Assignment	All enrolled participants will receive a 3-dose regimen of 9vHPV vaccine. The first 25 participants enrolled in the 9-15 years old group will receive Dose 3 if the safety from Dose 1 through 15 days post Dose 2 is acceptable by DMC. Stratification factors are provided in Section 6.3.1.1.
Analysis Populations	Immunogenicity: Per-protocol immunogenicity (PPI) population Safety: All Participants as Treated (APaT) population
Primary Endpoint(s)	Stage I: (1) H1 (9-19 years old vs. 20-26 years old): cLIA antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58; (2) H2 (27-45 years old vs. 20-26 years old): cLIA antibody seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.
Secondary Endpoints	Stage I: (1) H3 (9-19 years old vs. 20-26 years old): cLIA antibody seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58; (2) H4 (9-15 years old vs. 20-26 years old): cLIA antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Statistical Methods for Key Immunogenicity Analyses	Stage I: (1) H1: 9vHPV vaccine induces non-inferior immune responses in females 9 to 19 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval of GMT ratio (females 9 to 19 years of age vs. females 20 to 26 years of age) be greater than 0.67 for each HPV type.) (2) H2: 9vHPV vaccine induces non-inferior immune responses in females 27 to 45 years of age who are seronegative at Day 1 to the relevant HPV type compared to females 20 to 26 years of age who are seronegative at Day 1 to the relevant HPV type, as measured by the seroconversion percentage to each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3. (Each vaccine component will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval for the difference (females 27 to 45 years of age minus females 20 to 26 years of age) in seroconversion percentages be greater than -5% for each HPV type.)
Statistical Methods for Key Safety Analyses	Safety assessments will be descriptive in nature and will include calculation of proportions of participants with adverse events as well as 95% CI.
Interim Analyses	One interim analysis will be performed to evaluate the safety of the 9vHPV vaccine in 25 participants aged 9-15 years from Dose 1 through Day 15 post Dose 2. The safety data will be reviewed by a DMC. If the safety data are judged to be acceptable, then enrollment will be initiated to the rest of participants in the 9-15 years old group.
Multiplicity	• For the dual-primary hypotheses (H1 and H2), Bonferroni method is used to control overall one-sided type I error at level of 0.025. Each of the dual-primary hypotheses has a 0.0125 one-sided type I error. Success criterion of the study is the success on either of the dual-primary hypotheses; • Fixed sequence testing strategy is used to control multiplicity between primary hypothesis and secondary hypotheses.

Sample Size and Power	The planned sample size is 1990 female participants (9-19 years old: 690; 20-26 years old: 650; 27-45 years old: 650). The overall power to claim the study success based on the dual-primary hypotheses is >0.999. • Approximately an overall 99.1% power for H1 to demonstrate that females aged 9-19 years is non-inferior to females aged 20-26 years in terms of cLIA GMTs at 1 month post Dose 3 at an overall one-sided 1.25% alpha-level; • Approximately an overall 92.9% power for H2 to demonstrate that females aged 27-45 years is non-inferior to females aged 20-26 years in terms of cLIA seroconversion percentages at 1 month post Dose 3 at an overall one-sided 1.25% alpha-level.

9.2 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 is a non-randomized, open-label study, therefore participants, investigators, and SPONSOR personnel will be aware of participant treatment assignments when each participant is enrolled and treatment is assigned.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Immunogenicity Endpoints

Stage I (Day 1 to Visit 10)

The primary immunogenicity endpoints are cLIA antibody titer (for H1) and seroconversion (for H2) at 1 month post Dose 3 to each of 9 HPV types. Seroconversion is defined as participant's serostatus changing from seronegative at Day 1 to seropositive at 1 month post Dose 3. A participant with a cLIA titer at or above the serostatus cutoff value for a given HPV type is considered seropositive for that type. The cLIA antibody titers at Day 1 will also be summarized.

The secondary immunogenicity endpoints are cLIA antibody seroconversion (for H3) and titer (for H4) to each of 9 HPV types.

Anti-HPV antibody titer and seroconversion to each of 9 HPV types measured by IgG LIA will be summarized as secondary analyses of immunogenicity.

The exploratory endpoints for immunogenicity include antibody titer and seroconversion to each of 9 HPV types measured by PBNA, which was developed and performed by NIFDC.

Stage II (post Visit 10 to Visit 15)

For the second stage of study, anti-HPV antibody titer and seropositivity at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15 measured by cLIA and IgG LIA will be summarized to describe the persistence of the serum antibody responses to the 9 vaccine HPV types.

The exploratory endpoints for immunogenicity include PBNA antibody titer and seropositivity at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15.

9.4.2 Safety Endpoints

The key safety endpoints used to evaluate the safety of the 9vHPV vaccine will include proportions of participants with solicited injection-site AEs from Day 1 through Day 8 following any study vaccination, solicited systemic AE (elevated axillary temperature (≥37.1 ^{o} C)) from Day 1 through Day 8 following any study vaccination, proportions of participants with systemic AEs from Day 1 through Day 31 following any study vaccination, and proportion of participants experiencing SAEs at any time during the study. Pregnancy outcomes during the study will be summarized. Non-serious and serious adverse events and new medical conditions considered potentially indicative of autoimmune disorders will be analyzed as Conditions of Particular Attention (CPA) in this study as was done in previous 9vHPV vaccine studies [Moreira, E. D., et al 2016].

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

Per-Protocol Immunogenicity Population

The per-protocol immunogenicity (PPI) population will serve as the primary population for analysis of immune responses to the 9vHPV vaccine. To be included in this population, participants must:

(1) Have received all 3 study vaccinations with the correct dose of the correct clinical material, and each vaccination visit must occur within the vaccination visit window specified in Section 1.3 – SoA.

(2) Be seronegative at Day 1 for the HPV type being analyzed. In the analysis of HPV types 6 and 11, the participant must be seronegative to both HPV 6 and 11.

(3) Have provided post Dose 3 serum samples within the visit (i.e., Visit 10) window specified in Section 1.3 – SoA.

(4) Have no other protocol violation that could interfere with the evaluation of participant's immune response to the study vaccine.

All Type-Specific Naïve Participants with Serology Population

A supportive immunogenicity analysis will be carried out on the all type-specific naïve participants with serology (ANPS) population. To be included in this population, participants must:

(1) Have received all 3 study vaccinations.

(2) Be seronegative at Day 1 for the HPV type being analyzed. In the analysis of HPV types 6 and 11, the participant must be seronegative to both HPV 6 and 11.

(3) Have provided post Dose 3 serum samples.

Unlike the PPI population, the ANPS population will include participants who meet any exclusion criteria that were deemed to potentially interfere with the evaluation of immune responses to the 9vHPV vaccine. In addition, no day ranges on the timing of the vaccination and post Dose 3 serum sample collection will be applied.

9.5.2 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety data. The APaT population consists of all participants who received at least one dose of study vaccination and have clinical follow-up for safety.

9.6 Statistical Methods

This study composed of two stages with different objectives. Database will be locked and analysis will be conducted after completion of each stage. The immunobridging analysis of Stage I will be conducted when the last serological results at Day 1 and 1 month post Dose 3 of Stage I are available. The persistence of immunogenicity will be analyzed once the last serological results of Stage II are available. A separate report will be generated for Stage I and Stage II, respectively.

9.6.1 Statistical Methods for Immunogenicity Analyses

Stage I (Day 1 to Visit 10):

Two dual-primary hypotheses, H1 and H2 will share a one-sided alpha level 0.025. The success criterion of the study is the success on either of the dual-primary hypotheses.

To test H1, the immune responses as measured by anti-HPV cLIA GMTs at 1 month post Dose 3 will be analyzed separately for each of 9 HPV types. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval of GMT ratio (9 to 19 years of age vs. 20 to 26 years of age) be greater than 0.67 for each HPV type. The primary hypothesis H1 will be considered a success if the non-inferiority criteria for GMTs are met for all 9 HPV types in the comparisons between females 9 to 19 years of age vs. females 20 to 26 years of age.

For each HPV type, the hypothesis to be tested at α=0.0125 level (1-sided) are

$$H_0: GMT_1/GMT_2 \leq 0.67$$

$$H_a: GMT_1/GMT_2 > 0.67$$

where GMT_1 and GMT_2 represent the GMTs at 1 month post Dose 3, in the 9-19 years old group and in the 20-26 years old group, respectively. 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 test above will be conducted using an ANOVA model with a response of log individual titers and a fixed effect for comparison group.

To test H2, cLIA seroconversion percentages at 1 month post Dose 3 will be analyzed separately for each of 9 HPV types. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval of seroconversion percentages (27 to 45 years of age minus 20 to 26 years of age) be greater than -5% for each HPV type. The primary hypothesis H2 will be considered a success if the non-inferiority criteria for seroconversion percentages are met for all 9 HPV types in the comparisons between 27 to 45 years of age vs. 20 to 26 years of age.

The point estimate of seroconversion percentage for 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.

For each HPV type, the hypothesis to be tested at α=0.0125 level (1-sided) are

$$H_0: p_1-p_2 \leq -0.05$$

$$Ha: p_1-p_2 > -0.05$$

where p_1 is the proportion of participants who seroconvert by 1 month post Dose 3 in the 27-45 years old group and p_2 is the proportion of participants who seroconvert by 1 month post dose 3 in the 20-26 years old group.

The tests above will be conducted using the method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985]. The statistical criterion for non-inferiority requires that the lower bound of two-sided 97.5% confidence interval for the difference (27-45 years of age minus 20-26 years of age) in seroconversion percentages being greater than -5 percentage points for each HPV type.

Anti-HPV GMTs and seroconversion percentages measured by IgG LIA will be summarized as secondary objective of immunogenicity.

PBNA results (GMTs and seroconversion percentages) will be summarized as exploratory objective and will be provided in a supplemental report after the data are available.

The extended visit window of study vaccination may result in different intervals between doses, which has real potential to alter the read-out of the anti-HPV titers compared to the read-out expected from the original designated regimen (0, 2, 6 months). Besides, It is not

guaranteed that the effect that the time interval between doses will have on anti-HPV titer read-outs will be the same in each of the age groups. There is a real possibility that the variability of anti-HPV titers in each age group will affect the resulting GMTs in each age group in a way that the resulting GMT ratio is now different from the assumed GMT ratio used to power the non-inferiority hypothesis testing. If the shift in GMT ratio is in the direction greater than 1.0, the altered time interval between doses biased the hypothesis testing in favor of the age group represented by the numerator of the GMT ratio (i.e. 9-19 years old or 27-45 years old group). If the shift in GMT ratio is in the direction less than 1.0, then there is a risk that the hypothesis test will become underpowered. And the other situation would be no meaningful shift in the GMT ratio between age groups. So to investigate the potential impact, a supportive analysis on PPI population will be performed by HPV type using the following stepwise regression models.

- Step 1: A no-intercept regression model will be fitted on the natural logarithm of anti-HPV cLIA titers at 1 month post dose 3 (as dependent variable Y) with the following independent variables:
    - X1: Indicator for 9-19 years of age (X1=1 if 9-19 year-old, X1=0 if otherwise)
    - X2: Indicator for 20-26 years of age (X2=1 if 20-26 year-old, X2=0 if otherwise)
    - X3: Indicator for 27-45 years of age (X3=1 if 27-45 year-old; X3=0 if otherwise)
    - X4: Time (in months) from Dose 1 to Dose 2
    - X5: Time (in months) from Dose 2 to Dose 3
- The regression coefficients associated with X1, X2, and X3 represent the expected GMTs in natural logarithm scale (or log-GMT) in each of the 3 age groups.
- The regression coefficients associated with X4 and X5 represents the contribution of time interval between vaccinations on the expected log-GMTs.
- The association of log-GMT with X4 and X5, in addition to (or over and above) the association of log-GMT with the protocol-specified age groupings will be evaluated as follows:
    - The partial correlation coefficient associated with X4 and X5, given X1, X2, and X3 are already in the model, will be calculated and provided.
    - The nominal statistical significance of X4 and X5, given X1, X2, and X3 are already in the model, will be evaluated.
        - If X4 and X5 are nominally statistically significant (p-value ≤ 0.05), Step 2 outlined below will be performed.

- If X4 and X5 are not nominally statistically significant (p-value > 0.05), Step 2 outlined below will not be performed, and is an indication that there is no association between dosing interval and expected log-GMT. Step 2: The following explanatory variables will be added to the regression model specified in Step 1:
    - X1*X4: Time (in months) from Dose 1 to Dose 2 among 9-19 year-olds
    - X3*X4: Time (in months) from Dose 1 to Dose 2 among 27-45 year-olds
    - X1*X5: Time (in months) from Dose 2 to Dose 3 among 9-19 year-olds
    - X3*X5: Time (in months) from Dose 2 to Dose 3 among 27-45 year-olds
- These 4 explanatory variables provide insight on whether the effect of dosing interval varies by age group.
- The association of log-GMT with X1*X4, X3*X4, X1*X5, and X3*X5, in addition to (or over and above) the association of log-GMT with the protocol-specified age groupings and dosing intervals, will be evaluated as follows:
    - The partial correlation coefficient associated with X1*X4, X3*X4, X1*X5, and X3*X5, given X1, X2, X3, X4, and X5 are already in the model, will be calculated and provided.
    - The nominal statistical significance of X1*X4, X3*X4, X1*X5, and X3*X5, given X1, X2, X3, X4, and X5 are already in the model, will be evaluated.
        - A result indicating that X1*X4, X3*X4, X1*X5, and X3*X5 are nominally statistically significant at p-value ≤ 0.05 suggests that the effect of dosing interval on the expected cLIA anti-HPV GMT at 1 month post dose 3 varies by age group.

Table 3 summarizes the immunobridging analyses for Stage I.

Table 3 Analysis Strategy for Immunogenicity Variables – Stage I

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary Objectives				
Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at 1 month post Dose 3 (9-19yr vs. 20-26yr). (Each type will be tested separately.)	P	Point and 97.5% CI estimations as well as statistical testing will be performed by using an ANOVA model.	PPI	Observed data only
cLIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3 (27-45yr vs. 20-26yr). (Each type will be tested separately.)	P	Point and 97.5% CI estimations as well as statistical testing of binomial proportion are based on Miettinen & Nurminen method.	PPI	Observed data only
Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at Day 1 and 1 month post Dose 3 (9-19yr vs. 20-26yr).	S	Point and 95% CI estimations will be provided by using an ANOVA model; no statistical testing and between group 95% CI will be given.	ANPS	Observed data only
cLIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3 (27-45yr vs. 20-26yr).	S	Point and 95% CI estimations are based on exact method; no statistical testing and between group 95% CI will be given.	ANPS	Observed data only
Secondary Objectives				
cLIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3 (9-19yr vs. 20-26yr). (Each type will be tested separately.)	P	Point and 97.5% CI estimations as well as statistical testing of binomial proportion is based on Miettinen & Nurminen method.	PPI	Observed data only
Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at 1 month post Dose 3 (9-15yr vs. 20-26yr). (Each type will be tested separately.)	P	Point and 97.5% CI estimations as well as statistical testing will be performed by using an ANOVA model.	PPI	Observed data only
cLIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3 (9-15yr vs. 20-26yr).	S	Point and 95% CI estimations are based on exact method; no statistical testing and between group 95% CI will be given.	PPI	Observed data only

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at Day 1 and 1 month post Dose 3 (27-45yr vs. 20-26yr).	S	Point and 95% CI estimations will be provided by using an ANOVA model; no statistical testing and between group 95% CI will be given.	PPI	Observed data only
Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 IgG LIA GMTs at Day 1 and at 1 month post Dose 3.	S	Point and 95% CI estimations will be performed by using an ANOVA model; no statistical testing and between group 95% CI will be given.	PPI	Observed data only
IgG LIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3.	S	Point and 95% CI estimations are based on exact method; no statistical testing and between group 95% CI will be given.	PPI	Observed data only
Impact of the time between Vaccination 2 and 3 on anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at 1 month post Dose 3 by HPV type	S	Stepwise regression models	PPI	Observed data only

† P=Primary approach; S=Supportive approach.

ANPS = all type-specific naïve participants with serology; CI = confidence interval; GMT = geometric mean titer; PPI = per-protocol immunogenicity.

Stage II (post-Visit 10 to Visit 15):

In the second stage of study, participants 9 to 19 years of age enrolled in the Stage I who have completed 3 doses of study vaccination will be followed up to Visit 15 to evaluate the persistence of the serum antibody titers for each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15. Both cLIA and IgG LIA will be used to measure GMTs and seropositivity percentages.

Table 4 summarizes the immunogenicity persistence analyses for Stage II.

Table 4 Analysis Strategy for Immunogenicity Variables – Stage II

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
cLIA GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15	P	Point and 95% CI estimation will be performed by using an ANOVA model; no statistical testing and between group 95% CI will be given.	PPI	Observed data only
cLIA % seropositivity to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15	P	Point and 95% CI estimation based on exact method; no statistical testing and between group 95% CI will be given.	PPI	Observed data only
IgG LIA GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15	P	Point and 95% CI estimation will be performed by using an ANOVA model; no statistical testing and between group 95% CI will be given.	PPI	Observed data only
IgG LIA % seropositivity to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15	P	Point and 95% CI estimation based on exact method; no statistical testing and between group 95% CI will be given.	PPI	Observed data only

[†] P=Primary approach.

ANPS = all type-specific naïve participants with serology; CI = confidence interval; GMT = geometric mean titer; PPI = per-protocol immunogenicity.

PBNA results (GMTs and seropositivity percentages) will be summarized as exploratory objective and will be provided in a supplemental report after the data are available.

9.6.2 Statistical Methods for Safety Analyses

Safety will be assessed by statistical and clinical review of all safety data collected throughout the study. All participants who are vaccinated and who have safety follow-up data will be included in the safety analyses and summaries. To provide an overall assessment, safety measures that occurred in the pre-defined time interval during the study will be summarized, such as the incidence of

1. any adverse events;
2. any injection-site adverse events;
3. any systemic adverse events;

4. any serious adverse events;
5. any vaccination-related adverse events;
6. any vaccination-related serious adverse events;
7. conditions of particular attention (CPA*);
8. pregnancy outcomes;
9. new medical conditions.

*: More details about CPA will be provided in the sSAP.

Stage I (Day 1 to Visit 10):

Summary statistics, counts and percentages and 95% confidence interval will be provided by age groups: (1) 9- to 19-year-old group; (2) 20- to 26-year-old group; and (3) 27- to 45-year-old group which are summarized in Table 5.

Table 5 Analysis Strategy for Safety Parameters

Safety Endpoint	Within Group 95% CI	Descriptive Statistics
Injection-site adverse events prompted for on the VRC occurring Day 1 to Day 8 following any vaccination	×	×
Solicited systemic AE (elevated axillary temperature (≥37.1ºC)) from Day 1 through Day 8 following any vaccination	×	×
Injection-site adverse events not prompted for on the VRC occurring Day 1 to Day 8 following any vaccination in ≥1% of participants in any age group	×	×
Systemic adverse events in ≥1% of participants in any age group within 30 days following any vaccination	×	×
Serious adverse events at any time during study	×	×
Vaccination-related serious adverse events observed at any time during the study	×	×
Injection-site severe or more adverse events (by CFDA grading scale) occurring Day 1 to Day 8 following any vaccination	×	×
Injection-site severe adverse events (by Merck grading scale) occurring Day 1 to Day 8 following any vaccination	×	×
Systemic severe or more adverse events (by CFDA grading scale) within 30 days following any vaccination	×	×
Systemic severe adverse events (by Merck grading scale) within 30 days following any vaccination	×	×
Conditions of particular attention	×	×
All injection-site adverse events occurring Day 1 to Day 8 following any vaccination		×
All systemic adverse events within 30 days following any vaccination		×

Both Sponsor's criteria (Section 10.3 – Appendix 3) and CFDA's criteria (Section 10.4 - Appendix 4) will be applied to assess the intensity/toxicity of adverse events by investigator. The incidence of greatest intensity/toxicity based on the two criteria will be tabulated for injection-site AEs and systemic AEs.

All pregnancy outcomes and infant SAEs will be summarized.

Stage II (post-Visit 10 to Visit 15):

Summary statistics, including counts and proportions of participants with SAEs during the entire period of Stage II will be summarized for 9-19 years old participants.

In addition, all pregnancy outcomes and infants SAEs will be summarized.

9.6.3 Summaries of Baseline Characteristics, Demographics, and other Analyses

Baseline characteristics, demographic variables, medical history, prior and concomitant therapies of females 9 to 45 years of age will be summarized using descriptive statistics or categorical tables. No statistical hypothesis tests will be performed on these characteristics.

The number and percentage of participants screened, allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed.

New medical conditions will be collected during the entire period of the study. However, the data of new medication conditions will be separately summarized for Stage I and Stage II.

9.7 Interim Analyses

One interim analysis will be performed in this study to evaluate the safety of the 9vHPV vaccine from Dose 1 through Day 15 following Dose 2 in a subset of 25 participants aged 9-15 years. The safety data will be reviewed by a DMC. If the safety data are judged to be acceptable in the opinion of the DMC, then these 25 participants will receive the 3rd dose at Visit 8 and the enrollment will be initiated to the rest of participants in the 9-15 years old group. Available safety data from the 16-26 years old group will be provided along with the subset of 25 participants in the 9-15 years old group in order for the DMC to complete their safety evaluation.

This study is composed of two stages. Database will be locked and analyses will be conducted after completion of each stage. A full CSR will be generated for Stage I and a supplemental statistical report will be generated for Stage II.

9.8 Multiplicity

Figure 2 shows the multiplicity strategy for the study.

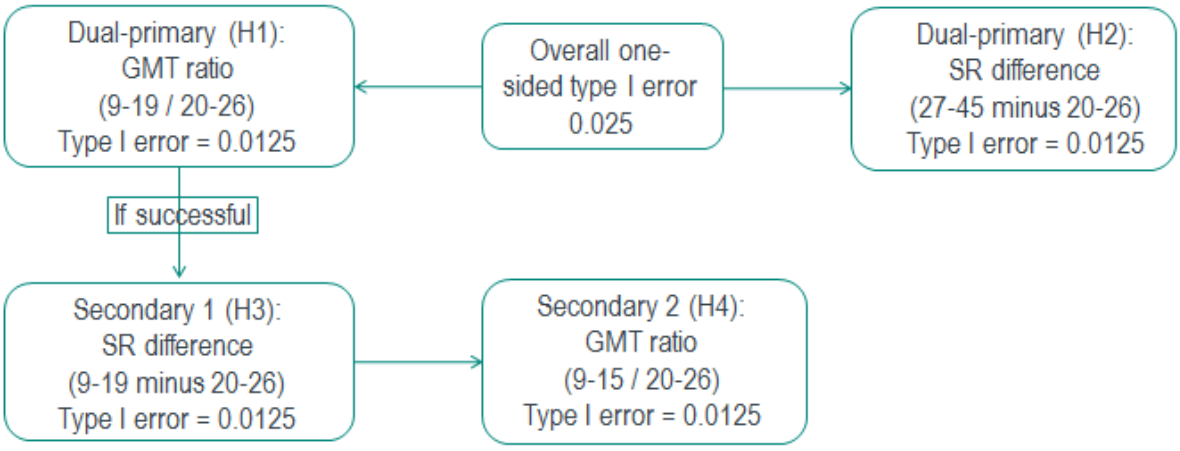


Figure 2 Multiple Strategies to Control Overall Type One Error Rate

For the dual-primary hypotheses (H1 and H2), Bonferroni method is used to control overall one-sided type I error at level of 0.025. Each of the dual-primary hypotheses has a 0.0125 one-sided type I error. The study would be successful if either H1 or H2 are met. If H1 is not met then no further testing (H3, H4) will be completed.

Fix sequence testing strategy is used to control multiplicity between dual-primary hypothesis (H1) and secondary hypotheses (H3 and H4). The testing order is as follows: H1 (GMT, 9-19yr vs.20-26yr) will be tested firstly and if H1 wins H3 (seroconversion percentages, 9-19yr vs. 20-26yr) will then be tested; if H3 wins H4 (GMT, 9-15yr vs. 20-26yr) will be tested. Each one will be tested at a level of 0.0125. If anyone failed to reject null the subsequent ones would not be tested.

Furthermore, success is required on all 9 HPV types for hypotheses testing GMT and seroconversion percentages, so no multiplicity adjustment is needed to account for the multiple HPV types.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity

Approximately 1990 participants will be enrolled in the study with the following allocated sample sizes for each age group as: 690 participants in 9-19yr age group (460 in 9-15yr and 230 in 16-19yr), 650 participants in 20-26yr age group, and 650 participants in 27-45yr age group. The overall power to claim the study success based on the dual-primary hypotheses is >0.999.

Two dual-primary hypotheses (H1 and H2) and two secondary hypotheses (H3 and H4) are considered when determine overall sample size and the sample sizes allocated to each age group. The calculations are based on the following assumptions:

1) HPV Types 6, 11, 16, 18, 31, 33, 45, 52, 58 responses are identical in 9-15yr, 9-19yr, and 20-26yr age groups;

2) HPV Types 6, 11, 16, 18, 31, 33, 45, 52, 58 seroconversion percentages are identical in 9-19yr, 20-26yr, and 27-45yr age groups;

3) The overall percentages of participants not eligible for per-protocol analyses for each HPV type are 15% in 9-15yr age group, 9-19yr age group, 30% in 20-26yr and 27-45yr age groups which are calculated based on:

   - percentage of the participants are initially seropositive to each HPV type
   - expected attrition rate through 1 month post Dose 3 (Visit 10)
   - expected percentage of participants excluded due to vaccinations or serology samples out of range

4) The standard deviations of the natural logarithm of the Visit 10 titers are no more than 1.2 for each HPV type when expressed as mMU/mL, the unitage used in previous HPV vaccine studies;

5) Regarding to the dual-primary hypotheses (H1 and H2), Type I error will be controlled by Bonferroni Method, i.e. one-sided 0.0125 for each hypothesis.

The estimates of exclusion rates and standard deviation are based on the data from previous qHPV vaccine and 9vHPV vaccine studies.

The overall power to establish the non-inferiority of the dual-primary endpoints: (1) cLIA GMTs in 9-19 yr vs. 20-26 yr; and (2) cLIA seroconversion percentages in 27-45yr vs. 20-26yr will be at least 99.1% and 92.9% respectively, at a level of 0.0125.

The overall power to establish the non-inferiority of the secondary endpoints: (1) cLIA seroconversion percentages in 9-19yr vs. 20-26yr and (2) cLIA GMTs in 9-15yr vs. 20-26y will be at least 98.4% and 95.8% respectively, at a level of 0.0125.

The detailed sample size and power results for immunogenicity endpoints are presented in Table 6, Table 7, and Table 8 by age groups.

Table 6 Power for Non-Inferiority Comparison in 9-19yr Group vs. 20-26yr Group

GMT ratio (Dual-primary, H1)					
Antigen	Assumed SD	Enrolled Sample Size (9-19yr/20-26yr)	Effective Sample Size (9-19yr/20-26yr)	Power	Overall Power†
Each HPV Type	1.2	690/650	586/455	0.999	0.991
Seroconversion percentage difference (Secondary, H3)					
Antigen	SR	Enrolled Sample Size (9-19yr/20-26yr)	Effective Sample Size (9-19yr/20-26yr)	Power	Overall Power†
Each HPV Type	98%	690/650	586/455	0.998	0.984

Note: Non-inferiority margin for GMT ratio is 0.67; non-inferiority margin for seroconversion rate is -5%.

† Overall power is calculated by multiplying the power for each HPV type.

Table 7 Power for Non-Inferiority Comparison in 9-15yr Group vs. 20-26yr Group

GMT ratio (Secondary, H4)					
Antigen	Assumed SD	Enrolled Sample Size (9-15yr/20-26yr)	Effective Sample Size (9-15yr/20-26yr)	Power	Overall Power†
Each HPV Type	1.2	460/650	391/455	0.995	0.958

Note: Non-inferiority margin for GMT ratio is 0.67.

† Overall power is calculated by multiplying the power for each HPV type.

Table 8 Power for Non-Inferiority Comparison in 27-45yr Group vs. 20-26yr Group

Seroconversion percentage difference (Dual-primary, H2)					
Antigen	SR	Enrolled Sample Size (27-45yr/20-26yr)	Effective Sample Size (27-45yr/20-26yr	Power	Overall Power†
Each HPV Type	98%	650/650	455/455	0.992	0.929

Note: Non-inferiority margin for seroconversion percentage is -5%;

† Overall power is calculated by multiplying the power for each HPV type.

The original GMT values are log transformed before analysis. As such, the CI for the means and the non-inferiority margin will be constructed on the natural log scale. The calculations are based on two-sample t-test and are carried out using PASS 2008. The minimum criterion for success is that the lower bound of two-sided 97.5% CI of difference between natural-log-transformed GMTs > log (0.67). Given the assumed SD of the natural-log-transformed titers at 1 month post Dose 3, this may occur when the observed difference between treatment groups is approximately log (0.82) or larger.

The calculations of power and sample sizes for seroconversion percentages are based on an asymptotic method proposed by Miettinen and Nurminen (1985) [Miettinen, O. and Nurminen, M. 1985] and are carried out using PASS 2008. The minimum criterion for success is that the lower bound of two-sided 97.5% CI of difference > -5%. Given the assumed seroconversion percentage 98%, this may occur when the observed difference in response rates is approximately -3% or larger.

9.9.2 Sample Size and Power for Safety

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.

Across seven clinical studies in the 9vHPV vaccine program, 356 of 15,778 (2.3%) individuals who were administered vaccine and had safety follow-up reported a SAE; 0.044% (7 out of 15,778) reported at least one SAE determined to be vaccine related [Moreira, E. D., et al 2016].

Assuming that all 650 participants enrolled in this study will have safety follow-up, then there is a greater than 99.9% chance of observing at least one SAE; and 24.9% chance of observing at least one vaccine related SAE, on at least one of the 650 participants. If no vaccine-related SAEs are observed among the 650 participants, this study will provide 95% confidence that the underlying percentage of participants with vaccine-related SAE is <0.46% (1 in every 217 participants) among 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. 1934].

9.10 Subgroup Analyses

Age groups, 9-19yr, 20-26yr and 27-45yr will be subgroup factors for this study. Age group 9-15 yr will also be analyzed for the secondary immunogenicity and safety objectives.

9.11 Compliance (Medication Adherence)

Compliance is defined in this study as receipt of all scheduled study vaccinations. To summarize compliance, the numbers of participants who receive each vaccination will be tabulated. Compliance with the planned vaccination schedule (Visit 1, Visit 4 and Visit 8) will be described by histograms of actual intervals between vaccinations relative to the expected interval.

9.12 Extent of Exposure

As indicated in Section 8.1.11, each study participant is planned to be administered 0.5 mL of 9vHPV vaccine at each vaccination visit. Thus, each participant is expected to be administered a total of 1.5 mL of 9vHPV vaccine.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are

reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD 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.

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

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 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/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF 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.

Committees Structure

Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) regarding the study.

Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (see Section 9.7 Interim Analyses) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

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 GCP (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 GCP); 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 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 any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

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.

10.2 Appendix 2: Contraceptive Guidance and Pregnancy Testing

Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described Table 9 in consistently and correctly from Day 1 through 1 month post Dose 3 (Visit 10).

Table 9 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (i.e., when used consistently and correctly). b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

All female participants of childbearing potential will have a urine or serum pregnancy testing (sensitive to 25 mIU/mL beta human chorionic gonadotropin [β-hCG]) performed at each vaccination visit (i.e. Visit 1, Visit 4, Visit 8) per the manufacturer's instructions.

The pregnancy testing results must be obtained prior to each study vaccination (on the day the participant is vaccinated). Any participant found to be pregnant at the Day 1 visit will not be allocated and will not participate in the study.

For enrolled participants who become pregnant after receiving one or two study vaccination, study visits and vaccination will be paused until resolution of the pregnancy (e.g. term, elective termination, spontaneous abortion). Study visits and study treatment in pregnant participants will be handled as described in Table 10.

Table 10 Guidelines for Pregnant Participants: Managing Study Visits and Study Vaccinations

Visit where pregnancy is detected	Action
Day 1 *(before first vaccination)*	• Do not enroll participant.
Between Day 1 and Visit 4 *(After study vaccine Dose 1 and before study vaccine Dose 2 was administered)*	• No scheduled visits (excluding VRC return visits) until resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion). • The Dose 2 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels. • The Dose 3 study vaccination should be administered 4 months after the Dose 2 study vaccination. • Visit 10 should be conducted 1 month after the Dose 3 study vaccination.
Between Visit 4 and Visit 8 *(After study vaccine Dose 2 and before study vaccine Dose 3 was administered)*	• No scheduled visits (excluding VRC return visits) until resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion). • The Dose 3 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels. • Visit 10 should be conducted 1 month after the Dose 3 study vaccination.
After Visit 8 *(After study vaccine Dose 3 was administered)*	• Continue with scheduled study visits during the pregnancy. • Safety follow-up will be conducted after resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion).

10.3 Appendix 3: 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. ● 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. ● 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. ● Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. ● New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. ● Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. ● Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. ● For all reports of overdose (whether accidental or intentional) with an associated AE, 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." ● 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. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● 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. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to Section 8.4.5 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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● 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 ● 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 an SAE. 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 ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● 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.
e. Is a congenital anomaly/birth defect ● in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- 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.

  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, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor. ● Is a cancer; ● 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. ● The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination. ● 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. ● 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. ● 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 sufficient 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 within 7 days post each vaccination will be evaluated by maximum size**.

Assessment of causality

- Did the Sponsor's product cause the AE?
  - The determination of the likelihood that the Sponsor's product caused the AE 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 initialled 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 AE 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 AE:
    - **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 AE 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 IRB/IEC.

- **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 CRFs/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 AEs, SAEs, 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 8.4.1 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 EDC 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 EDC 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 EDC 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. ● 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. ● 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. ● Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

10.4 Appendix 4: Country-specific Requirements

China Food and Drug Administration (CFDA)'s Criteria on Assessment of Toxicity of Adverse Events

Guideline of the Grading Standards for Adverse Events Toxicity in Clinical Trials on Prophylactic Vaccines

Foreword

Vaccines are a class of special drugs usually used in healthy population to prevent diseases. Healthy subjects are selected for the clinical trials at different stages on the majority of prophylactic vaccines, and most prophylactic vaccines are used in healthy children. Therefore, safety concerns in the process of clinical studies of prophylactic vaccines are particularly important, and the requirements should be higher than those for general therapeutic drugs.

Standardized standards for the evaluation and grading of adverse events have been gradually widely used in the evaluation of safety of therapeutic drugs in patients with specific diseases, but these grading standards apply to patients who may experience adverse events mild, moderate or severe clinical or laboratory abnormalities in the disease process, so the parameters may not be suitable for healthy volunteers. The aim of this guideline in formulating grading standards for the adverse events of prophylactic vaccines is to minimize the risks for healthy subjects in clinical trials. The defined values of parameters adopted in such adverse events grading standards are based on experience obtained from clinical trials on already marketed vaccines and information that has been made public in combination with consideration of the current reality of China.

1. Overview

This Guideline applies to innovative prophylactic vaccines, and is applicable to the evaluation of severity of clinical and laboratory abnormalities (i.e. strength of adverse reactions) occurring in clinical trials in which the subjects are healthy adults and adolescents. Meanwhile, it can serve as the unblinding standards stipulated in the design of clinical trials on general prophylactic vaccine, as well as the reference for whether to terminate clinical studies. In addition, the uniform adverse events grading standards provided by this guideline are conducive for comparison of safety data of prophylactic vaccines between different treatment groups in the same clinical trial or between different clinical trials.

Clinical trials on prophylactic vaccines should strictly comply with the Good Clinical Practices (GCP) and meet relevant regulatory requirements. Management regulations require that adverse events occurring in clinical studies of vaccines should be inspected by related regulatory authorities and monitored by related main bodies (registration applicant, ethics committee and investigators), and appropriately reported for filing.

Investigators of clinical trials on prophylactic vaccines must timely, comprehensively, objectively and accurately record all safety observation values and related data for evaluation of adverse events or adverse reactions; registration applicants must monitor the entire process of clinical studies. These adverse reaction grading standards are conducive for safety monitoring, timely judgment and appropriate reporting as required.

The aim of this Guideline and guidelines related to clinical trials on vaccines that have been issued are to provide references for the evaluation of safety of prophylactic vaccines for clinical trials, and the classification and grading standards for adverse reactions here provide supplements to the integrity of safety data in clinical studies.

2. Basic Contents

The grading indicators for adverse reactions in clinical trials on prophylactic vaccines provided by this Guideline include two parts (see details in the toxicity grading table). One part is clinical indicators (local reactions, systemic reactions, vital sign measurements), and the other part is laboratory indicators (blood chemistry, hematology and urinalysis), but not all safety indicators to be observed in clinical trials on prophylactic vaccines have been covered herein. For some special vaccines in the process of development, additional monitoring indicators may need to be added, or the specific defined values of parameters in the tables should be modified. For example, extra parameters are based on safety suggestions in pre-clinical toxicological studies or experience from previously marketed similar products.

Appropriate observation indicators may be selected from the adverse reactions grading tables herein according to the characteristics of different vaccines for clinical trials, and reasonable safety monitoring and evaluation should be performed according to the respective characteristics of vaccines and disease prevalence.

(1) Adverse reactions grading tables

a. Clinical observation indicators (Table 11~Table 13)

Table 11 Local Reactions Grading

Local reactions	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Pain	Does not affect activities	Affects activities or requires repeated use of non-narcotic analgesics	Affects activities or requires repeated use of narcotic analgesics	Emergency treatment or hospitalization
Skin and mucosa	Redness and itching	Diffuse, maculopapular rash, dryness, desquamation	Blisters, dampness, desquamation or ulceration	Peeling dermatitis, mucosal involvement, or erythema multiforme, or suspected Stevens-Johnsons syndrome
Induration *	<15 mm	15~30 mm	>30 mm	Gangrene or exfoliative dermatitis
Redness*	<15 mm	15~30 mm	>30 mm	Gangrene or exfoliative dermatitis
Swelling**	<15 mm and does not affect activities	15~30 mm or affects activities	>30 mm or restrains daily activities	Gangrene
Rash (injection site)	<15 mm	15~30 mm	>30 mm	

Local reactions	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Pruritus	Mild pruritus at the injection site	Moderate pruritus of the injection limb	Systemic pruritus	

* In addition to the grading and evaluation of local reactions by most directly measuring the diameter, the development of and changes in the measurements should also be recorded.

** The evaluation and grading of swelling should be based on the functional grades and actual measurements.

Table 12 Vital Signs Grading

Vital signs*	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Fever, axillary temperature*	37.1~37.5°C	37.6~39.0°C	>39.0°C	
Oral temperature **	37.7~38.5	38.6~39.5°C	39.6~40.5°C	>40°C
Tachycardia (beats/min)	101~115	116~130	>130	Emergency treatment or hospitalization due to arrhythmia
Bradycardia (beats/min)	50~54	45~49	<45	Emergency treatment or hospitalization due to arrhythmia
Hypertension (systolic blood pressure mmHg)***	141~150	151~155	>155	Emergency treatment or hospitalization due to severe hypertension
Hypertension (diastolic blood pressure mmHg)***	91~95	96~100	>100	Emergency treatment or hospitalization due to severe hypertension
Hypotension (systolic blood pressure mmHg) ***	85~89	80~84	<80	Emergency treatment or hospitalization due to hypotensive shock
Respiratory frequency (times/min)	17~20	21~25	>25	Requires intubation

* It is cited from China's Prophylactic Vaccination Manual. The subjects should be tested in a stationary state.

** Oral temperature; the subjects should not drink cold or hot beverage or smoke before the detection.

*** It is necessary to compare with baseline blood pressure value before the use of vaccines in order to determine blood pressure abnormalities for specific analysis.

Table 13 Systemic Reactions Grading

Systemic reactions	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Hypersensitivity	Itching without rash	Local urticaria	Extensive urticaria, angioedema	Severe hypersensitivity
Headache	Does not affect activities and require no treatment	Transient, slightly affects activities and requires treatment (repeated use of non-narcotic analgesics)	Significantly affects daily activities, with response to initial anesthetic treatment	Refractory, requires repeated anesthetic treatment. Emergency treatment or hospitalization
Fatigue, weakness	Normal activities were weakened for<48, and it does not affect activities	Normal activities were weakened by 20%~50% for >48 hours, and it slightly affects activities	Normal activities were weakened by>50%, and it significantly affects daily activities, making the subject unable to work	The subject cannot take care of himself/herself. Emergency treatment or hospitalization
Nausea, vomiting	Once to twice per 24 hours, normal intake, does not affect activities	2~5 times/24 hours, significantly decreased intake or restrained activities	> 6 times within 24 hours, no significant intake, requires intravenous infusion	Requires hospitalization or nutrition through other means due to hypotensive shock
Diarrhea	Mild or transient, loose stool 2~3 times/day, or mild diarrhea lasting < 1 week	Moderate or continuous, 4~5 times/day, or diarrhea lasting > 1 week	Watery stool > 6 times/day, or bloody diarrhea, orthostatic hypotension, electrolyte imbalance, requires intravenous infusion > 2L	Hypotensive shock, requires hospitalization for treatment
Myalgia	Does not affect daily activities	Muscle tenderness not at the injection site, slightly affects daily activities	Severe muscle tenderness, significantly affects daily activities	Significant symptoms, muscle necrosis, requires emergency treatment or hospitalization
Cough	Transient, does not require treatment	Persistent cough, and treatment is effective	Paroxysmal cough which cannot be controlled by treatment	Emergency treatment or hospitalization
Other discomfort or clinical adverse reactions (according to the corresponding determination standards)	Does not affect activities	Slightly affects activities and does not require drug treatment	Significantly affects daily activities and requires drug treatment	

b. Laboratory indicators (Table 14~Table 16)

Since all laboratory indicators as reference standards must be determined according to the stipulated normal values, the range of stipulated normal values should be provided to prove their reasonableness and feasibility. The following indicators are for reference only.

Table 14 Blood Chemistry Measurements Grading

Serum	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Liver function—elevated ALT and AST caused by influencing factors	1.25~2.5 ×ULN*	2.6~5 ×ULN	5.1~10 ×ULN	>10×ULN
Creatinine	1.1~1.5×ULN	1.6~3.0×ULN	3.1~6×ULN	>6×ULN
BUN	1.25~2.5×ULN	2.6~5×ULN	5.1~10×ULN	>10×ULN
Bilirubin: elevated due to influencing factors, but functional test proves normal	1.1~1.5×ULN	1.6~2.0×ULN	2.0~3.0×ULN	>3.0×ULN
Bilirubin: elevated due to influencing factors accompanied by elevated indicators for liver function test	1.1~1.25×ULN	1.26~1.5×ULN	1.51~1.75×ULN	>1.75×ULN
Pancreatic enzymes—amylase, lipase	1.1~1.5×ULN	1.6~2.0×ULN	2.1~5.0×ULN	>5.0×ULN
CPK-mg/dL	1.25~1.5×ULN	1.6~3.0×ULN	3.1~10×ULN	>10×ULN

*"ULN": Refers to the upper limit of normal

Table 15 Hematology Measurements Grading

Blood	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Hemoglobin (female) (g/dL)	12.0~13.0	10.0~11.9	8.0~9.9	<8.0
Hemoglobin (female) and changes (gm/dL) compared to before trial	Growth~1.5	1.6~2.0	2.1~5.0	>5.0
Hemoglobin (male) (g/dL)	12.5~14.5	10.5~12.4	8.5~10.4	<8.5
Hemoglobin (male) and changes (gm/dL) compared to before trial	Growth~1.5	1.6~2.0	2.1~5.0	>5.0

Blood	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Leukocytosis (number/mm^3)	>13,000/mm^3	13,000~ 15,000/mm^3	15,000~ 30,000/mm^3	>30,000
Leukopenia (number/mm^3)	2500~3500	1500~2499	1000~1499	<1000
Clotting time—prolongation caused by influencing factors	1.0~1.10×ULN	1.11~1.20×ULN	1.21~1.25×ULN	>1.25×ULN
Partial thromboplastin time—prolongation caused by influencing factors	1.0~1.2×ULN	1.21~1.4×ULN	1.41~1.5×ULN	>1.5×ULN

"ULN": Refers to the upper limit of normal

Table 16 Urinalysis Measurements Grading

Urine	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Protein	Trace	1+	2+	>2+
Urine glucose	Trace	1+	2+	>2+
Blood cells (microscopy) number of red blood cells under each high-power field (rbc/hpf)	1~10	11~50	>50 or/and densely distributed red blood cells	Hospitalization for treatment or requires infusion of blood cell concentrates

Grading indicators in the tables above are not recommended for safety monitoring of healthy volunteers in clinical trials on all vaccines, and do not include all safety monitoring indicators. It is recommended to select monitoring indicators to be used in subjects in clinical trials on the corresponding prophylactic vaccines.

Whereas some physiological indicators for healthy infants and young children are significantly different from those for adults, it is recommended to make appropriate adjustments to such indicators combined with the specific conditions of clinical trials for specific applications.

(2) General evaluation principles for the grading of adverse reactions

For clinical abnormalities not involved in the above grading tables, adverse reactions should be graded and evaluated according to the following standards:

Grade I, mild, short-term discomfort (<48 hours), requiring no medical treatment;

Grade II, moderate, mildly to moderately restrain daily activities, requiring no or only a little medical intervention;

Grade III, severe, significantly restrains daily activities, requiring care of daily life and medical treatment, or maybe hospitalization;

Grade IV, life-threatening, extremely restrains daily activities, significantly requiring care of daily life, medical treatment and hospitalization;

(3) Severe or life-threatening adverse reactions

In clinical studies of prophylactic vaccines, the strength of any clinical events identified by clinical physicians as severe or life-threatening should be considered as Grade IV, including seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse bruising, numbness or paralysis, acute psychosis, severe depression, etc.

The discovery of severe or rare adverse reactions usually requires clinical studies with large sample sizes, and sometimes such reactions need to be further evaluated after marketing. However, in pre-marketing clinical studies, the sample size should be enlarged as much as possible in order to find uncommon or rare severe adverse reactions. For vaccines whose primary applicable population is healthy individuals including infants and young children, their safety requirements are stricter than those for other drugs, and more cautious considerations should be taken into account. If necessary, clinical studies with safety observation indicators as the clinical evaluation endpoints may be carried out, and the minimal sample size should meet the statistical requirements.

The China Food and Drug Administration will make timely modifications and improvements to this Guideline according to the status of clinical studies of prophylactic vaccines.

10.5 Appendix 5: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
APaT	all participants as treated
ASC-H	atypical squamous cells – cannot exclude HSIL
ASC-US	atypical squamous cells – undetermined significance
ANPS	all type-specific naïve participants with serology
β-hCG	beta human chorionic gonadotropin
CAC	Clinical Adjudication Committee
CIN	cervical intraepithelial neoplasia
cLIA	competitive Luminex Immunoassay
CONSORT	Consolidated Standards of Reporting Trials
CPA	Conditions of Particular Attention
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
eCTA	exploratory Clinical Trial Application
CTFG	Clinical Trial Facilitation Group
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMT	geometric mean titer
9vHPV	9-valent human papillomavirus

Abbreviation	Expanded Term
qHPV	quadrivalent human papillomavirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVIG	intravenous gamma globulin
JRA	juvenile rheumatoid arthritis
NDA	New Drug Application
NIFDC	National Institutes for Food and Drug Control
NIMP	Non-Investigational Medicinal Product
PBNA	pseudovirion-based neutralization assay
PK	pharmacokinetic
PPI	per-protocol immunogenicity
SAC	Scientific Advisory Committee
SAE	serious adverse event
SIL	squamous intraepithelial lesion
SLE	systemic lupus erythematosus
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
UDS	urine drug screen
VaIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia

Abbreviation	Expanded Term
VLP	virus-like particle
VRC	vaccination report card
WOCBP	woman/women of childbearing potential

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