Official Protocol Title:	A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years
NCT number:	NCT03493542
Document Date:	13-Jan-2023

Title Page

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This protocol amendment is applicable only to China.

Protocol Title: A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years

Protocol Number: 213-03

Compound Number: V501

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
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Regulatory Agency Identifying Number(s):

IND NUMBER: To Be Determined

EudraCT NUMBER: Not Applicable

Approval Date: 13 January 2023

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
V501-213-03	13-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.
V501-213-02	07-DEC-2018	The primary reason for this amendment is to extend the duration of immunogenicity follow-up from 7 months to 60 months in participants aged 9 to 19 years.
V501-213-01	13-FEB-2018	Current literatures present the updated study procedures and methods of data analysis and ensure the consistency in the safety data collection throughout the protocol of this study.
V501-213-00	28-NOV-2017	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment [03]

Overall Rationale for the Amendment:

Sponsor underwent an entity name change and update the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 12.1 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.

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1 Synopsis

Protocol Title:

A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years

Short Title:

Immunobridging study of V501 in Chinese girls and young women

Objectives/Hypotheses and Endpoints:

In Chinese girls aged 9-19 years and young women aged 20-26 years (Base Stage):

Objective/Hypothesis	**Endpoint**
Primary	
• Objective: To demonstrate that administration of a 3-dose regimen of V501 induces non-inferior geometric mean titers (GMTs) for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18 in girls aged 9-19 years compared to young women aged 20-26 years. • Hypothesis (H1): 3-dose regimen of V501 induces non-inferior immune responses in girls aged 9-19 years who are seronegative at Day 1 to the relevant HPV type compared to young women aged 20-26 years who are seronegative at Day 1 to the relevant HPV type, as measured by anti-HPV 6, 11, 16, and 18 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 95% confidence interval of GMT ratio (girls vs. young women) be greater than 0.67 for each HPV type.)	• Competitive Luminex immunoassay (cLIA) GMTs to each of HPV 6, 11, 16, and 18 at 1 month post dose 3

Secondary	
• Key objective: To demonstrate that a 3-dose regimen of V501 induces non-inferior immune responses with respect to seroconversion percentages to HPV types 6, 11, 16, and 18 in girls aged 9-19 years compared to young women 20-26 years. • Hypothesis (H2): 3-dose regimen of V501 induces non-inferior immune responses in girls aged 9-19 years who are seronegative at Day 1 to the relevant HPV type compared to young women aged 20-26 years who are seronegative at Day 1 to the relevant HPV type, as measured by the percentage of participants who seroconvert to each of HPV types 6, 11, 16, and 18 by 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 95% confidence interval for the difference (girls minus young women) in seroconversion percentages be greater than -5 percentage points for each HPV type.)	• cLIA seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3
• Objective: To summarize immune responses (including GMTs and seroconversion percentages) to HPV types 6, 11, 16, and 18 assessed using HPV total IgG Luminex immunoassay (IgG LIA).	• IgG LIA GMTs and seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3
• Objective: To evaluate the safety and tolerability of V501 in girls aged 9-19 years and young women aged 20-26 years.	• Proportion of participants experiencing solicited injection-site adverse events (AEs) • Proportion of participants experiencing solicited systemic AEs • Proportion of participants experiencing serious adverse events (SAEs)

In Chinese girls 9 to 19 years of age (Extension Stage):	
Objective/Hypothesis	**Endpoint**
Primary	
• Objective: To evaluate persistence of immune responses induced by V501 in girls 9 to 19 years of age.	• cLIA GMTs and seropositivity percentages to each of HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60. • IgG LIA GMTs and seropositivity percentages to each of HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60.
Secondary	
• Objective: To evaluate the safety of V501 in girls 9 to 19 years of age.	• Proportion of participants experiencing SAEs.

Overall Design:

Study Phase	Phase 3
Clinical Indication	Prevention of HPV types 16- and 18-related cervical cancer, cervical intraepithelial neoplasia (CIN) 1/2/3, and cervical adenocarcinoma in situ among Chinese women.
Population	Healthy Chinese women
Study Type	Interventional
Type of Design	Single-arm, Single-site
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 62 months from the time the first participant signs the informed consent/assent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 766 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	All enrolled participants will intramuscularly receive a 3-dose regimen of V501 at Day 1, Month 2, and Month 6.
Duration of Participation	Each participant will participate in the study for approximately 7 months from the time the participant signs the informed consent/assent through the final contact in the base stage. Each participant will be receiving 3 doses of V501 and will be followed up to Month 7 in the base stage. Participants 9 to 19 years of age who have received 3 doses of V501 during the base stage will be eligible to participate in the extension stage and will be followed up to Month 60.

Study governance considerations are outlined in Appendix 1. A list of abbreviations used in this document can be found in Appendix 6.

2 Schedule of Activities (SoA)

Study Stage	Base Stage (Participants 9-26 years of age)						Extension Stage (Participants 9-19 years of age)					Notes
Study Visit Number/ Title	**Visit 1 Day 1 Vaccination 1**	**Visit 2 Month 1**	**Visit 3 Month 2 Vaccination 2**	**Visit 4 Month 3**	**Visit 5 Month 6 Vaccination 3**	**Visit 6 Month 7**	**Visit 7 Month 12**	**Visit 8 Month 24**	**Visit 9 Month 36**	**Visit 10 Month 48**	**Visit 11 Month 60**	
Scheduled Day	**1**	**32**	**62**	**93**	**184**	**215**	**366**	**732**	**1097**	**1462**	**1827**	
Scheduling Window:	**± 0 days**	**31 to 38 days after Vaccination 1**	**± 21 days**	**31 to 52 days after Vaccination 2**	**± 28 days**	**31 to 49 days after Vaccination 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Administrative Procedures												
Informed Consent/ Assent (Base Stage)	X											Written consent is obtained from participants aged 18-26 years. For participants aged 9-17 years, written consent is obtained from their parents(s) or legal guardian(s), and written assent will be obtained from the participant. Consent/assent must be obtained before any study procedures.
Informed Consent/ Assent (Extension Stage)						X						Written consent/assent is to be obtained at the Month 7 visit (if possible), or can be obtained at the Month 12 visit for participants eligible for the extension stage prior to any study procedure pertaining to the extension stage.
Assign Screening Number	X											

Study Stage	**Base Stage (Participants 9-26 years of age)**						**Extension Stage (Participants 9-19 years of age)**					**Notes**
Study Visit Number/ Title	**Visit 1 Day 1 Vaccination 1**	**Visit 2 Month 1**	**Visit 3 Month 2 Vaccination 2**	**Visit 4 Month 3**	**Visit 5 Month 6 Vaccination 3**	**Visit 6 Month 7**	**Visit 7 Month 12**	**Visit 8 Month 24**	**Visit 9 Month 36**	**Visit 10 Month 48**	**Visit 11 Month 60**	
Scheduled Day	**1**	**32**	**62**	**93**	**184**	**215**	**366**	**732**	**1097**	**1462**	**1827**	
Scheduling Window:	**± 0 days**	**31 to 38 days after Vaccination 1**	**± 21 days**	**31 to 52 days after Vaccination 2**	**± 28 days**	**31 to 49 days after Vaccination 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Review Inclusion/ Exclusion Criteria (Base stage)	X											
Review Inclusion/ Exclusion Criteria (Extension stage)						X						Eligibility for participation into extension stage will be reviewed on the same day of written consent/assent for Study Extension.
Participant Identification Card	X											

Study Stage	Base Stage (Participants 9-26 years of age)						Extension Stage (Participants 9-19 years of age)					Notes
Study Visit Number/ Title	**Visit 1 Day 1 Vaccination 1**	**Visit 2 Month 1**	**Visit 3 Month 2 Vaccination 2**	**Visit 4 Month 3**	**Visit 5 Month 6 Vaccination 3**	**Visit 6 Month 7**	**Visit 7 Month 12**	**Visit 8 Month 24**	**Visit 9 Month 36**	**Visit 10 Month 48**	**Visit 11 Month 60**	
Scheduled Day	**1**	**32**	**62**	**93**	**184**	**215**	**366**	**732**	**1097**	**1462**	**1827**	
Scheduling Window:	**± 0 days**	**31 to 38 days after Vaccination 1**	**± 21 days**	**31 to 52 days after Vaccination 2**	**± 28 days**	**31 to 49 days after Vaccination 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Medical History/ New Medical Condition	X	X	X	X	X	X	X	X	X	X	X	**Base stage:** At Day 1, medical history for 1 year prior to Day 1 is collected. After Day 1, new conditions not already recorded as medical history or adverse events are collected. For the participants who have had sexual intercourse, sexual history, lifetime gynecologic history, pregnancy history, and method of contraception are also collected at Day 1. After Day 1, sexual activity/current method of contraception is collected at Month 2, Month 6, and Month 7. **Extension stage:** Only new medical conditions not already recorded as medical history or adverse events are to be collected.
Review Medications and Non-Study Vaccination	X	X	X	X	X	X	X	X	X	X	X	**Base stage:** See Section 9.1.5. **Extension stage:** Only non-study HPV vaccine mistakenly administered during the extension stage will be collected.

Study Stage	**Base Stage (Participants 9-26 years of age)**						**Extension Stage (Participants 9-19 years of age)**					**Notes**
Study Visit Number/ Title	**Visit 1 Day 1 Vacci-nation 1**	**Visit 2 Month 1**	**Visit 3 Month 2 Vacci-nation 2**	**Visit 4 Month 3**	**Visit 5 Month 6 Vacci-nation 3**	**Visit 6 Month 7**	**Visit 7 Month 12**	**Visit 8 Month 24**	**Visit 9 Month 36**	**Visit 10 Month 48**	**Visit 11 Month 60**	
Scheduled Day	**1**	**32**	**62**	**93**	**184**	**215**	**366**	**732**	**1097**	**1462**	**1827**	
Scheduling Window:	**± 0 days**	**31 to 38 days after Vacci-nation 1**	**± 21 days**	**31 to 52 days after Vacci-nation 2**	**± 28 days**	**31 to 49 days after Vacci-nation 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Perform Physical Examination (Optional)	X											Optional, per investigator's discretion; perform if needed to assess inclusion/exclusion criteria
Pregnancy Testing (Urine or Serum)	X		X		X							Pregnancy testing must be performed prior to each study vaccination in woman participant of childbearing potential according to the manufacturer's instructions. The pregnancy test must be sensitive to 25 mIU/mL β-hCG. Results should be negative prior to vaccination.
Vital Signs Prior to Vaccination	X		X		X							Height and weight are to be measured at Day 1 only. Axillary temperature, pulse rate, respiratory rate, and blood pressure are to be taken prior to each vaccination. 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.

Study Stage	**Base Stage (Participants 9-26 years of age)**						**Extension Stage (Participants 9-19 years of age)**					**Notes**
Study Visit Number/ Title	**Visit 1 Day 1 Vaccination 1**	**Visit 2 Month 1**	**Visit 3 Month 2 Vaccination 2**	**Visit 4 Month 3**	**Visit 5 Month 6 Vaccination 3**	**Visit 6 Month 7**	**Visit 7 Month 12**	**Visit 8 Month 24**	**Visit 9 Month 36**	**Visit 10 Month 48**	**Visit 11 Month 60**	
Scheduled Day	**1**	**32**	**62**	**93**	**184**	**215**	**366**	**732**	**1097**	**1462**	**1827**	
Scheduling Window:	**± 0 days**	**31 to 38 days after Vaccination 1**	**± 21 days**	**31 to 52 days after Vaccination 2**	**± 28 days**	**31 to 49 days after Vaccination 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Assign Treatment/ Randomization Number	X											
Study Vaccine Administration	X		X		X							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. 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 of Day 1 vaccination.
Efficacy procedures												
Serum for Anti-HPV Antibody Testing	X					X	X	X	X	X	X	The serum collected at Day 1 for anti-HPV measurements must be collected before vaccination.

Study Stage	Base Stage (Participants 9-26 years of age)						Extension Stage (Participants 9-19 years of age)					Notes
Study Visit Number/ Title	**Visit 1 Day 1 Vaccination 1**	**Visit 2 Month 1**	**Visit 3 Month 2 Vaccination 2**	**Visit 4 Month 3**	**Visit 5 Month 6 Vaccination 3**	**Visit 6 Month 7**	**Visit 7 Month 12**	**Visit 8 Month 24**	**Visit 9 Month 36**	**Visit 10 Month 48**	**Visit 11 Month 60**	
Scheduled Day	**1**	**32**	**62**	**93**	**184**	**215**	**366**	**732**	**1097**	**1462**	**1827**	
Scheduling Window:	**± 0 days**	**31 to 38 days after Vaccination 1**	**± 21 days**	**31 to 52 days after Vaccination 2**	**± 28 days**	**31 to 49 days after Vaccination 3**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	**± 28 days**	
Safety procedures												
30-minute Post-Vaccination Observation Period	X		X		X							
Provide Vaccination Report Card (VRC) to Participant	X		X		X							
Review and Collect VRC data		X		X		X						Phone call contacts are to be conducted every week for each participant by study site personnel before the VRCs are returned. The main purpose of phone call visit is to remind the participant to record the VRC and answer any questions related to VRC from participants.
Clinical Follow-up for Safety	X	X	X	X	X	X	X	X	X	X	X	

3 Introduction

3.1 Study Rationale

Human papillomavirus (HPV) infection is a sexually transmitted disease. The incidence of HPV infection peaks soon after the onset of sexual activity. Therefore, an effective program to prevent HPV infection and disease through prophylactic immunization would ideally target individuals immediately prior to sexual contact. Preadolescents and adolescents represent an attractive target age group to implement HPV vaccination programs. However, direct efficacy evaluation of prophylactic HPV vaccines in preadolescents and adolescents aged 9-15 years is not feasible due to social, cultural, and legal constraints surrounding the notion of sexual activity among younger adolescents. In the MSD's HPV vaccine program, efficacy claims for the recombinant human papillomavirus quadrivalent (Types 6, 11, 16, 18) vaccine (V501) in young women aged 16-26 years were extended to preadolescents and adolescents based on the demonstration of similar safety and immunogenicity in the two populations.

For registration of V501 in China, two Phase 3 clinical trials were conducted, an immunogenicity study among Chinese girls and women aged 9-45 years and boys aged 9-15 years (PN030) and an efficacy study among Chinese women aged 20-45 years (PN041). These studies have demonstrated that V501 is highly effective and safe in Chinese women aged 20-45 years and is highly immunogenic and generally well tolerated in Chinese girls and women aged 9-45 years and boys aged 9-15 years. Although an ad-hoc analysis on the immunogenicity data of PN030 was performed which demonstrated the non-inferior immune responses in girls aged 9-19 years compared with 20-26 years old and 27-45 years old, the PN030 study was not originally designed to prove non-inferiority of immune responses in girls aged 9-19 years compared with women aged 20-45 years with limited sample size. Therefore, V501 was approved in China only for women aged 20-45 years. And Chinese regulatory authority requires a local clinical study to demonstrate the immunogenicity of V501 in girls aged 9-19 years is non-inferior to that of women aged 20-26 years. This is a mandatory post-marketing requirement from the local regulatory authority.

Thus, an immunobridging study is required to demonstrate that at 1 month post-vaccination, HPV 6, 11, 16 and 18 antibody responses induced by V501 in girls aged 9-19 years are non-inferior to those in women aged 20-26 years.

The main purpose of the Study Extension is to evaluate persistence of immune responses to V501 in Chinese girls aged 9 to 19 years. The global long-term follow-up study has demonstrated that administration of V501 to the younger age group induced durable immune responses and protection through 10 years post-vaccination. Durable immune responses to V501 up to 3.5 years post-vaccination was also demonstrated among Chinese women aged 9-45 years in an extension study of PN030, but the sample size was very limited for the younger age group, therefore it is important to generate more comprehensive long-term immunogenicity data of V501 in Chinese girls.

3.2 Background

Refer to the Investigator's Brochure (IB)/ approved labeling for detailed background information on V501.

3.2.1 Pharmaceutical and Therapeutic Background

V501 consists of highly purified virus-like particles (VLPs) of the L1 capsid polypeptide for the HPV 6, 11, 16, and 18 virus types.

Over 50% of sexually active adults become infected with HPV during their lifetime [Kotloff, K. L., et al 1998] [Koutsky, L. 1997]. HPV infection causes benign and malignant dysplastic disease, localized primarily in the anogenital area and aerodigestive tract, in both men and women [Paavonen, J. 2007] [Madkan, V. K., et al 2007] [Stamataki, S., et al 2007]. Persistent HPV infection significantly increases the risk of cervical and other anogenital cancers, and oropharyngeal cancers [Forman, D., et al 2012]. HPV disease is frequently multicentric (i.e., affecting more than one anatomic site). For instance, strong positive associations have been reported between vulvar and vaginal cancers and histories of anogenital warts and cervical neoplasia [Madsen, B. S., et al 2008]. Also, individuals with genital warts have an elevated long-term risk of anogenital cancers and head and neck cancers [Blomberg, M., et al 2012]. Similarly, high prevalence of anal and oropharyngeal HPV infection has been reported in women with abnormal cervical cytology [Crawford, R., et al 2011]. Overall, HPV is responsible for approximately 5% of the global cancer disease burden [Parkin, D. M. and Bray, F. 2006].

Over 90 HPV types have been identified [Alani, R. M. and Münger, K. 1998]. HPV 16 and 18 cause ~70% of high-grade cervical dysplasia (cervical intraepithelial neoplasia 2/3) cases and cervical and anal cancers, whereas HPV 6 and 11 cause >90% of genital warts [Koutsky, L. 1997]. HPV 6, 11, 16, or 18 are present in ~50% of low-grade cervical dysplasia (CIN 1) cases [Koutsky, L. 1997]. Therefore, a prophylactic vaccine that reduces infection with these 4 HPV types will greatly reduce the burden of HPV disease in men and women.

3.3 Benefit/Risk Assessment

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

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.

4 Objectives/Hypotheses and Endpoints

In Chinese girls aged 9-19 years and young women aged 20-26 years (Base Stage):

Objective/Hypothesis	**Endpoint**
Primary	
• Objective: To demonstrate that administration of a 3-dose regimen of V501 induces non-inferior geometric mean titers (GMTs) for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18 in girls aged 9-19 years compared to young women aged 20-26 years. • Hypothesis (H1): 3-dose regimen of V501 induces non-inferior immune responses in girls aged 9-19 years who are seronegative at Day 1 to the relevant HPV type compared to young women aged 20-26 years who are seronegative at Day 1 to the relevant HPV type, as measured by anti-HPV 6, 11, 16, and 18 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 95% confidence interval of GMT ratio (girls vs. young women) be greater than 0.67 for each HPV type.)	• Competitive Luminex immunoassay (cLIA) GMTs to each of HPV 6, 11, 16, and 18 at 1 month post dose 3

Objective/Hypothesis	Endpoint
Secondary	
• Key objective: To demonstrate that a 3-dose regimen of V501 induces non-inferior immune responses with respect to seroconversion percentages to HPV types 6, 11, 16, and 18 in girls aged 9-19 years compared to young women 20-26 years. • Hypothesis (H2): 3-dose regimen of V501 induces non-inferior immune responses in girls aged 9-19 years who are seronegative at Day 1 to the relevant HPV type compared to young women aged 20-26 years who are seronegative at Day 1 to the relevant HPV type, as measured by the percentage of participants who seroconvert to each of HPV types 6, 11, 16, and 18 by 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 95% confidence interval for the difference (girls minus young women) in seroconversion percentages be greater than -5 percentage points for each HPV type.)	• cLIA seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3
• Objective: To summarize immune responses (including GMTs and seroconversion percentages) to HPV types 6, 11, 16, and 18 assessed using HPV total IgG Luminex immunoassay (IgG LIA).	• IgG LIA GMTs and seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3

Objective/Hypothesis	**Endpoint**
• Objective: To evaluate the safety and tolerability of V501 in girls aged 9-19 years and young women aged 20-26 years.	• Proportion of participants experiencing solicited injection-site adverse events (AEs) • Proportion of participants experiencing solicited systemic AEs • Proportion of participants experiencing serious adverse events (SAEs)
Exploratory	
• Objective: To summarize immune responses (including GMTs and seroconversion percentages) to HPV types 6, 11, 16, and 18 assessed using pseudovirion-based neutralization assay (PBNA).	• PBNA GMTs and seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3
In Chinese girls 9 to 19 years of age (Extension Stage):	
Objective/Hypothesis	**Endpoint**
Primary	
• Objective: To evaluate persistence of immune responses induced by V501 in girls 9 to 19 years of age.	• cLIA GMTs and seropositivity percentages to each of HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60 • IgG LIA GMTs and seropositivity percentages to each of HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60
Secondary	
• Objective: To evaluate the safety of V501 in girls 9 to 19 years of age.	• Proportion of participants experiencing SAEs
Exploratory	
• Objective: To summarize persistence of immune responses to HPV types 6, 11, 16, and 18 assessed using PBNA in girls 9 to 19 years of age.	• PBNA GMTs and seropositivity percentages to each of HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60

5 Study Design

5.1 Overall Design

This is a single-arm, multi-site, open-label, immunogenicity, safety and tolerability study of V501 in Chinese girls aged 9-19 years and young women aged 20-26 years at the time of Day 1 vaccination. The study will evaluate whether V501 administered in girls aged 9-19 years has a non-inferior immunogenicity compared with V501 in young women aged 20-26 years as a comparative control for all the 4 vaccine HPV types.

A total of approximately 766 participants who meet eligibility will be enrolled. All enrolled participants will receive one dose of V501 under open-label conditions at the Day 1, Month 2, and Month 6 visits.

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

Serum samples will be obtained from each participant at Day 1 prior to vaccination and Month 7 (1 month post dose 3) for measurement of anti-HPV antibodies for HPV 6, 11, 16, and 18 in the base stage. For participants who will enter the extension stage, serum samples will be obtained at the time points of Month 12, Month 24, Month 36, Month 48, and Month 60 for measurement of anti-HPV antibodies.

A Vaccination Report Card (VRC) will be provided to each participant for recording all adverse events (AEs) within 30 days following each study vaccination. SAEs, cancers, overdoses, pregnancy events, lactation events, and infant SAEs will be collected during the entire period of study.

A pregnancy test will be performed prior to each study vaccination on all female participants of childbearing potential. Any participant with a positive pregnancy test at Day 1 will not be vaccinated and will not be allowed to participate in the study. Any Participant with a positive pregnancy test after Day 1 will not be vaccinated until pregnancy outcome. Pregnant participants who receive less than 3 study vaccinations during the study will be offered the possibility to complete the vaccination course. Pregnancies and any associated AEs will be followed to outcome.

The estimated duration of base stage will be approximately 9 months from the time the first participant signs the informed consent/assent until the last participant's last study-related phone call or visit. The final study visit of base stage will be Month 7.

Participants in the 9-19 years old group who have received 3 doses of V501 in the base stage will be eligible to participant in the extension stage. Participants who continue in the extension stage will be followed up to Month 60, which is the final visit for Study Extension.

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 serology assay result 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 Study SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Study Diagram

The study design is depicted in Figure 1.

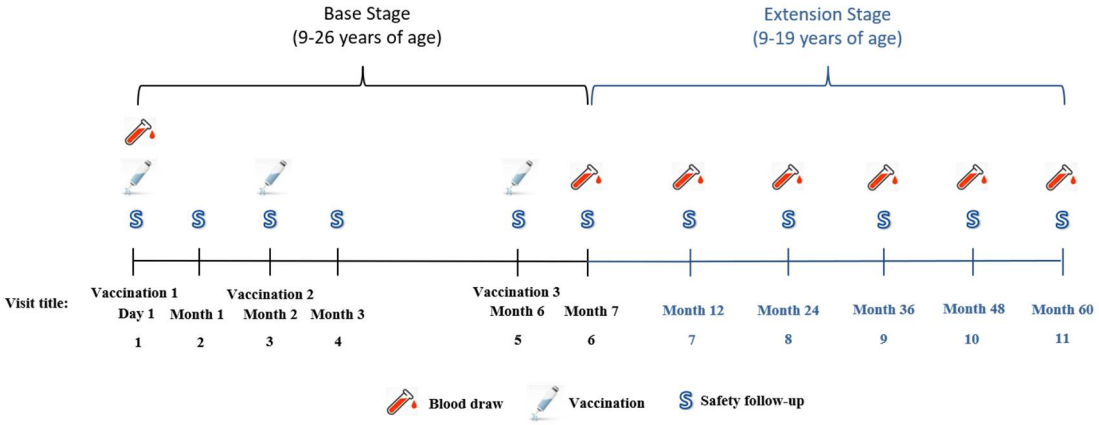

Figure 1 Study Diagram

5.2 Number of Participants

Approximately 766 participants will be enrolled as described in Section 10.9. Enrollment will be stratified in a 1:1 ratio between two age strata: 9-19 years and 20-26 years (see Section 7.3.1). Enrollment will be managed by investigator by limiting the total number of participants per each age group at each study site.

Participants 9 to 19 years of age who have received 3 doses of V501 in the base stage will be eligible to participate into the extension stage.

5.3 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent/assent form. The overall study ends when the last participant completes the last study-related phone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

5.3.1 Clinical Criteria for Early Study Termination

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

5.4 Scientific Rationale for Study Design

The purpose of this trial is to fulfill the post-approval requirement in China to conduct an immunobridging study in girls aged 9-19 years and young women aged 20-26 years. Study Extension is to generate more comprehensive long-term immunogenicity data of V501 in Chinese girls aged 9-19 years.

5.4.1 Rationale for Endpoints

5.4.1.1 Immunogenicity Endpoints

Anti-HPV 6, 11, 16, and 18 measured by competitive Luminex immunoassay (cLIA) will be analyzed as the primary indicator of immune responses post dose 3 to each vaccine component. cLIA is a standard assay to evaluate the immune responses to vaccination in HPV clinical programs.

Serum will be collected from all participants at Day 1 prior to study vaccination and Month 7. Serum samples collected at Day 1 will be used to determine participant who had an HPV infection prior to enrollment.

HPV total IgG Luminex immunoassay (IgG LIA) will be used as a secondary measurement, complementary to cLIA. IgG LIA GMTs and seroconversion percentages to the 4 vaccine HPV types will be summarized.

Pseudovirion-based neutralization assay (PBNA) developed by National Institutes for Food and Drug Control (NIFDC), will be used as an exploratory method to characterize the immune responses to the 4 vaccine HPV types. This method was required by the local authority which is the method recommended by WHO for anti-HPV measurement.

In the extension stage, serum samples will be obtained at Month 12, Month 24, Month 36, Month 48, and Month 60 for measurement of antibodies for HPV 6, 11, 16, and 18. The GMTs and seropositivity percentages measured by cLIA and IgG LIA methods will be used as primary immunogenicity endpoints, which is consistent with prior HPV studies. PBNA GMTs and seropositivity percentages to HPV 6, 11, 16, 18 will be the exploratory endpoints.

5.4.1.2 Safety Endpoints

The safety endpoints in this study were selected based on the product's safety profile demonstrated in prior clinical studies. A list of the safety endpoints to evaluate safety and tolerability in the study population is provided in Section 9.5.1 and 10.4.2.

5.5 Justification for Dose

The formulation and regimen of V501 are identical with prior global and local studies.

6 Study Population

Healthy girls between the ages of 9 and 19 years (inclusive) and healthy young women between the ages of 20 and 26 years (inclusive) will be enrolled in this study.

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

6.1 Inclusion Criteria

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

6.1.1 Inclusion Criteria for Base Stage

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 26 years and 364 days on the day of Day 1 vaccination.
3. A female participant is eligible to participate if she is not pregnant (see Appendix 2), and 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 Month 7 period, she should not have sexual intercourse with males without effective contraception, and that the use of the rhythm method, withdrawal, and emergency contraception are not acceptable methods per the protocol.

Informed Consent/Assent

4. (Participants aged 9-17 years only) Participant's parent or legal guardian provides written informed consent for the study. The participant provides written informed assent for the study.
5. (Participants aged 18-26 years only) Participant provides written informed consent for the study.

General

6. Participant agrees to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes.

6.1.2 Inclusion Criteria for Extension Stage

1. Participant was enrolled in the 9-19 years old group in the base stage.
2. Participant has received 3 doses of V501 during the base stage.
3. Participant and participant's legally acceptable representative (if applicable) provides written informed consent/assent for Study Extension.

6.2 Exclusion Criteria

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

The following exclusion criteria are only applicable for the base stage.

Participants enrolled in the 20-26 years old group will not participate in the extension stage, and participants enrolled in the 9-19 years old group who reported overdose or received non-study HPV vaccine during the base stage will be excluded from the extension stage.

Medical Conditions[†]

1. Participant has a fever (defined as 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).
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 is allergic to any vaccine component, including aluminum, yeast, or BENZONASETM (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).
4. Participant with known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
5. 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 reheumatoid arthritis (JRA), inflammatory bowel disease, or other autoimmune condition.
6. Participant has a history of splenectomy.
7. Participant has any condition which in the opinion of the investigator might interfere with the evaluation of the study objectives.
8. Participant has a history of recent or ongoing alcohol or other drug abuse. Alcohol abusers are defined as those who drink despite recurrent social, interpersonal, and legal problems as a result of alcohol use.
9. Participant has a history of a positive test for HPV.
10. Participant has any history of abnormal Pap test showing squamous intraepithelial lesion (SIL) or ASC-US, ASC-H, or biopsy showing cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ or cervical cancer.
11. Participant has a history of external genital wart, vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), vulvar cancer or vaginal cancer.
12. Participant has undergone hysterectomy (either vaginal or total abdominal hysterectomy).

[†] The history of medical conditions will be based on the self-report or medical chart provided by participant.

Prior/Concomitant Therapy

13. 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 steroids are considered eligible for the study.
14. Participant who has received immune globulin product (including RhoGAMTM [Ortho-clinical Diagnostics]) or blood-derived product within 6 months prior to Day 1 vaccination, or plan to receive any such product during Day 1 through Month 7 of the study.
15. Participant has received a marketed HPV vaccine, or has participated in an HPV vaccine clinical trial and has received either active agent or placebo.
16. Participant who has received inactivated or recombinant vaccines within 14 days prior to Day 1 vaccination or receipt of live vaccines within 21 days prior to Day 1 vaccination.

Prior/Concurrent Clinical Study Experience

17. Participant is concurrently enrolled in clinical studies of investigational agents.

Diagnostic Assessments

Not Applicable.

Other Exclusions

18. Participant with >4 lifetime sexual partners.
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. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this study.

6.3 Lifestyle Restrictions

No lifestyle restrictions are required.

6.4 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 or serious adverse events (SAE) meeting reporting requirements as outlined in the data entry guidelines.

6.5 Participant Replacement Strategy

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

7 Treatments

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

7.1 Treatments Administered

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

Table 1 Study Treatment

Study Treatment Name:	Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (Gardasil® [V501])
Dosage Formulation:	A single-dose prefilled syringe
Unit Dose Strength(s):	Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein
Dosage Level(s):	0.5-mL per dose administered at Day 1, Month 2, and Month 6
Route of Administration:	Intramuscular injection
Sourcing:	Provided locally by the Sponsor

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

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

7.2 Dose Modification

Not Applicable.

7.3 Method of Treatment Assignment

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

7.3.1 Stratification

A total of approximately 766 participants will be enrolled in a 1:1 ratio between two age strata: 9-19 years and 20-26 years. All enrolled participants will receive a 3-dose regimen of V501.

7.4 Blinding

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

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

Processes for preparation and administration of the study vaccine are described in Section 9.1.8. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

7.5.2 Handling, Storage and Accountability

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

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

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

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

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

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

7.6 Treatment Compliance

Interruptions from the protocol specified vaccination schedule (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.

7.7 Concomitant Therapy

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

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

If possible, the participant should not receive systemic corticosteroids, immunosuppressive therapies, immune globulin or blood-derived products during Day 1 through Month 7 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 recorded as described in Section 9.1.5.

7.7.1 Rescue Medications and Supportive Care

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

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

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

8 Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of vaccination regimen will still continue to participate in the study as specified in Section 2 and Section 9.10.2.

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

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 an 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 2 and Section 9.10.2 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.

8.2 Withdrawal from the Study

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

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

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

8.3 Lost to Follow Up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the pre-specified statistical data handling and analysis guidelines.

9 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The Investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant for the immunogenicity objectives over the duration of the base stage, including any extra assessments that may be required, will not exceed 20 mL.

The maximum amount of blood collected from each participant who will continue in the extension stage for the immunogenicity objectives over the duration of the extension stage, including any extra assessments that may be required, will not exceed 50 mL.

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

9.1 Administrative and General Procedures

9.1.1 Informed Consent/Assent

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

9.1.1.1 General Informed Consent/Assent

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

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

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

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

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

9.1.2 Inclusion/Exclusion Criteria

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

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information

(including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

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

9.1.4 Medical History

At the Day 1 visit, the participant's medical history for 1 year prior to Day 1 will be collected. For the participants who have had sexual intercourse, sexual history, lifetime gynecologic history, pregnancy history, and method of contraception will also be collected at the Day 1 visit. After the Day 1 visit, sexual activity and current method of contraception will be collected at the Month 2, Month 6, and Month 7 visits.

After the Day 1 visit, any new medical condition that has not been previously documented (either as adverse events or as medical history conditions) will be collected.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

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

- "Special medications" (corticosteroids, immunosuppressive therapies, immune globulins, and blood-derived products) from the year prior to Day 1 through Month 7.
- "Other medications" from 3 days prior to each study vaccination through 14 days after each study vaccination.
- "Non-study inactivated or recombinant vaccines" for 14 days prior to each study vaccination through 14 days after each study vaccination.
- "Non-study live vaccines" for 21 days prior to each study vaccination through 14 days after each study vaccination.

9.1.5.2 Concomitant Medications

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

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.

9.1.6 Assignment of Screening Number

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

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

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Although treatment is allocated by non-random assignment, the numbers assigned are called "treatment/randomization numbers". Treatment allocation will be managed by investigator. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

9.1.8 Treatment Administration

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

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

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.

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 of Day 1 vaccination.

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 testing (see Section 9.2.1). Pregnant participants should not be vaccinated (see Section 9.5.2 for management of study visits and study vaccinations for pregnant participants).

Section 9.10.1 provides additional information on other prerequisites for vaccination visits.

9.1.8.1 Preparation of Study Vaccine for Administration

Study vaccine is provided by the Sponsor in single-dose syringes containing sufficient volume to administer a 0.5-mL dose.

Study vaccine must be stored between 2°C to 8°C. Freezing destroys the study vaccine. If study vaccine freezes or is subjected to freezing temperature, or goes outside of the temperature ranges (2°C to 8°C), it should not be used. Refrigerator temperature logs should

be maintained at each vaccine storage site and storage temperatures should be monitored daily.

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. No dilution is required before administration. The vaccine syringe should be thoroughly mixed before administration by gently rolling the syringe between the palms of both hands for 30 seconds. 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.

9.1.8.2 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 25 gauge, for participants weighing < 90 kg; 1½-inch needle, 22 to 25 gauge, for participants weighing ≥ 90 kg. If the injection is given in the thigh, a 1½ -inch needle, 22 to 25 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.

9.1.8.3 Timing of Dose Administration

Study vaccine will be administered at the following time points: Day 1, Month 2 (Day 62), and Month 6 (Day 184) (See Section 2 - SoA).

Acceptable day ranges for vaccination visits are as follows:

- Dose 1: Day 1 (±0 days)
- Dose 2: Day 62 (± 21 days)
- Dose 3: Day 184 (± 28 days)

The Day 1 visit is defined as the day that the first study vaccination is given (i.e., the date when Dose 1 of V501 is injected).

9.1.9 Discontinuation and Withdrawal

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3.

- Month 7 is the final visit for Base Stage (exception: serum collection at Month 7 should not be done if the participant has not received all 3 scheduled doses of study vaccine and only safety information will be collected).
- Month 60 is the final visit for Extension Stage.

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

9.1.10 Participant Blinding/Unblinding

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

9.1.11 Calibration of Critical Equipment

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

Critical Equipment for this study includes:

- Refrigerator equipped with an appropriate temperature monitoring device to ensure the temperature is maintained at 2°C to 8°C for storage of study 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

9.1.12 Other Assessments

9.1.12.1 Physical Examinations and Vital Signs Prior to Study Vaccination

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

Height, weight, axillary temperature, pulse rate, respiratory rate, and blood pressure will be taken before study vaccination at Day 1.

Axillary temperature, pulse rate, respiratory rate, and blood pressure will also be taken before study vaccination at Month 2 and Month 6.

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.

Height, weight and axillary temperature will be documented in the data collection system and the other vital signs will be documented in the participant's chart.

9.2 Efficacy Assessments

9.2.1 Serum for Anti-HPV Antibody Testing

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

A 10-mL blood sample will be collected from each participant at each scheduled time point (Section 2- SoA) and serum will be separated for anti-HPV measurements.

9.2.2 Immunogenicity Measurements

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

The 9-valent cLIA assay is used to measure antibodies to HPV VLPs, serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58 before and after vaccination with the 9-valent HPV vaccine (V503) in V503 clinical program. The quadrivalent HPV (qHPV) cLIA was developed and used in prior clinical trials of V501. However, it has been replaced with 9-valent HPV cLIA, which is now used in V501 program. Therefore 9-valent HPV cLIA will be used in this study and only results of the 4 vaccine types (HPV 6, 11, 16, and 18) will be reported for the immunogenicity objective of the study.

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

A fixed type-specific cutoff for serostatus will be used in the assay. The cutoffs were derived by repeatedly testing a panel of positive and negative samples against the standard curve. Any sample with a value less than the cutoff will be considered seronegative. Sample with a value equal to or greater than the cutoff will be considered seropositive. Samples are read from a standard curve, corrected for dilution as needed, and reported in mMU/mL.

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

9-valent IgG LIA was designed to measure a broader subset of the total antibody concentrations to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, determined in a multiplexed, direct binding format by measuring the amount of VLP-specific IgG bound to VLP-microspheres on the Luminex platform. Yeast-derived VLPs are coupled to a set of 9 distinct fluorescent Luminex microspheres. Following incubation with human serum, fluorescent signal from an anti-human IgG detection antibody that binds directly to serum IgG and equally to each IgG subclass (1-4) is directly proportional to the individual's HPV type-specific anti-VLP IgG antibody levels. Results for the assay are reported as concentration of antibody in mMU/mL. However, only results of anti-HPV 6, 11, 16, and 18 will be reported for the immunogenicity objective of this study.

PBNA developed by NIFDC will be used in the exploratory analysis to characterize the immune responses to the 4 vaccine HPV types following study vaccination.

All the immunoassays listed above will also be used to evaluate the persistence of immune responses in the extension stage.

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

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 3 (Section 12.3).

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

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

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

From the time of allocation/randomization through 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 timeframes as indicated in Table 2.

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

Type of Event		**Reporting Time Period:** **Consent to Randomization/ Allocation**	**Reporting Time Period:** **Randomization/ Allocation through Protocol-Specified Follow-up Period**	**Reporting Time Period:** **After the Protocol Specified Follow-up Period**		**Timeframe to Report Event and Follow-up Information to SPONSOR:**
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
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

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

A VRC will be used by the participant to document any AEs within 30 days following each study vaccination.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy (if the participant received at least 1 vaccine dose) and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3. The investigator will make an assessment of intensity for each AE and SAE reported during the study based on Sponsor's criteria (See "Assessment of Intensity" in Appendix 3, Section 12.3) and CFDA's criteria (See Appendix 5 – Country-specific Requirements, Section 12.5).

9.3.4 Regulatory Reporting Requirements for SAE

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

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

Not applicable to this study.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the 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 female participants of childbearing potential will undergo urine or serum pregnancy testing prior to each study vaccination (See Section 2 - SoA). Participants found to be pregnant at Day 1 are not eligible to participate in the study (Section 6.1 - Inclusion Criteria). Participants of childbearing potential are instructed to use effective contraception through Month 7 (See Appendix 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 3 (Section 9.5.2 - Pregnancy Testing). 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 during the study must be reported as described in Section 9.3.1.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor. There are no ECIs for this study.

9.4 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.

9.5 Safety

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

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

9.5.1 Patient Reported Outcome

All participants will receive a VRC at the Day 1, Month 2, and Month 6 study vaccination visits. Using the VRC, the participant or the parent/legal guardian of the participant 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, for 14 days after each study vaccination; solicited injection-site AEs (injection-site redness, swelling, induration, pain, and pruritus), solicited systemic AEs (hypersensitivity, headache, fatigue, vomiting, nausea, diarrhea, myalgia, pyrexia, and cough), and all other AEs within 14 days (Day 1 to Day 15) after each study vaccination; all AEs from Day 16 to Day 31 after each study vaccination. The participant or the parent/legal guardian of the participant will also be asked to record concomitant medications and concomitant vaccinations within 14 days following each study vaccination on VRC.

The Day 1 VRC will be returned at the Month 1 visit. The Month 2 VRC will be returned at the Month 3 visit, and the Month 6 VRC will be returned at the Month 7 visit. However, phone call contacts will be conducted every week for each participant by study site personnel before the VRCs are returned. The main purpose of phone call contact is to remind the participant to record the VRC and answer any questions related to VRC from participants.

SAEs, cancer, overdose, pregnancy events (including non-randomized subjects with a positive Day 1 pregnancy test), lactation events and infant SAEs will be collected for the entire duration of study as instructed in the Section 9.3. In addition, new medical conditions not present at baseline and not reported as an adverse event will be collected throughout the study.

9.5.2 Pregnancy Testing

All women participants of childbearing potential will have a urine or serum pregnancy test (sensitive to 25 mIU/mL beta human chorionic gonadotropin [β-hCG]) performed at each vaccination visit (i.e. Day 1, Month 2, Month 6) per the manufacturer's instructions.

The pregnancy test results must be obtained prior to each study vaccination (on the day the participant is vaccinated). Any participant found to be pregnant at 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 3.

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

Visit where pregnancy is detected.	Action
Day 1	• Do not enroll participant.
Between Day 1 and Month 2	• No scheduled visits (excluding Month 1 visit) until resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion). • The Month 2 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels. • The Month 6 study vaccination should be administered 4 months after the Month 2 study vaccination. • The Month 7 visit should be conducted 1 month after the Month 6 study vaccination.
Between Month 2 and Month 6	• No scheduled visits (excluding Month 3 visit) until resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion). • The Month 6 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels. • The Month 7 visit should be conducted 1 month after the Month 6 study vaccination.
After Month 6	• 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).

9.5.3 Post-vaccination Observation Period (30 minutes)

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

9.5.4 Clinical Laboratory Assessments

Refer to Section 12.4, Appendix 4 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- All protocol-required laboratory assessments, as defined in Appendix 4, must be conducted in accordance with the manufacturer's instructions.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment, repeat assessments may be performed as determined by the investigator.

9.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Biomarkers

Biomarkers are not evaluated in this study.

9.9 Future Biomedical Research Sample Collection

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

9.10 Visit Requirements

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

9.10.1 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 Administrative Binder for a summary of deviations that require documentation in this study.

See the inclusion/exclusion criteria for specific restrictions at Day 1 (see Section 6.1 and 6.2). At the Month 2 and Month 6 study vaccination visits, study personnel should verify by questioning the participant and/or by examination that:

1. The participant has not had a fever, i.e. axillary temperature <37.1°C, within the 24-hour period prior to the Month 2 and Month 6 study vaccination visits.
2. The participant has not received any systemic (oral or parenteral) corticosteroids within 2 weeks prior to the Month 2 and Month 6 study vaccination visits.
3. The participant has not received a non-study inactivated or recombinant vaccine within 14 days prior to the Month 2 and Month 6 study vaccination visits or a non-study live vaccine within 21 days prior to the Month 2 and Month 6 study vaccination visits.

4. The participant is not pregnant as confirmed by a urine or serum pregnancy test.

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

9.10.2 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study vaccinations but continue in the study may attend study visits per the SoA (Section 2). However, serum will not be collected at the Month 7 study visit from participants who did not complete the 3-dose regimen of study vaccination.

10 Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes made to primary and/or key secondary 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. A full CSR will be generated for Base Stage and a supplemental statistical report will be generated for Extension Stage.

10.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 10.2-10.12.

Study Design Overview	A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years.
Treatment Assignment	It is a single-arm, open-label study. All enrolled participants will receive a 3-dose regimen of V501. Stratification factors are provided in Section 7.3.1.
Analysis Populations	Immunogenicity: Per protocol immunogenicity (PPI) population Safety: All Participants as Treated (APaT) population

Primary Endpoint(s)	Base stage: The primary endpoints are cLIA GMTs to each of HPV 6, 11, 16, and 18 at 1 month post dose 3. Extension stage: • cLIA GMTs and seropositivity percentages to each of HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60. • IgG LIA GMTs and seropositivity percentages to each of HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60.
Secondary Endpoints	Base stage: The key secondary endpoints are cLIA seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3. Extension stage: Proportion of participants experiencing SAEs.
Statistical Methods for Key Immunogenicity Analyses	Base stage: The primary hypotheses (H1) of non-inferiority of GMTs for each of HPV types 6, 11, 16, and 18 will be addressed by 4 one-sided tests of non-inferiority, with H_0: $GMT_1/GMT_2 \leq 0.67$ and H_a: $GMT_1/GMT_2 > 0.67$, at $\alpha=0.025$. GMT_1 and GMT_2 represent the GMTs at 1 month post dose 3 in girls aged 9-19 years and young women aged 20-26 years, respectively. Extension stage: GMTs and seropositivity percentages to the each of HPV types 6, 11, 16, 18 will be summarized and plotted.
Statistical Methods for Key Safety Analyses	All safety data will be summarized as frequencies and percentages for the two age groups in the base stage and for the 9-19 years old group in the extension stage.
Interim Analyses	No interim analysis is planned.

Multiplicity	Since success is required on all 4 vaccine HPV types for each of the primary (H1) and secondary (H2) hypotheses, no multiplicity adjustment will be made for the multiple tests within each hypothesis. In addition, no adjustments will be made between primary and secondary hypotheses. No multiplicity will be adjusted for the extension stage.
Sample Size and Power	The planned sample size is 766 participants. Success criterion of the study is the success on the primary hypothesis (H1) of the base stage; the overall power to claim the study success based on H1 is approximately 92% to demonstrate that girls aged 9-19 years is non-inferior to young women aged 20-26 years at an overall one-sided 2.5% alpha-level under the assumptions listed in Section 10.9.1. The sample size of the extension stage is based on the number of participants eligible for entering the extension stage.

10.2 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as a single-arm, open-label study, i.e., all participants in this trial will receive V501; participants, investigators, and Sponsor personnel will be aware of participant treatment after each participant is enrolled.

10.3 Hypotheses/Estimation

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

10.4 Analysis Endpoints

10.4.1 Immunogenicity Endpoints

Base stage:

The primary immunogenicity endpoints are cLIA GMTs to HPV 6, 11, 16 and 18 at 1 month post dose 3. The cLIA GMTs to HPV 6, 11, 16 and 18 at Day 1 will also be summarized.

The key secondary immunogenicity endpoints are the cLIA seroconversion percentages to each of HPV 6, 11, 16 and 18 at 1 month post dose 3. Seroconversion is defined as changing serostatus 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.

Anti-HPV 6, 11, 16, and 18 GMTs and seroconversion percentages measured by IgG LIA will be summarized as secondary objective of immunogenicity.

The exploratory endpoints for immunogenicity include GMTs and seroconversion percentages to each of HPV 6, 11, 16, and 18 measured by PBNA, which was developed by NIFDC.

Extension stage:

Anti-HPV GMTs and seropositivity percentages to HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60 measured by cLIA and IgG LIA will be summarized to describe persistence of serum antibody responses to the 4 vaccine HPV types.

The exploratory endpoints for immunogenicity include PBNA GMTs and seropositivity percentages to the 4 vaccine HPV types.

10.4.2 Safety Endpoints

Base stage:

Safety endpoints that will be used to evaluate the safety and tolerability of V501 will include proportions of participants who reported solicited injection-site AEs and solicited systemic AEs within Day 1 to Day 15 after study vaccination, and all AEs within Day 1 to Day 31 after study vaccination. In addition, SAEs occurring at any time during the base stage and maximum axillary temperatures reported from Day 1 to Day 5 after study vaccination will be summarized. Pregnancy outcomes and infants SAEs during the base stage will also be summarized.

Extension stage:

SAEs, pregnancy outcomes, and infants SAEs during the extension stage will be summarized.

10.5 Analysis Populations

10.5.1 Immunogenicity Analysis Populations

Per-Protocol Immunogenicity Population

The per-protocol immunogenicity (PPI) population will serve as the primary population for the analysis of immune response to each of the 4 HPV types (6, 11, 16, and 18). 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 2 – SoA.

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

(3) Have provided Month 7 serum sample within the visit window specified in Section 2 – SoA.

(4) At any time from Day 1 through Month 7, not meet any exclusion criteria that are deemed to potentially interfere with the evaluation of immune response to injections of V501.

All Type-Specific Naïve Participants with Serology (ANPS) Population

A supportive immunogenicity analysis will be carried out on the all type-specific naïve participants with serology 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, a participant must be seronegative for both HPV types 6 and 11.

(3) Have provided Month 7 serum sample.

Unlike the PPI population, this population will include participants who meet any exclusion criteria that were deemed to potentially interfere with the evaluation of immune responses to injections of V501. In addition, no day ranges on the timing of the vaccination and the collection of Month 7 serum sample will be applied.

10.5.2 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study vaccination and had clinical follow-up for safety.

10.6 Statistical Methods

10.6.1 Statistical Methods for Immunogenicity Analyses

Base stage:

V501 induced immune responses, as measured by cLIA anti-HPV 6, 11, 16 and 18 GMTs at 1 month post dose 3, will be analyzed separately. The statistical criterion for non-inferiority requires that the lower bound of two-sided 95% confidence interval of GMT ratio (girls vs. young women) being greater than 0.67 for each HPV type. The study will be considered a success for immunobridging if the non-inferiority criteria for GMTs are met for all 4 HPV types for the comparisons between girls aged 9-19 years vs. young women aged 20-26 years. Success on the seroconversion endpoints will provide further supporting evidence but is not required to declare study success. Anti-HPV 6, 11, 16, and 18 GMTs and seroconversion percentages measured by IgG LIA will be summarized as secondary objective of immunogenicity.

Immunobridging analysis

The primary hypotheses (H1) of non-inferiority of GMTs for each of HPV types 6, 11, 16 and 18 will be addressed by 4 one-sided tests of non-inferiority (one corresponding to each HPV type) conducted at the α=0.025 level (1-sided). For each HPV type, the hypotheses to be tested 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 GMTs 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. The statistical criterion for non-inferiority requires that the lower bound of two-sided 95% confidence interval of GMT ratio (9-19 years old vs. 20-26 years old) being greater than 0.67.

The secondary hypothesis (H2) of non-inferiority of seroconversion percentages for each of the vaccine HPV types (6, 11, 16 and 18) will be addressed by 4 one-sided tests of non-inferiority (one corresponding to each HPV type) conducted at the α=0.025 level (1-sided).

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 who had evaluable Month 7 serology result based on serum sample collected within 31 to 49 days post dose 3.

For each HPV type, the hypotheses to be tested are

$$H_0: p_1\text{-}p_2 \leq -0.05$$

$$H_a: p_1\text{-}p_2 > -0.05$$

where p_1 is the proportion of participants who seroconvert by 1 month post dose 3 in the 9-19 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 95% confidence interval for the difference (9-19 years old minus 20-26 years old) in seroconversion percentages being greater than -5 percentage points for each HPV type.

Table 4 summarizes the immunogenicity analyses for the base stage.

Table 4 Analysis Strategy for Immunogenicity Variables– Base Stage

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Objective				
Anti-HPV 6, 11, 16 and 18 cLIA GMTs at Month 7 (each type will be tested separately)	P	Point and 95% CI estimation as well as statistical testing will be performed by using an ANOVA model.	PPI	Observed data only
Anti-HPV 6, 11, 16 and 18 cLIA GMTs at Day 1 and Month 7	S	Point and 95% CI estimation will be provided by using an ANOVA model.	ANPS	Observed data only

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Secondary Objective				
cLIA % seroconversion to HPV 6, 11, 16, 18 by Month 7 (each type will be tested separately).	P	Point and 95% CI estimation as well as statistical testing of binomial proportion based on Miettinen &Nurminen method	PPI	Observed data only
Anti-HPV 6, 11, 16 and 18 IgG LIA GMTs at Day 1 and Month 7	S	Point and 95% CI estimation will be performed by using an ANOVA model.	PPI	Observed data only
IgG LIA % seroconversion to HPV 6, 11, 16, 18 by Month 7	S	Point and 95% CI estimation based on exact method	PPI	Observed data only

† P=Primary approach; S=Supportive approach.

‡ Statistical models are described in further detail below:

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

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

Extension stage:

Participants in the 9-19 years old group who have completed 3 doses of study vaccination will be followed up to Month 60 to evaluate the persistence of the serum antibody titers for each of HPV 6, 11, 16 and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60. Both cLIA and IgG LIA will be used to measure GMTs and seropositivity percentages.

Table 5 summarizes the immunogenicity persistence analyses for the extension stage.

Table 5 Analysis Strategy for Immunogenicity Variables – Extension Stage

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
cLIA GMTs to HPV 6, 11, 16 and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60	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 and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60	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 and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60	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 and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60	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
cLIA GMTs to HPV 6, 11, 16 and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60	S	Reverse cumulative distribution curve (RCD) at Month 12, Month 24, Month 36, Month 48, and Month 60	PPI	Observed data only

† P=Primary approach; S=Supportive approach.
CI = confidence interval; GMT = geometric mean titer; PPI = per-protocol immunogenicity.

PBNA results (GMTs and seropositivity percentages) will be summarized as exploratory objective. The results of PBNA may be summarized in a supplemental report upon its availability.

10.6.2 Statistical Methods for Safety Analyses

Base stage:

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

Summary statistics, counts and percentage without confidence interval, will be provided by age group. Proportions of participants with solicited injection-site AEs, solicited systemic AEs within 14 days following study vaccination will be given. Maximum axillary temperatures recorded on the VRC from Day 1 to Day 5 post-vaccination will be summarized.

In addition, proportions of participants with all injection-site and systemic AEs (including solicited and non-solicited AEs) within 30 days following study vaccination, and proportions of participants with SAEs through to Month 7 will also be summarized.

Both Sponsor's criteria (See "Assessment of Intensity" in Section 12.3 Appendix 3) and CFDA's criteria (See Section 12.5 Appendix 5 – Country-specific Requirements) will be applied to assess the intensity of adverse events. The incidence of greatest adverse event intensity reported by a participant based on both the two criteria will be tabulated for: all injection-site AEs and all systemic AEs within 30 days following any study vaccination.

All pregnancy outcomes and infant SAEs will be summarized.

Extension stage:

Summary statistics, including counts and proportion of participants with SAEs during the extension stage will be summarized for 9-19 years old participants.

In addition, pregnancy outcomes and infants SAEs during the extension stage will be summarized.

10.6.3 Summaries of Baseline Characteristics, Demographics, and other Analyses

Baseline characteristics, demographic variables, medical history, prior and concomitant therapies of the two age groups (9-19 years old vs. 20-26 years old) 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. The data of new medical conditions will be separately summarized for each base and extension stage.

10.7 Interim Analyses

No interim analyses are planned for this study.

10.8 Multiplicity

Base stage:

For immunobridging primary (H1) and secondary (H2) hypotheses, success is claimed if hypotheses for all 4 HPV types are met. Therefore, no multiplicity adjustment will be made to account for the multiple HPV types. In addition, no multiplicity adjustment will be made between primary and key secondary hypotheses.

Extension stage:

There is no multiplicity adjustment as there is no hypothesis for the extension stage.

10.9 Sample Size and Power Calculations

The sample size of the study is driven by the hypothesis for the base stage. The sample size in the extension stage is based on the number of eligible participants for entering the extension stage.

10.9.1 Sample Size and Power for Immunogenicity Analyses

Approximately 766 participants will be enrolled. Table 6 summarizes the power calculation for the primary endpoint of cLIA GMT ratio under each HPV type. Success criterion of the study is the success on the primary hypothesis (H1) of the base stage. The overall power of study success based on H1 is 91.6% to establish that the non-inferiority of the primary endpoint cLIA GMT in girls aged 9-19 years vs. in young women aged 20-26 years at an overall one-sided, 2.5% alpha-level, if the underlying GMT ratio is greater than 0.67 for each HPV type.

The calculations are based on the following assumptions:

1. The participants allocation ratio of 9-19 years old group vs. 20-26 years old group is 1:1;
2. The true GMT ratio between the two age groups is 1 for HPV types 6, 11, 16 and 18;
3. The standard deviation of the natural-log-transformed Month 7 titers is 1.2;
4. Non-inferiority margin for GMT ratio is 0.67;
5. The overall percentages of unevaluable participants are 27.3%, 23.1%, 27.3% and 23.1% for HPV Types 6, 11, 16, and 18, respectively. More specifically, 15%, 10%, 15% and 10% of the participants are initially seropositive to HPV Types 6, 11, 16, and 18, respectively; the expected attrition rate through the Month 7 time point is 10%; the expected percentage of participants excluded due to vaccinations or serology samples out of range is no more than 5%. Take HPV 6 as an example, 27.3% is calculated as (1-(1-0.15)*(1-0.1)*(1-0.05))*100%.

The estimates of exclusion rates and standard deviation are based on data from previous V501 studies.

Table 6 Power for cLIA GMT ratio based on 766 enrolled participants calculated from the secondary endpoint seroconversion rate

Antigen	Assumed SD	Enrolled participants	Effective sample size	Power
HPV 6	1.2	383	278	0.975
HPV 11	1.2	383	294	0.981
HPV 16	1.2	383	278	0.975
HPV 18	1.2	383	294	0.981
Overall power	0.916[†]			

[†]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 calculation is based on the two-sample t-test in 9-19 years old group and 20-26 years old group and carried

out using PASS 2008. The minimum criterion for success is that the lower bound of two-sided 95% CI of difference between natural-log-transformed GMTs > log(0.67). Given the assumed SD of the natural-log-transformed Month 7 titers, this may occur when the observed difference between treatment groups is approximately log(0.82) or larger.

For the key secondary endpoint, cLIA seroconversion rate, there is an overall 84.2% power to establish that girls aged 9-19 years is non-inferior to young women aged 20-26 years at an overall one-sided, 2.5% alpha-level, if the difference (girls minus young women) in seroconversion rates is greater than -5 percentage points for each HPV type. Table 7 shows the sample size and power calculations for different HPV type under various assumed seroconversion rates for the reference group (young women aged 20-26 years).

The calculations are based on the following assumptions:

1. The participants allocation ratio of 9-19 years old group vs. 20-26 years old group is 1:1;
2. The true seroconversion rates are the same between the two age groups for HPV types 6, 11, 16, and 18;
3. Non-inferiority margin for seroconversion rate is -5%;
4. The cLIA seroconversion rates for young women aged 20-26 years are 98.08%, 98.15%, 98.08% and 98.11% corresponding to HPV 6, 11, 16 and 18 respectively, using the results of China V501-PN030 study;
5. The overall percentages of unevaluable participants are 27.3%, 23.1%, 27.3% and 23.1% for HPV Types 6, 11, 16, and 18, respectively. More specifically, 15%, 10%, 15% and 10% of the participants are initially seropositive to HPV Types 6, 11, 16, and 18, respectively; the expected attrition rate through the Month 7 time point is 10%; the expected percentage of participants excluded due to vaccinations or serology samples out of range is no more than 5%.

Table 7 Sample size and power calculated based on cLIA seroconversion difference in proportion testing

Antigen	Seroconversion rates for young women aged 20-26 years	Enrolled subjects	Effective sample size	Power
HPV 6	98.08%	383	278	0.951
HPV 11	98.15%	383	294	0.966
HPV 16	98.08%	383	278	0.951
HPV 18	98.11%	383	294	0.964
Overall power	0.842[†]			

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

The estimates of exclusion rates are based on data from previous V501 studies. The calculation is based on an asymptotic method proposed by Miettinen and Nurminen (1985) [Miettinen, O. and Nurminen, M. 1985] and is carried out using PASS 2008. The minimum criterion for success is that the lower bound of two-sided 95% CI of difference > -5%. Given the assumed seroconversion rate of 98% in the 20-26 years old group, this may occur when

the observed difference in response rates is approximately -3% or larger.

10.9.2 Sample Size and Power for Safety Analyses

The probability of observing a specific AE in this study depends on the number of vaccinated participants with safety follow-up and the underlying incidence of that specific AE in the study population.

Across six clinical studies, 19 participants out of 3,420 (0.56%) 9-17-year old girls who received V501 reported serious AEs; 0.058% (2 out of 3,420) participants reported serious vaccine-related AEs *(*MSD data on file*)*.

Assuming that all 383 participants aged 9-19 years enrolled in this study will have safety follow-up, then there is a 88.2% chance of observing at least one serious AE; and 20.1% chance of observing at least one serious vaccine-related AE, on at least one of the 383 participants in the 9-19 years old group. If no serious vaccine-related AEs are observed among the 383 participants in the 9-19 years old group, this study will provide 95% confidence that the underlying percentage of participants with vaccine-related serious systemic AEs is <0.78% (one in every 128 participants) in the 9-19 years old group. This is based on calculation of a 1-sided 95% upper confidence limit of a binomial proportion using exact binomial method of Clopper and Pearson [Clopper, C. J. 1934].

10.10 Subgroup Analyses

Age group (9-19 years old and 20-26 years old) will be a natural subgroup factor for the base stage. No subgroup analysis will be conducted for the extension stage.

10.11 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 (Day 1, Month 2 and Month 6) will be described by histograms of actual intervals between vaccinations relative to the expected interval.

10.12 Extent of Exposure

As indicated in Section 9.1.8, each study participant is planned to be administered 0.5 mL of V501 at each vaccination visit (Day 1, Month 2, and Month 6). Thus, each participant is expected to be administered a total of 1.5 mL of V501 over a 6-month duration.

11 References

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12 Appendices

12.1 Appendix 1: Study Governance 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 institutional review board, ethics review committee (IRB/IEC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

Confidentiality of IRB/IEC Information

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

Publication Policy

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

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

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

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the

Sponsor and agrees not to submit any information about this study or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

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

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

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

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

Data Quality Assurance

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

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

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

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

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection,

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

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

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

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

Source Documents

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

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

Study and Site Closure

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

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

12.2 Appendix 2: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal 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 hormonal 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 non-hormonal 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 in Table 8 consistently and correctly during Day 1 through Month 7.

Table 8 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

WOCBP will have a urine or serum pregnancy test (sensitive to 25 mIU/mL β-hCG) prior to each study vaccination. Any participant found to be pregnant at the Day 1 visit will not be allocated and will not participate in the study (See Section 9.5.2).

12.3 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, 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 adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." ● 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 9.3.5 for protocol specific exceptions

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● 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 a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● 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, adverse events 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 Adverse Event case report forms/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 sufficiently discomfort and interferes with normal everyday activities. (for pediatric studies, definitely acting like something is wrong)
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities). **Injection site redness or swelling from the day of vaccination through Day 15 post-vaccination will be evaluated by maximum size**.

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a vaccine-induced effect?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study); or (3) Sponsor's product(s) is/are used only one time.)

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

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor’s product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event

before the initial transmission of the SAE data to the Sponsor.

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

Follow-up of AE and SAE

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

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

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

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

SAE Reporting to the Sponsor via Paper CRF
● If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor. ● 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).

12.4 Appendix 4: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory according to the manufacturer's instructions.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 and 6.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters
Screening Tests	• Urine or serum β human chorionic gonadotropin (β-hCG) pregnancy test (for all women participants of childbearing potential at all study vaccination visits)

12.5 Appendix 5: Country-specific Requirements

CFDA's Criteria on Assessment of Intensity of Adverse Events

Guideline of the Grading Standards for Adverse Events Intensity 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 (Appendix Table 1~3)

Appendix Table 1 Local Reactions Grading Table

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	
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.

Appendix Table 2 Vital Signs Grading Table

Vital signs*	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)	Potentially life-threatening (Grade IV)
Fever, axillary temperature*	37.1~37.5℃	37.6~39.0℃	>39.0℃	
Oral temperature **	37.7~38.5℃	38.6~39.5℃	39.6~40.5℃	>40℃
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.

Appendix Table 3 Systemic Reactions Grading Table

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 due to hypotensive shock or nutrition through other means
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 (Appendix Table 4~6)

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.

Appendix Table 4 Blood Chemistry Measurements Grading Table

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

Appendix Table 5 Hematology Measurements Grading Table

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
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

Appendix Table 6 Urinalysis Measurements Grading Table

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.

12.6 Appendix 6: Abbreviations and Trademarks

Abbreviation/Term	Definition
AE	adverse event
ANPS	all type-specific naïve participants with serology
APaT	all participants as treated
ASC-H	atypical squamous cells, cannot exclude HSIL
ASC-US	atypical squamous cells of undetermined significance
CFDA	China Food and Drug Administration
CI	confidence interval
CIN	cervical intraepithelial neoplasia
cLIA	competitive Luminex immunoassay
CONSORT	Consolidated Standards of Reporting Trials
CSR	clinical study report
ECI	events of clinical interest
eCRF	electronic case report form
GMTs	geometric mean titers
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
IB	Investigators Brochure
ICF	informed consent form
IAF	informed assent form
IgG LIA	total IgG Luminex immunoassay
IVIG	intravenous gamma globulin
JRA	juvenile reheumatoid arthritis
mAbs	monoclonal antibodies
mMU	milli-Merck Unites
NIFDC	National Institutes for Food and Drug Control
NSAE	non-serious adverse event
PBNA	pseudovirion-based neutralization assay
PE	phycoerythrin
PPI	per-protocol immunogenicity
qHPV	quadrivalent human papillomavirus
SAE	serious adverse event
SAP	statistical analysis plan
SIL	squamous intraepithelial lesion
SLE	systemic lupus erythematosus
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reactions
VaIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia
VLP	virus-like particle
VRC	vaccination report card
WOCBP	woman participant of childbearing potential