

Official Protocol Title:	A Phase 3, Open-label Clinical Study to Evaluate the Immunogenicity and Safety of 9vHPV Vaccine, in Japanese Boys and Girls, 9 to 15 Years of Age.
NCT number:	NCT04772534
Document Date:	19-Sep-2022

Title Page

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Protocol Title: A Phase 3, Open-label Clinical Study to Evaluate the Immunogenicity and Safety of 9vHPV Vaccine, in Japanese Boys and Girls, 9 to 15 Years of Age.

This protocol amendment is applicable only to Japan.

Protocol Number: 066-02

Compound Number: V503

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

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Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

EudraCT	2020-001170-29
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Approval Date: 19 September 2022

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2 (066-02)	19-SEP-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA.
Amendment 1 (066-01)	15 MAR 2021	Enrollment of girls aged 9 to 14 years old will be initiated prior to that of boys aged 9 to 15 years old to support earlier filing of the 2-dose girl arm data.
Original Protocol	23 NOV 2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

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

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations Throughout	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.

Section # and Name	Description of Change	Brief Rationale
10.1.1 Code of Conduct for Clinical Trials II. Scientific Issues / A. Trial Conduct	<p>Updated to include the following in each section:</p> <p>1. Trial Design</p> <p>All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups.</p> <p>2. Site Selection</p> <p>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.</p> <p>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.</p>	To align with updated Sponsor template text.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Open-label Clinical Study to Evaluate the Immunogenicity and Safety of 9vHPV Vaccine, in Japanese Boys and Girls, 9 to 15 Years of Age.

Short Title: Phase 3 Study for Immunogenicity and Safety of the 9vHPV Vaccine in Japanese Boys and Girls

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

This study will evaluate 2 different dose regimens of the 9-valent human papillomavirus (9vHPV) vaccine: a 3-dose regimen in Japanese boys aged 9 to 15 years old and a 2-dose regimen in Japanese boys and girls aged 9-14 years old. The base phase of the study (Period I) will assess the immunogenicity and safety of the 9vHPV vaccine through 7 months following the first dose. The extension phase of the study (Period II) will assess the safety and the antibody persistence to the 9vHPV vaccine through 30 months following the first dose.

Primary Objectives	Primary Endpoints
- To estimate percent seroconversion for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 in Japanese boys aged 9 to 15 years who received 3 doses of the 9vHPV vaccine	- Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
- To estimate percent seroconversion for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 in Japanese boys aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	- Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
- To estimate percent seroconversion for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 in Japanese girls aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	- Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
- To evaluate the safety and tolerability of the 9vHPV vaccine in Japanese boys aged 9 to 15 years who received 3 doses and Japanese boys and girls aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	- Solicited injection-site adverse events - Systemic adverse events - Serious adverse events

Secondary Objectives	Secondary Endpoints
- To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 including geometric mean titers (GMTs) in Japanese boys aged 9 to 15 years who received 3 doses of the 9vHPV vaccine	- Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
- To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 including GMTs in Japanese boys aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	- Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
- To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 including GMTs in Japanese girls aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	- Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	<ul style="list-style-type: none"> – Prevention of premalignant lesions and cancers affecting the cervix, vulva, vagina, anus and head and neck caused by vaccine HPV types – Prevention of genital warts (Condyloma acuminata) caused by vaccine HPV types – 2-dose (0, 6-12 months) schedule in 9 through 14 years old
Population	Japanese boys and girls aged 9 to 15 years old
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	No control
Study Blinding	Unblinded Open-label

Blinding Roles	No Blinding
Estimated Duration of Study	<p>The Sponsor estimates that the study will require approximately 40 months from the time the first participant's legally acceptable representative provides documented informed consent until the last participant's last study-related contact.</p> <p>For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.</p>

Number of Participants:

Approximately 300 participants will be allocated in three arms (approximately 100 participants will be allocated for each arm).

Intervention Groups and Duration:

Intervention Groups	<p>The study will enroll participants in three groups:</p> <ol style="list-style-type: none">3-dose in 9 to 15 years old boys2-dose in 9 to 14 years old boys2-dose in 9 to 14 years old girls <p>Detailed explanation for the age group differences between 3-dose regimen (9 to 15 years old) and 2-dose regimen (9 to 14 years old) is shown in Section 4.2.</p> <p>All participants will receive open-label 9vHPV vaccine (V503).</p> <table><tr><th>Arm Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Vaccination Regimen</th><th>Use</th></tr><tr><td>3-dose in 9 to 15 years old boys</td><td>V503 (9vHPV vaccine)</td><td>HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/ 20 mcg per dose</td><td>3 Doses</td><td>Intra-muscular</td><td>Day 1, Month 2 Month 6</td><td>Experimental</td></tr><tr><td>2-dose in 9 to 14 years old boys</td><td>V503 (9vHPV vaccine)</td><td>HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/ 20 mcg per dose</td><td>2 Doses</td><td>Intra-muscular</td><td>Day 1, Month 6</td><td>Experimental</td></tr><tr><td>2-dose in 9 to 14 years old girls</td><td>V503 (9vHPV vaccine)</td><td>HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/ 20 mcg per dose</td><td>2 Doses</td><td>Intra-muscular</td><td>Day 1, Month 6</td><td>Experimental</td></tr></table> <p>9vHPV=9-valent human papillomavirus, HPV=human papillomavirus, VLP=virus-like particle</p> <p>Other current or former names or aliases for study intervention are as follows: the 9vHPV vaccine, SILGARD®9 and GARDASIL™9.</p>	Arm Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Vaccination Regimen	Use	3-dose in 9 to 15 years old boys	V503 (9vHPV vaccine)	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/ 20 mcg per dose	3 Doses	Intra-muscular	Day 1, Month 2 Month 6	Experimental	2-dose in 9 to 14 years old boys	V503 (9vHPV vaccine)	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/ 20 mcg per dose	2 Doses	Intra-muscular	Day 1, Month 6	Experimental	2-dose in 9 to 14 years old girls	V503 (9vHPV vaccine)	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/ 20 mcg per dose	2 Doses	Intra-muscular	Day 1, Month 6	Experimental
Arm Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Vaccination Regimen	Use																							
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2-dose in 9 to 14 years old boys	V503 (9vHPV vaccine)	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/ 20 mcg per dose	2 Doses	Intra-muscular	Day 1, Month 6	Experimental																							
2-dose in 9 to 14 years old girls	V503 (9vHPV vaccine)	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/ 20 mcg per dose	2 Doses	Intra-muscular	Day 1, Month 6	Experimental																							
Total Number of Intervention Groups/ Arms	3 arms																												

Duration of Participation	Each participant will participate in the study for approximately 30 months from the time the participant's legally acceptable representative provides documented informed consent through the final contact. Each participant will be receiving total 3 doses at Day 1, Month 2 and Month 6, or total 2 doses at Day 1 and Month 6. After the completion of vaccination and Month 7 visit (Period I), each participant will be followed through Month 30 (Period II).
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Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

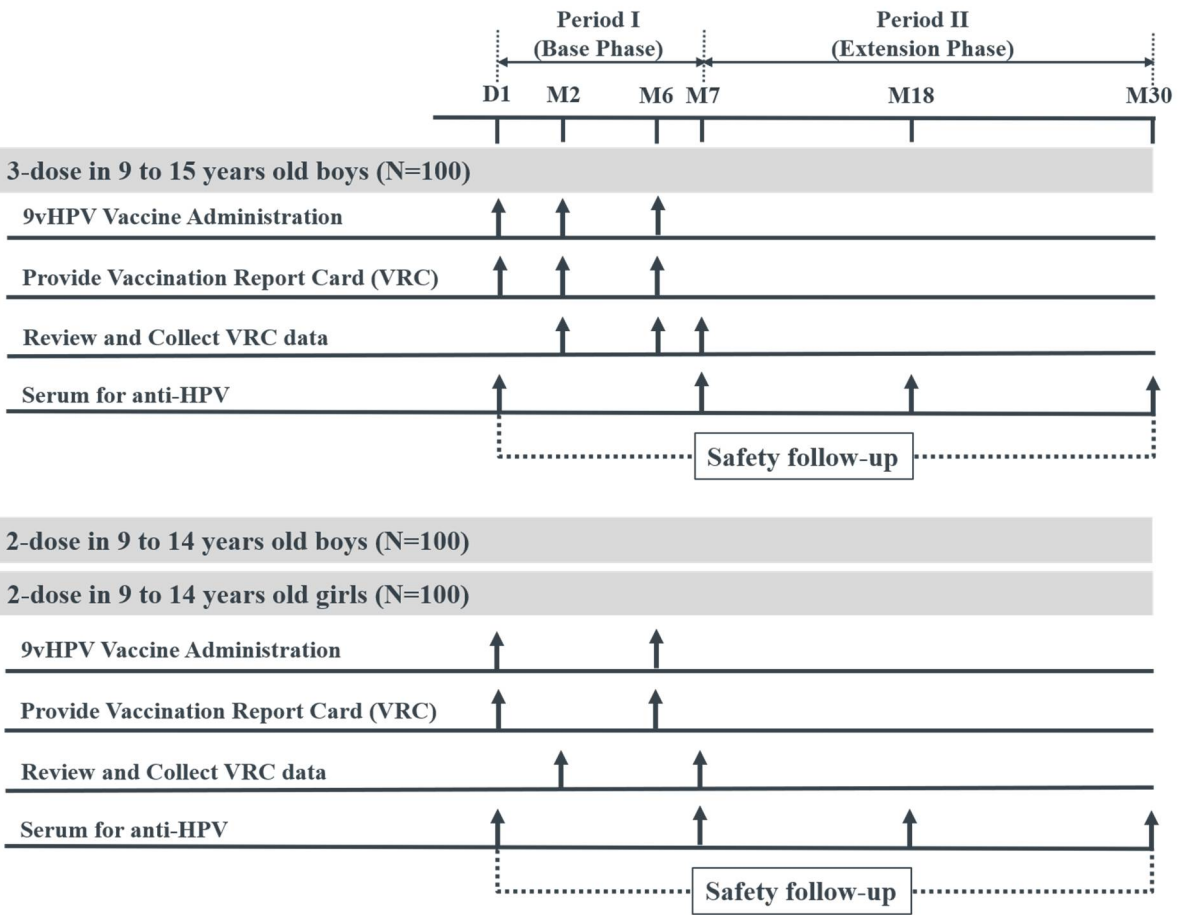


Figure 1 Study Design

1.3 Schedule of Activities

Schedule of Activities for 3-dose in 9 to 15 years old boys (vaccination at Day 1, Month 2 and Month 6)

Study Period	Period I				Period II		Notes
Visit Number	1	2	3	4	5	6	
Scheduled Day/Month	Day 1	Month 2	Month 6	Month 7	Month 18	Month 30	
Visit Window*		± 3 weeks	± 4 weeks	3 to 7 weeks after Month 6	± 4 weeks	± 4 weeks	To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Administrative Procedures							
Obtain Informed Consent/Assent	X						Obtain documented assent from the participant as far as possible
Obtain Informed Consent/Assent for Future Biomedical Research	X						Participation in future biomedical research is optional and consent must be obtained before collection of blood [deoxyribonucleic acid (DNA)] samples. Obtain documented assent from the participant as far as possible
Review Inclusion/Exclusion Criteria	X						
Assign Participant Identification Card	X						
Collect Medical History	X						
Update Medical History (new conditions not already recorded as medical history or adverse events)		X	X	X	X	X	
Review Prior/Concomitant Medication and Non-study Vaccination	X	X	X	X	X	X	See Section 6.5 for prerequisites for medications and non-study vaccines and Section 8.1.6 for data collection timeframe.
Vaccine Allocation/Randomization	X						

Study Period	Period I				Period II		Notes
Visit Number	1	2	3	4	5	6	
Scheduled Day/Month	Day 1	Month 2	Month 6	Month 7	Month 18	Month 30	
Visit Window*		± 3 weeks	± 4 weeks	3 to 7 weeks after Month 6	± 4 weeks	± 4 weeks	To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Clinical and Laboratory Procedures							
Measure Oral Temperature	X	X	X				Prior to each vaccination and Day 1 blood sample collection. Participants who have a fever (defined as an oral temperature of $\geq 37.5^{\circ}\text{C}$) within the 24-hour period prior to vaccination should not receive study vaccine and the vaccination visit must be rescheduled.
Record Height and Weight	X						Prior to vaccination
Physical Examination (optional, per investigator's discretion; perform if needed to assess inclusion/exclusion criteria)	X						
Blood Sample Collection (Serum for anti-HPV)	X			X	X	X	Serum for anti-HPV antibody testing must be collected before vaccination on Day 1
Blood Sample Collection (DNA) for Future Biomedical Research	X						Prior to vaccination from enrolled participants only (optional)
9vHPV Vaccine Administration	X	X	X				
30-minute postvaccination observation period	X	X	X				Observe participants for 30 minutes after each vaccination for immediate untoward effects
Provide Vaccination Report Card (VRC)	X	X	X				See Section 8.3.4 for data collected in VRC.
Review and Collect VRC data		X	X	X			Telephone contacts after 15 days from Day 1, Month 2 and Month 6, respectively to remind the participant's legally acceptable representative of completing VRC
Adverse Events Monitoring	X	X	X	X	X	X	

* Regarding protocol study visit windows, the following situations require consultation between the investigator and the Sponsor and written documentation of the collaborative decision: a participant needs to be scheduled earlier than the start of a visit window or the study site is considering skipping a visit.

Schedule of Activities for 2-dose in 9 to 14 years old boys and girls (vaccination at Day 1 and Month 6)

Study Period	Period I				Period II		Notes
Visit Number	1	2	3	4	5	6	
Scheduled Day/Month	Day 1	Month 2	Month 6	Month 7	Month 18	Month 30	
Visit Window*		± 3 weeks	± 4 weeks	3 to 7 weeks after Month 6	± 4 weeks	± 4 weeks	To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Administrative Procedures							
Obtain Informed Consent/Assent	X						Obtain documented assent from the participant as far as possible
Obtain Informed Consent/Assent for Future Biomedical Research	X						Participation in future biomedical research is optional and consent must be obtained before collection of blood (DNA) samples. Obtain documented assent from the participant as far as possible
Review Inclusion/Exclusion Criteria	X						
Assign Participant Identification Card	X						
Collect Medical History	X						
Update Medical History (new conditions not already recoded as medical history or adverse events)		X	X	X	X	X	
Review Prior/Concomitant Medication and Non-study Vaccination	X	X	X	X	X	X	See Section 6.5 for prerequisites for medications and non-study vaccines and Section 8.1.6 for data collection timeframe.
Vaccine Allocation/Randomization	X						
Clinical and Laboratory Procedures							
Measure Oral Temperature	X		X				Prior to each vaccination and Day 1 blood sample collection. Participants who have a fever (defined as an oral temperature of $\geq 37.5^{\circ}\text{C}$) within the 24-hour period prior to vaccination should not receive study vaccine and the vaccination visit must be rescheduled.
Record Height and Weight	X						Prior to vaccination

Study Period	Period I				Period II		Notes
Visit Number	1	2	3	4	5	6	
Scheduled Day/Month	Day 1	Month 2	Month 6	Month 7	Month 18	Month 30	
Visit Window*		± 3 weeks	± 4 weeks	3 to 7 weeks after Month 6	± 4 weeks	± 4 weeks	To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Physical Examination (optional, per investigator's discretion; perform if needed to assess inclusion/exclusion criteria)	X						
Urine Pregnancy Testing (females)	X		X				Pregnancy testing results should be negative prior to vaccination
Blood Sample Collection (Serum for anti-HPV)	X			X	X	X	Serum for anti-HPV antibody testing must be collected before vaccination on Day 1
Blood Sample Collection (DNA) for Future Biomedical Research	X						Prior to vaccination from enrolled participants only (optional)
9vHPV Vaccine Administration	X		X				
30-minute postvaccination observation period	X		X				Observe participants for 30 minutes after each vaccination for immediate untoward effects
Provide VRC	X		X				See Section 8.3.4 for data collected in VRC.
Review and Collect VRC data		X		X			Telephone contacts after 15 days from Day 1 and Month 6, respectively to remind the participant's legally acceptable representative of completing VRC
Adverse Events Monitoring	X	X	X	X	X	X	

* Regarding protocol study visit windows, the following situations require consultation between the investigator and the Sponsor and written documentation of the collaborative decision: a participant needs to be scheduled earlier than the start of a visit window or the study site is considering skipping a visit.

2 INTRODUCTION

2.1 Study Rationale

HPV infection causes benign and malignant dysplastic disease, localized primarily in the anogenital area and upper airway, in both males and females [Paavonen, J., 2007] [Madkan, V.K., et al 2007] [Stamatiki, S., et al 2007]. Persistent HPV infection significantly increases the risk of developing cervical, anogenital, and oropharyngeal cancers [Forman, D., et al 2012]. HPV disease is frequently multicentric (i.e., affecting more than one anatomic site). Individuals with genital warts due to HPV infection have an elevated long-term risk of developing anogenital and head and neck cancers [Blomberg, M., et al 2012].

Vaccination against HPV has been shown to aid in reducing the burden of HPV diseases in males and females. In contrast to cervical cancer in females, there is no widespread screening program for any HPV related cancers in males, making prophylactic vaccination a readily practical preventive measure for HPV diseases especially in males, in both developed and developing countries. An additional potential benefit of HPV vaccination in males is the generation of herd protection, which in turn could lead to a substantial reduction of HPV diseases in both males and females [Baseman, J.G., et al 2005]. Previous public health experience has shown that gender-restricted vaccination programs are substantially less effective than universal vaccination [WHO 2017]. Moreover, gender-neutral vaccination programs are expected to be more resilient to sudden drops in vaccine uptake [Elfström, K. M., et al 2016]. It is likely that the most effective means to reduce the burden of HPV disease using a safe and effective prophylactic vaccine is to vaccinate both males and females. In fact, gender neutral vaccination of HPV vaccine is increasing internationally, as over 40 countries or regions have adopted this approach as of March 2020.

HPV infection is transmitted via contact with an infected individual or a contaminated object and occurs most often during sexual activity. About sixty percent of sexual partners of infected individuals develop lesions a few weeks to 8 months after exposure [Oriel, J.D., 1971]. HPV is often acquired immediately after sexual debut and the risk of HPV infection is strongly correlated with the number of lifetime sexual partners [Xi, L.F., et al 1997] [Koutsky, L. 1997]. Males and females in their late teens and early twenties are at the highest risk for HPV infection, as early sexual activity is accompanied with a higher likelihood of having multiple sexual partners, thus increasing the risk of exposure to the virus. The incidence of HPV infection increases with age during the teen years and peaks in the early twenties; The probability of acquiring a new genital HPV infection is similar for sexually active males and females [Partridge, J.M., et al 2007]. The prevalence of anogenital HPV infection in men remains relatively consistent throughout their lifespan while women generally exhibit decreased prevalence with age [Giuliano, A.R., et al 2011]-2 [Palefsky, J.M., et al 2010] [Castle, P.E. et al 2005] [Schiffman, M., et al 2007]. Men exhibit diminished immune response to natural HPV infection, which may contribute to their higher HPV prevalence across ages [Giuliano, A.R., et al 2015] [Lu, B., et al 2012]. Therefore, HPV

vaccination in younger individuals can play a key role in prevention of HPV-related diseases both in males and females.

On the other hand, direct efficacy evaluation of prophylactic HPV vaccine in 9 to 15 years old subjects is not feasible because younger adolescents are generally not exposed to HPV. Thus, immunogenicity bridging by comparison of immunogenicity data between younger adolescents and adults is a reasonable means to extend the efficacy confirmed in adults to preadolescents and adolescents.

Global clinical studies have demonstrated that the quadrivalent HPV (qHPV) vaccine (V501) can prevent external genital and intra-anal persistent infection, anal precancers and anogenital warts caused by HPV 6, 11, 16 and 18 in males [Giuliano, A.R., et al 2011] [Palefsky, J.M., et al 2011] [Ferris, D.G., et al 2017]. A local clinical study conducted in Japanese males aged 16 to 26 years also demonstrated that qHPV vaccine prevents external genital and intra-anal persistent infection caused by HPV 6, 11, 16, and 18 [Mikamo, H., et al 2019]. In addition, high immune responses in younger males have been demonstrated by another immunogenicity bridging study in Japanese boys aged 9 to 15 years [Murata, S., et al 2019].

The 9vHPV vaccine (V503) was developed to cover the 4 HPV types addressed by qHPV vaccine and the addition 5 high-risk HPV serotypes (31, 33, 45, 52, and 58). HPV 6 and 11 which are responsible for approximately 90% of genital wart cases [Pitisuttithum, P., et al 2015] [Garland, S.M., et al 2009], and HPV types 16, 18, 31, 33, 45, 52, and 58 are responsible for approximately 90% globally of cervical cancers and HPV-related vulvar, vaginal, and anal cancers [Serrano, B., et al 2012] [de Sanjosé, S., et al 2013] [Alemany, L., et al 2015] [Alemany, L., et al 2014] [Lacey, C.J.N., et al 2006] [de Sanjosé, S., et al 2019]. The 9vHPV vaccine was initially licensed in the USA in December 2014 and has been licensed in many countries under the name GARDASIL™9. In Japan, the 9vHPV vaccine was approved for female as SILGARD®9 Aqueous Suspension for Intramuscular Injection Syringes in July 2020. The 9vHPV vaccine has demonstrated efficacy for the prevention of genital diseases caused by vaccine 9vHPV types in 16- to 26-year-old females and high immune responses in 9- to 15-year-old girls, including Japanese [Joura, E.A., et al 2015] [Huh, W.K., et al 2017] [Garland, S.M., et al 2018] [Iwata, S., et al 2017]. Efficacy of the 9vHPV vaccine in boys 9-15 years of age was inferred based on an immunogenicity bridging study which demonstrated non-inferior HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses in boys who received 3 doses of 9vHPV vaccine versus females 16-26 years who also received 3 doses [Van Damme, P., et al 2015]. In males 16-26 years of age, efficacy of the 9vHPV vaccine was inferred based on 2 immunogenicity bridging studies: one pivotal study which demonstrated non-inferior HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses in males who received the 9vHPV vaccine versus females who received the 9vHPV vaccine [Castellsagué, X., et al 2015]; and one supportive study which demonstrated non-inferior HPV 6, 11, 16, and 18 antibody responses in males who received the 9vHPV vaccine compared with males who received qHPV vaccine [Van Damme, P., et al 2016]. Thus, a study to confirm efficacy of the 9vHPV vaccine in Japanese males aged 16 to 26 years (Protocol V503-064) is ongoing for the use of the 9vHPV vaccine for prevention of condyloma acuminata and anal cancers and related precancers caused by vaccine 9vHPV

types in Japanese males, and this immunogenicity study for boys aged 9 to 15 years (Protocol V503-066) will be conducted to bridge the 9vHPV vaccine efficacy findings in young Japanese males.

In addition, it is becoming increasingly important to study the immune response of young adolescents using alternative vaccination regimens to the 3-dose regimen of HPV vaccine as a schedule with fewer doses may positively impact vaccination programs by increasing acceptability and compliance while reducing costs. Based on the result in Protocol V503-010 that immune responses after 2-dose (at Day 1 and Month 6 or Day 1 and Month 12) regimen of the 9vHPV vaccine in girls and boys 9 to 14 years of age were non-inferior to those after 3-dose in young females 16 to 26 years of age [Iversen, O.E., et al 2016], 2-dose (0 and 6 to 12 months) regimen of the 9vHPV vaccine has been approved as an alternative regimen and included in the national immunization program in some foreign countries. In World Health Organization (WHO) position paper published in 2017, 2-dose schedule (0 and 5 to 13 months) of the 9vHPV vaccine is recommended for girls and boys aged 9 to 14 years [WHO 2017]. In addition, recent research has demonstrated non-inferiority of immune responses up to 120 months postvaccination after 2-dose of qHPV vaccine in girls aged 9 to 13 years compared with that after 3-dose in adult females aged 16 to 26 years [Donken, R. et al 2019]. These have encouraged the interest in the 2-dose regimen.

This study will evaluate the immunogenicity and safety of the 9vHPV vaccine following a 3-dose regimen in Japanese boys aged 9 to 15 years as well as that following a 2-dose regimen in Japanese boys and girls aged 9 to 14 years. The scientific rationale for the study design is described in Section 4.2.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

The 9vHPV vaccine is an aluminum-adjuvanted recombinant protein vaccine prepared from the highly purified virus-like particles (VLPs) of the recombinant major capsid (L1) protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The 9vHPV vaccine is currently indicated for the prevention of cervical, vulvar, vaginal, and anal cancers, and precancerous or dysplastic lesions, genital warts, and infection caused by the 9 HPV types targeted by the vaccine in many countries. In USA, the 9vHPV vaccine was conditionally approved for the prevention of oropharyngeal and other head and neck cancer. In Japan, the 9vHPV vaccine was approved for the prevention of cervical cancer, cervical precancers, vulvar and vaginal precancers, and genital warts caused by 9vHPV types in females.

2.2.1.1 Disease Burden and Epidemiology for HPV-related Disease

Anogenital Warts

Anogenital warts are generally benign, exophytic, hyperkeratotic lesions on the penile shaft (most common site of lesions), scrotum, perineum, and anus in males. In females, the lesions may appear over the vulva, urethra, vagina, perineum, and anus. In general, the lesions do not cause any physical discomfort [Chuang, T.Y., et al 1984]. Some patients experience itching, burning, bleeding, moisture, irritation or soreness, especially with lesions in the perianal region. Patients are often distressed by the lesions' appearance. Genital warts (condyloma acuminata) are caused by HPV-6 or -11 account for approximately 75 to 90% of cases in both males and females [Aubin, F., et al 2008] [Garland, S.M., et al 2009] [Chan, P.K., et al 2009] [Yanofsky, V.R., et al 2012]. The incubation period following exposures is 3 weeks to 8 months [Yanofsky, V.R., et al 2012]. Treatment consists of chemical or physical ablation and is often unsuccessful. Recurrence rates are high [Stone, K.M., 1995]. In Japan, genital warts are categorized as one of the sentinel reporting diseases of Category V Infectious Diseases by The Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections (Infectious Diseases Control Law). According to the Infectious Diseases Weekly Report based on Infectious Diseases Control Law, the total reported number of genital warts cases in 2019 was 6263 (males: 4113, females: 2150) [MHLW. 2019]. The prevalence of genital warts in Japan peaks at ages 25 to 29 years in males and 20 to 24 years in females [NIID. 2018].

Anal Cancer

Triggered by HPV infection, anal cancer develops through persistent infections and precursor lesions [Valvo, F., et al 2019]. The association between anal cancer and HPV infection is strongly suggested by the results of clinical trials. In a report by de Martel et al., HPV-DNA was demonstrated in 35,000 of 40,000 worldwide cases of anal cancer [de Martel, C., et al 2017]. Similarly, HPV-DNA was detected in 88.3% of anal cancers in a large-scale global study [Alemany, L., et al 2015]. Of the HPV types detected in invasive anal cancer in males, HPV type 16 (73.4%) was most common, followed by type 18 (5.2%), and type 6, 11, 31, 33 and 45 were also detected [De Vuyst H., et al 2009]. HPV type 16 and 18 were also detected in anal adenocarcinoma [Herfs, M., et al 2018]. In Japan, though HPV type distribution data is limited, 1086 new anal cancer cases occurred in 2017 based on national cancer incidence data from the National Cancer Registration and Statistics Cancer Information Service of the National Cancer Research Center [Japan National Cancer Center 2017]. In addition, Daling et al. reported that HPVs were detected in 78.0% and 97.7% anal cancer of heterosexual males and males who have sex with males, respectively [Daling, J.R., et al 2004].

Cervical Cancer and Precancerous Dysplasia

Cervical cancer is the fourth most common cancer in females worldwide [de Martel, C., et al 2017]. Approximately 570,000 new patients diagnosed and approximately 310,000 patients die each year worldwide [Bray, F., et al 2018]. Eighty percent (80%) of these cases of cervical cancers occur in developing countries. In Japan, the number of cervical cancer patients was reported to be around 11,000 in 2017 [Japan National Cancer Center 2017], and

the number of deaths due to cervical cancer was reported to be 2,871 in 2018 [Japan National Cancer Center 2018]. In developed countries, implementation of cervical cancer screening programs using the Pap test has reduced the incidence of cervical cancer by 75%. Nonetheless, an estimated 13,800 new cervical cancers and 4,290 cervical cancer deaths will occur in the USA in 2020 [American Cancer Society 2020]. Moreover, the screening rate for cervical cancer in Japan is low (approximately 40%) [Japan National Cancer Center 2019].

Vulvar and Vaginal Cancer

About 50% of vulvar and vaginal cancers are caused by HPV. These cancers arise from pre-malignant precursor lesions and rates of HPV-related vulvar and vaginal cancers have increased (these cancers share epidemiologic features with cervical cancer, and they are often found in females with cervical precancer and cancer) [Bosch, F.X., et al 2002] [Christensen, N.D. 2005].

Head and Neck Cancer

Head and neck cancers are a heterogeneous group of tumors at different anatomic sites with various etiologies. The majority of head and neck tumors are squamous cell carcinomas arising from mucosal surfaces of the oral cavity, pharynx, and larynx [Dufour, X., et al 2012]. Traditional risk factors for head and neck cancers predominantly included tobacco and excessive alcohol use. However, in the recent years, HPV infection was found to be associated with a substantial proportion of head and neck tumors, especially in the oropharynx [Castellsagué, X., et al 2016] [de Martel, C., et al 2017]. Although oral HPV infection is an established independent risk factor for head and neck squamous cell carcinoma [Gillison, M. L., et al 2012] [Mork, J., et al 2001] [Tam, S., et al 2018] [Wood, Z. C., et al 2017], early detection of HPV-related head and neck cancers is difficult due to challenges in identification of precancerous lesions and the apparent rapid progression to invasive disease [Gillison, M. L., et al 2015].

In Japan, the number of head and neck cancer patients was reported to be over 27,000 in 2017 [Japan National Cancer Center 2017], and the number of deaths due to head and neck cancer was reported to be around 8,400 in 2018 [Japan National Cancer Center 2018]. Globally, approximately 38,000 to 45,000 head and neck cancers are attributed to HPV each year, and the incidence is increasing [de Martel, C., et al 2017]. In the USA, HPV causes approximately 15,700 new oropharyngeal cancers annually, of which approximately 10,400 (66%) are attributed to the high-risk HPV types prevented by the 9vHPV vaccine [Viens, L. J., et al 2016]. In Europe, HPV causes approximately 13,800 cases each year [de Martel, C., et al 2017], and most of the HPV positive head and neck cancer cases are attributed to the high-risk HPV types in the 9vHPV vaccine [Hartwig, S., et al 2017] [de Martel, C., et al 2017].

Recurrent Respiratory Papillomatosis (RRP)

This disease is manifested as rapidly-growing exophytic lesions in the upper airway, most often in the larynx, causing severe respiratory and speech impairment. Repeated surgical excision is often needed [Glikman, D., et al 2005] [Szeps, M., et al 2005].

2.2.2 Preclinical and Clinical Studies

Refer to the IB for information on completed preclinical and clinical studies conducted with the 9vHPV vaccine.

2.2.2.1 Completed Clinical Studies

A global phase 3 study (Protocol V503-001) was conducted to evaluate the efficacy, immunogenicity and safety in females aged 16 to 26 years including Japanese females [Joura, E.A., et al 2015] [Huh, W.K., et al 2017] [Garland, S.M., et al 2018]. The 9vHPV vaccine prevented infection and disease caused by the HPV vaccine types and was generally well-tolerated. For younger adolescents, Protocol V503-002 was conducted and it has been demonstrated that competitive Luminex Immunoassay (cLIA) GMTs for the vaccine HPV types following 3 doses in both non-Japanese boys and girls aged 9 to 15 years were non-inferior to those in females aged 16 to 26 years, thereby supporting the bridging of efficacy findings in 16- to 26-year-old females to 9- to 15-year-old preadolescent and adolescent girls [Van Damme, P., et al 2015]. A local study (Protocol V503-008) also showed that a 3-dose regimen of the 9vHPV vaccine induced high HPV antibody responses and was generally well tolerated in Japanese girls aged 9 to 15 years [Iwata, S., et al 2017].

To investigate 2-dose regimen, a phase 3 study (Protocol V503-010) was conducted in non-Japanese boys and girls aged 9 to 14 years. The immune responses for girls and boys aged 9 to 14 years who received a 2-dose series were non-inferior to immune responses for young females aged 16 to 26 years who received a 3-dose series [Iversen, O.E., et al 2016].

Details of completed clinical studies with the 9vHPV vaccine are shown in the IB.

2.2.2.2 Ongoing Clinical Studies in Japan

A global phase 3 study (Protocol V503-049) is currently being conducted to evaluate the efficacy, immunogenicity and safety of the 9vHPV vaccine in the prevention of oral persistent infection caused by any of the high-risk HPV types covered by the vaccine in adult males 20 to 45 years of age including Japanese males.

A local phase 3 study (Protocol V503-064) is currently being conducted to evaluate the efficacy, immunogenicity and safety of the 9vHPV vaccine in Japanese males 16 to 26 years of age, in order to pursue indications for anal cancer and its precancerous or dysplastic lesions caused by vaccine 9vHPV types in both males and females, and genital warts in males in Japan.

2.3 Benefit/Risk Assessment

The 9vHPV vaccine has been shown to be beneficial and efficacious in preventing persistent genital HPV infection and disease associated with the 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58). The frequency, severity, and magnitude of adverse events (AEs) identified in previous studies [Moreira, E.D.J, et al 2016] [Moreira, E.D.J, et al 2018] and post marketing

surveillance [Shimabukuro, T.T., et al 2019] [Donahue, J.G., et al 2019] support a favorable benefit-risk for the 9vHPV vaccine in this study population.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

This study will evaluate 2 different dose regimens of the 9-valent human papillomavirus (9vHPV) vaccine: a 3-dose regimen in Japanese boys aged 9 to 15 years old and a 2-dose regimen in Japanese boys and girls aged 9-14 years old. The base phase of the study (Period I) will assess the immunogenicity and safety of the 9vHPV vaccine through 7 months following the first dose. The extension phase of the study (Period II) will assess the safety and the antibody persistence to the 9vHPV vaccine through 30 months following the first dose.

Objectives	Endpoints
Primary	
– To estimate percent seroconversion for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 in Japanese boys aged 9 to 15 years who received 3 doses of the 9vHPV vaccine	– Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
– To estimate percent seroconversion for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 in Japanese boys aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	– Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
– To estimate percent seroconversion for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 in Japanese girls aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	– Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
– To evaluate the safety and tolerability of the 9vHPV vaccine in Japanese boys aged 9 to 15 years who received 3 doses and Japanese boys and girls aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	– Solicited injection-site adverse events – Systemic adverse events – Serious adverse events

Objectives	Endpoints
Secondary	
– To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 including geometric mean titers (GMTs) in Japanese boys aged 9 to 15 years who received 3 doses of the 9vHPV vaccine	– Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
– To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 including GMTs in Japanese boys aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	– Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
– To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 including GMTs in Japanese girls aged 9 to 14 years who received 2 doses of the 9vHPV vaccine	– Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
Tertiary/Exploratory	
– To assess the persistence of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 antibody responses at Month 18 and 30	– Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58

4 STUDY DESIGN

4.1 Overall Design

This is a phase 3 open-label study to evaluate the immunogenicity and safety of a 9vHPV (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine (V503) in Japanese boys and girls aged 9 to 15 years. This study will consist of two periods. Period I of the study is to evaluate the immunogenicity and safety/tolerability of the 9vHPV vaccine up to the time point of Month 7. Period II of the study is to evaluate the long-term immunogenicity and safety from Month 7 to Month 30. Analysis of the base phase (Period I) for the 2-dose arm in girls aged 9 to 14 years old is planned to be conducted when all girl participants have completed their Period I (Month 7 visit) or discontinued from study before that time. Analysis of the base phase (Period I) for the 2-dose and 3-dose arms in boys and extension phase (Period II) for all arms will be conducted at the end of study.

This study will enroll approximately 300 Japanese boys and girls in total, and approximately 100 participants will be allocated to each of the following three arms:

- 3-dose (Day 1, Month 2 and Month 6) in boys aged 9 to 15 years
- 2-dose (Day 1 and Month 6) in boys aged 9 to 14 years
- 2-dose (Day 1 and Month 6) in girls aged 9 to 14 years

Enrollment of the girl cohort will be initiated first. Enrollment of the boy cohorts will be initiated at a later time to be determined by the Sponsor.

Blood samples will be collected on Day 1 immediately before vaccination, and subsequently Month 7, Month 18 and Month 30 to evaluate HPV antibody responses.

Participants will be followed for injection-site AEs and systemic AEs from Day 1 through Day 15 following each vaccination. SAEs will be recorded regardless of causality from the time of allocation/randomization through 6 months post last dose. Vaccine-related SAEs and deaths will be collected throughout the study. New medical conditions (defined as incident medical conditions occurring outside of a Days 1 to Days 15 period following each vaccination and not considered SAEs) will be recorded for all participants at each study visit throughout the study.

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

4.2 Scientific Rationale for Study Design

This study is designed to evaluate immunogenicity against the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) and safety of 3-dose of the 9vHPV vaccine in Japanese boys aged 9 to 15 years as well as 2-dose of the 9vHPV vaccine in Japanese boys and girls aged 9 to 14 years. Immunogenicity result (cLIA GMTs) in this study will be used for cross-study comparison.

Efficacy and safety of 3-dose regimen in Japanese males aged 16 to 26 years will be evaluated in Protocol V503-064. Efficacy in Japanese boys 9-15 years of age who received 3 doses and in Japanese boys 9-14 years of age who received 2 doses will be inferred based on demonstration of non-inferior immunogenicity at Month 7 in the cohorts of Japanese boys in this study versus Japanese males 16-26 years of age who will have received 3 doses in V503-064.

Efficacy and safety of 3-dose regimen in Japanese females aged 16 to 26 years was demonstrated in Protocol V503-001. Efficacy in Japanese girls 9-14 years of age who received 2 doses will be inferred based on demonstration of non-inferior immunogenicity at Month 7 in the cohort of Japanese girls in this study versus Japanese females 16-26 years of age who received 3 doses in V503-001.

The age range in this study (9 to 15 years old for 3-dose regimen and 9 to 14 years old for 2-dose regimen) is consistent with the indication for 9vHPV vaccine in foreign countries where 2-dose regimen has been approved for boys and girls aged 9 to 14 years whereas 3-dose regimen has been approved for 9 years old or older.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 will be analyzed as the indicator of immune responses using previously established methods including cLIA as the primary immunoassay [Roberts, C., et al 2014]. The assay has been used in previous clinical studies within the 9vHPV vaccine program. Details on the immunogenicity endpoints evaluated in this study can be found in Section 8.2.1 and Section 9.4.1.

4.2.1.2 Safety Endpoints

Safety assessments in this study are consistent with those used in previous studies of the 9vHPV vaccine and qHPV vaccine. Paper Vaccination Report Card (VRC) will be used to record AEs during the postvaccination periods. Details for the VRC are provided in Section 8.3.4.

Details on the safety endpoints evaluated in this study can be found in Section 8.3 and Section 9.4.2.

Details on AEs, including definitions and reporting requirements, can be found in Appendix 3.

4.2.1.3 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

4.3 Justification for Dose

The 0.5 mL dose administered as a 3-dose regimen (Day 1, Month 2, Month 6) is based on the global efficacy, immunogenicity, and safety clinical studies that supported the licensure of the 9vHPV vaccine and is consistent with the approved dosing and product labeling of the 9vHPV vaccine (Japan, USA, EU, and other countries).

The rationale for the selection of both the 2-dose regimen and the interval used in applying the 2 doses is based on the result from Protocol V503-010 that immune responses, measured by cLIA GMT, for girls and boys 9 to 14 years of age who received a 2-dose series at Day 1 and Month 6 were non-inferior to immune responses for young female 16 to 26 years of age who received a 3-dose series at Day 1, Month 2 and Month 6 [Iversen, O.E., et al 2016]. The 2-dose regimen has been approved in some foreign countries as an alternative regimen and WHO also recommended 2-dose schedule (0 and 5 to 13 months) of the 9vHPV vaccine for girls and boys aged 9 to 14 years [WHO 2017]. Therefore, the 2-dose regimen is expected to demonstrate high immune responses also in Japanese boys and girls aged 9 to 14 years.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant's legally acceptable representative provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Healthy male and female participants between the ages of 9 and 15 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

The history of medical conditions will be based on the self-report or medical chart provided by participant's legally acceptable representative.

Type of Participant and Disease Characteristics

1. Is healthy and is judged to be in good physical health based on medical history and physical examination.

Demographics

2. Is Japanese male or female.

3. Is aged at the time of providing the documented informed consent (inclusive).

(3-dose boy arm) male from 9 years to 15 years old

(2-dose boy arm) male from 9 years to 14 years old

(2-dose girl arm) female from 9 years to 14 years old

Informed Consent

4. The participant's legally acceptable representative has provided documented informed consent for the study and when applicable, the participant has provided documented informed assent. The participant/legally acceptable representative may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

5. Agrees to provide study personnel at the study site with a primary telephone number as well as an alternate means of contact, if available (such as an alternate telephone number, SNS or e-mail) for follow-up purposes.
6. Has a legally acceptable representative who can read, understand and complete the VRC.
7. Must not yet have had coitarche and does not plan on becoming sexually active during the Day 1 through Month 7.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

The history of medical conditions will be based on the self-report or medical chart provided by participant's legally acceptable representative. For items with an asterisk (*), if the exclusion criterion is met, then the Day 1 visit may be rescheduled for a time when the criterion is not met.

Medical Conditions

1. *Has a fever (defined as oral temperature $\geq 37.5^{\circ}\text{C}$) within the 24-hour period prior to the Day 1 visit.
2. 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. Is allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]). For this exclusion criterion, an allergy to vaccine components is defined as an allergic reaction that met the criteria for severe AEs or SAEs defined in Appendix 3.

4. Has known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
5. Is currently immunocompromised or has been diagnosed as having a congenital or acquired immunodeficiency, HIV infection, lymphoma, leukemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, or other auto immune condition.
6. Has a history of splenectomy.
7. Has a history of genital warts or positive test for HPV.
8. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might confound the results of the study, or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate by judgement of investigator.
9. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within 12 months) of drug or alcohol abuse or dependence at the discretion of the investigator. Alcohol abusers are defined as those who drink despite recurrent social, interpersonal, and/or legal problems because of alcohol use.
10. (Female only) Is pregnant as determined by urine pregnancy test.

Prior/Concomitant Therapy

11. Has received within 12 months prior to enrollment, is receiving, or plans to receive during Day 1 through Month 7 of the study, the following immunosuppressive therapies: radiation therapy, cyclophosphamide, azathioprine, methotrexate, any chemotherapy, cyclosporin, leflunomide, TNF- α antagonists, monoclonal antibody therapies (including rituximab), intravenous gamma globulin (IVIG), antilymphocyte sera, or other therapy known to interfere with the immune response. Regarding systemic corticosteroids, a participant will be excluded if the participant 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.
12. Has received within the 3 months prior to the Day 1 vaccination, is receiving, or plans to receive during Day 1 through Month 7 of the study, any immune globulin product (including Rho(D) human immune globulin [Beneis™]) or blood-derived product other than IVIG.
13. *Has received inactivated or recombinant vaccines within 14 days prior to Day 1 vaccination or receipt of live vaccines within 28 days prior to Day 1 vaccination.

14. Has previously received a marketed HPV vaccine, or has participated in a clinical trial for any HPV vaccine (receiving either active agent or placebo).

Prior/Concurrent Clinical Study Experience

15. Is concurrently enrolled in other clinical studies of investigational agents.

Diagnostic Assessments

None.

Other Exclusions

16. 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 when study visits would need to be scheduled.
17. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

No lifecycle restrictions are required.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in [Table 1](#).

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Admin.	Vaccination Regimen	Use	IMP/NIMP	Sourcing
3-dose in 9 to 15 years old boys	Experimental	V503 (9vHPV vaccine)	Biological/Vaccine	Sterile Suspension	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/20 mcg per dose	0.5 mL	IM	Day 1, Month 2, Month 6	Experimental	IMP	Provided centrally by Sponsor
2-dose in 9 to 14 years old boys	Experimental	V503 (9vHPV vaccine)	Biological/Vaccine	Sterile Suspension	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/20 mcg per dose	0.5 mL	IM	Day 1, Month 6	Experimental	IMP	Provided centrally by Sponsor
2-dose in 9 to 14 years old girls	Experimental	V503 (9vHPV vaccine)	Biological/Vaccine	Sterile Suspension	HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/20 mcg per dose	0.5 mL	IM	Day 1, Month 6	Experimental	IMP	Provided centrally by Sponsor
9vHPV=9-valent human papillomavirus, HPV=human papillomavirus, VLP=virus-like particle, IM=Intramuscular The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in [Table 1](#) will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3. Information on preparation and administration of study vaccine is provided in Section 6.3.1 and Section 8.1.9.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

IRT system will be used to allocate participants to either the 3-dose or 2-dose regimen arms based on gender and age at the time of providing the informed consent.

Fifteen-years-old boys will be assigned to the 3-dose regimen arm until the boys 3-dose regimen arms reaches 100 participants. Girls aged 9 to 14 years will be assigned to the 2-dose regimen arm without randomization until the girls 2-dose regimen arm reaches 100 participants.

Boys aged 9 to 14 years will be randomized in a 1:1 ratio to either 3-dose or 2-dose regimen until 100 participants are enrolled in each of the 3-dose and 2-dose regimen arms. If the combined 9- to 14-year-old boys randomized to the 3-dose regimen and the 15-year-old boys assigned to the 3-dose regimen reach 100 participants before the 9- to 14-year-old boys randomized to the 2-dose regimen reaches 100 participants, randomization of 9 to 14 year-old boys to the 3-dose regimen will be stopped, and subsequent 9- to 14-year-old boys enrolled will be allocated to the 2-dose regimen until the boys 2-dose regimen arm reaches 100 participants. Similarly, if the boys 2-dose regimen arm reaches 100 participants before the boys 3-dose regimen arm reaches 100 participants, randomization of 9- to 14-year-old boys into the 2-dose regimen arm will be stopped and subsequent 9-to 14-year-old boys enrolled will be allocated to the 3-dose regimen until the boys 3-dose regimen arm reaches 100 participants.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified vaccination plan specified in Section 1.3 require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination (Section 5.2). If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention 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 intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination:

- See the exclusion criteria for specific restriction for prior and concomitant medications at Day 1 (Section 5.2) and prerequisites for other vaccination visits (Section 8.9.2).
- If possible, participants should not receive “Special medications” (corticosteroids, immunosuppressive therapies, immune globulin products, and blood-derived products) from Day 1 through Month 7, non-study inactivated or recombinant vaccines from 14 days prior to each study vaccination through 14 days after each study vaccination, or non-study live vaccines from 28 days prior to each study vaccination through 14 days after each study vaccination.
- “Non-study HPV vaccine” must not be used at any time during the study.
- 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 8.1.6.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification

No dose modification is allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention 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 intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.9.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10 and Section 8.9.3.

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

For participants who are discontinued from study intervention but continue to be monitored in the study, see Section 1.3 and Section 8.9.3 for those procedures to be completed at each specified visit.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

acceptable representative. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The total volume of blood collected for immunogenicity testing and blood (DNA) for future biomedical research is outlined in Table 2. The maximum amount of blood collected from each participant over the duration of the study will not exceed approximately 48.5 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 2 Blood Collection Volumes

	Visit 1	Visit 4	Visit 5	Visit 6
Anti-HPV Immunogenicity Testing	10 mL	10 mL	10 mL	10 mL
Blood (DNA) for Future Biomedical Research	8.5 mL	-	-	-
Total Volume	18.5 mL	10 mL	10 mL	10 mL

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant's legally acceptable representative prior to participating in this clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place. The documented assent should be obtained as far as possible.

8.1.1.1 General Informed Consent

Informed consent given by the participant's legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the participant's legally acceptable representative and of the person conducting the consent discussion. Informed assent should be obtained from the participant as far as possible.

A copy of the signed and dated informed consent form should be given to the participant's their legally acceptable representative before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant's legally acceptable representative must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant's 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 form or addendum to the original consent form that captures the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant's legally acceptable representative before performing any procedure related to future biomedical research. The documented assent should be obtained as far as possible.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant's legally acceptable representative provides documented informed consent. At the time of intervention 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 healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator. At Visit 1 (Day 1), the participant's medical history for the year prior to Visit 1 will be collected.

After the Day 1 visit, any new medical history that has not been previously documented (ie, incident medical conditions occurring outside of Days 1 to Days 15 period following each vaccination and not considered SAEs) will be collected.

8.1.5 Demographics

Demographics will be collected in the data collection system, as discussed in the electronic Case Report Form (eCRF) entry guidelines.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator or qualified designee will review prior medications or vaccinations on Day 1. A participant receiving any of the prior medications or vaccinations prohibited in the exclusion criteria (Section 5.2) should not be enrolled into the study. Prior and concomitant medications or vaccinations should be documented in the data collection system per the following timeframe.

- “Special medications” (corticosteroids, immunosuppressive therapies as defined in the exclusion criteria, immune globulin products, and blood-derived products) from 3 days 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” from 14 days prior to each study vaccination through 14 days after each study vaccination.
- “Non-study live vaccines” from 28 days prior to each study vaccination through 14 days after each study vaccination.
- “Non-study HPV vaccine” must not be used at any time during the study. However, for the specific case where a participant mistakenly receives any non-study HPV vaccines, the non-study HPV vaccine must be reported on the appropriate eCRF, regardless of when the non-study vaccine was received.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study time frames specified in Section 8.1.6.1.

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

8.1.7 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 randomization/intervention allocation. Each participant will be assigned only 1 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. Specific details on the screening/rescreening visit requirements are in Section 8.9.1.

8.1.8 Assignment of Treatment/Randomization Number

All eligible fifteen-years-old boys and girls aged 9 to 14 years will be allocated by nonrandom assignment, and boys aged 9 to 14 years will be randomly allocated. They will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.9 Study Intervention Administration

Preparation of Study Vaccine

The study vaccine must be stored at 2.0°C to 8.0°C. Do NOT freeze the study vaccine. Protect the study vaccine from light. The study vaccine must be used as supplied (no dilution before administration). The vaccine vial should be thoroughly mixed before administration by gently rolling vial between the palms of both hands for 30 seconds before withdrawing the 0.5 mL dose of vaccine from single-dose vial using a sterile needle and syringe. **The study vaccine should be a whitish, semi-translucent suspension when thoroughly mixed.** If the appearance of vaccine is otherwise, do not administer, and contact the Sponsor immediately.

Adequate treatment provision, including epinephrine and equipment for maintaining an airway should be available for immediate use in case that an anaphylactic or anaphylactoid reaction occur [Center for Disease Control and Prevention 2015].

Study Vaccine Administration

Study vaccine should be administered by the designated physician at Day 1, Month 2 (only for 3-dose boy arm), and Month 6. At each vaccination visit, participant will receive the 9vHPV vaccine as a 0.5 mL intramuscular injection. The deltoid muscle of the nondominant arm is the preferred site of vaccination. Study vaccinations should not be administered in the buttocks area. Injections should not be given within 2 cm of a tattoo, scar, or skin deformation.

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

Observing Participants After Vaccination

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

Vaccination information, such as Component Identification Number and time of vaccination, must be recorded on the appropriate eCRF as per the data entry guidelines.

8.1.9.1 Timing of Dose Administration

The first dose of study vaccine will be administered at Day 1, which should be the day of allocation/randomization. For 3-dose regimen arm, the second and third (final) doses of study vaccine will be administered at Month 2 (\pm 3 weeks) and Month 6 (\pm 4 weeks), respectively. For 2-dose regimen arms, the second (final) doses of study vaccine will be administered at Month 6 (\pm 4 weeks) (Section 1.3).

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the scheduled vaccination regimen should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.9.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the next study visit (exception: serum sample collection should not be performed unless the participant has received all scheduled doses of the study vaccine) at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants or participants' legally acceptable representatives may withdraw their consent for future biomedical research. Participants or participants' legally acceptable representatives may withdraw consent at any time by contacting the investigator. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant's legally acceptable representative of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between

the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.12 Calibration of Equipment

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

8.2 Immunogenicity Assessments

8.2.1 Blood Sample Collection for Serum Anti-HPV Antibody Testing

Blood samples will be collected for analysis of antibodies specific for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers in serum. On Day 1, blood samples will be collected prior to the first study vaccination to identify participants who have been exposed to study vaccine HPV types prior to enrollment. Serology results on Day 1 are not part of the inclusion/exclusion criteria; thus, no participant will be excluded from the study based on these results. After Day 1, serum specimens will be collected at Month 7, Month 18, and Month 30 to evaluate persistence of immune responses.

Blood sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. Blood samples will be collected for anti-HPV antibody testing per the schedule indicated in the SoA (Section 1.3).

After completion of immunogenicity testing to evaluate the study objectives, all leftover serum samples will be stored for up to 15 years. The samples may be used to conduct any additional study-related testing, biomarker testing, or to support HPV assay development/validation activities as required by regulatory agencies or the Sponsor.

8.2.2 Competitive Luminex Immunoassay

The 9vHPV cLIA will be used as a primary method to evaluate antibodies specific for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 in serum. The purpose of the assay is to detect these HPV antibodies before and after vaccination with the 9vHPV vaccine. The testing will be performed by Q Squared Solutions (California, USA).

For the 9vHPV cLIA, HPV type-specific, yeast-derived VLPs are coupled to 9 distinct Luminex magnetic microspheres. Each VLP-coupled microsphere has its own distinct

fluorescent dye that can be recognized by excitation with an infrared laser, allowing for the measurement of antibodies against multiple HPV types from a single test of an individual's serum. HPV type-specific monoclonal antibodies labeled with R-Phycoerythrin (PE) compete with an individual's serum antibodies for binding to the neutralizing epitopes of the VLPs. The fluorescent signal from the PE-labeled, type-specific monoclonal antibodies is inversely proportional to the anti-HPV antibody concentration of a sample. Antibody concentrations are derived from a standard curve, which is generated using a reference standard made from a pool of serum from individuals immunized against the nine HPV types. A standard curve for each HPV type is calculated using a weighted 4 parameter logistic curve fit. Results are expressed as milli-Merck Units per milliliter (mMU/mL).

The assay was validated at Q Squared Solutions. Validation evaluated precision, linearity, lower limit of quantitation, upper limit of quantitation, and relative accuracy/dilutability for the quantitation of antibodies specific to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Serostatus cutoffs for each HPV type will be predefined. A participant will be considered seropositive to a given HPV type at Day 1 if the participant's anti-HPV titer, as assessed by cLIA, is greater than or equal to the corresponding serostatus cutoff for that HPV type. A participant will be considered seronegative to a given HPV type at Day 1 if the participant's anti-HPV titer, as assessed by cLIA, is less than the corresponding serostatus cutoff for that HPV type.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A physical examination is optional and will be conducted by an investigator on Day 1 to determine whether the participant meets eligibility criteria for enrollment.

Height and weight will be recorded on Day 1 before administration of the study vaccine.

Physical examination details will be recorded in the participant's study chart. Any medical condition identified during physical examination will be documented in the data collection system. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Oral Temperature Measurements

Oral temperature will be assessed before study vaccine administration on Day 1, Month 2 (only for 3-dose boy arm), and Month 6 as well as blood sample collection on Day 1. If the participant has a fever (defined as an oral temperature of $\geq 37.5^{\circ}\text{C}$) within the 24-hour period prior to receiving a study vaccination, the participant should not receive the study vaccine, and the vaccination visit should be rescheduled until after the fever has resolved.

Postvaccination, if an oral temperature indicates a fever (defined as an oral temperature of $\geq 37.5^{\circ}\text{C}$), then an AE of “fever” must be documented in the eCRF.

8.3.3 Clinical Safety Laboratory Assessments

There will be no protocol-specific clinical safety laboratory assessments for this study. 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 discontinuation of the study vaccine), then the results must be recorded in the appropriate case report form (CRF) (eg, SLAB).

8.3.4 Vaccination Report Card

The investigator or delegate will train the participant’s legally acceptable representative in the use of the VRC at Visit 1 (Day 1). Temperatures, injection-site reactions, other complaints or illnesses, and concomitant medications or vaccinations will be recorded on the VRC by the participant’s legally acceptable representative. The participant’s legally acceptable representative should be informed to contact the investigator immediately in the event of a hospitalization or visit to another physician.

The participant’s legally acceptable representative will use the VRC to document the following information:

- Oral temperatures measured from Day 1 (day of vaccination) through Day 5 postvaccination.
 - Participant’s legally acceptable representative will record participant’s oral temperature in the evening after each study vaccination and daily, at the same time of day, for 4 days after each study vaccination for the purpose of identifying febrile events
 - Note: If an oral temperature indicates a fever (defined as an oral temperature of $\geq 37.5^{\circ}\text{C}$), the AE of “fever” must be documented in the appropriate eCRF
- Solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) from Day 1 through Day 5 postvaccination
- Injection-site and systemic AEs from Day 1 through Day 15 postvaccination
- Concomitant medications and non-study vaccinations from Day 1 through Day 15 postvaccination

In order to ensure that the VRC is being filled out without delay, telephone contacts to remind the participant’s legally acceptable representative will be conducted after 15 days postvaccination.

All participant's legally acceptable representative will be expected to bring the VRC to the study site at the next scheduled visit. The investigator or delegate will review the data captured on the VRC with the participant's legally acceptable representative at Visit 2 (Month 2), Visit 3 (Month 6, only for 3-dose boy arm), and Visit 4 (Month 7). For the AEs outlined above, the investigator will use the information provided by the participant's legally acceptable representative both on the VRC, and verbally at the time of VRC review, to apply the appropriate assessment of causality as described in Appendix 3. At the time of VRC review at the next scheduled visit, participant's legally acceptable representative will be questioned regarding any new medical conditions that occurred beyond Day 15 postvaccination. The investigator will determine if the medical condition is to be reported as an SAE using the reporting guidelines provided in Section 8.4.

8.3.5 Postvaccination Observation Period (30 Minutes)

All participants will be observed for at least 30 minutes after each vaccination for any immediate reactions. If any immediate AEs (including allergic reactions) are observed during this period, the time at which the event occurred within this timeframe, as well as the event itself, any concomitant medications that were administered, and resolution of the event, must be recorded on the appropriate eCRF.

8.3.6 Pregnancy Testing

- Pregnancy testing
 - Pregnancy testing requirements for study exclusion are described in Section 5.2.
 - Pregnancy testing (urine) should be conducted prior to vaccination at Visit 1 and Visit 3.
 - For participants who become pregnant after receiving a 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 vaccination in pregnancy participants will be handled as described in [Table 3](#). Breastfeeding is not a contraindication to receiving study vaccinations. Pregnancy and exposure during breastfeeding must be reported as described in Section 8.4.5.
 - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator to establish the absence of pregnancy at any time during the participant's participation in the study.

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

Visit Where Pregnancy is Detected	Action
Day 1	Do not enroll the participant
Between First and Second Vaccination Visits	<ul style="list-style-type: none">No scheduled visits until resolution of the pregnancy (e.g. term, elective termination, spontaneous abortion).The second study vaccination visit should be administered at least 4 weeks following resolution of pregnancy, after normalization of β-human chorionic gonadotropin (β-hCG) , and in accordance to the intervention group assigned and visit windows in Section 1.3.
After Second Vaccination Visits	<ul style="list-style-type: none">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).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant's legally acceptable representative provides documented informed consent 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, or a procedure.

From the time of allocation/randomization through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, all AEs, SAEs, and other reportable safety events must be reported by the investigator. All SAEs and other reportable safety events that occur from the time of allocation/randomization through 6 months following the last vaccination must be reported by the investigator, regardless of whether the events are considered to be vaccine-related by the investigator.

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

- A death that occurs prior to the participant completing the study, but outside the time period specified in the previous paragraph.

OR

- An SAE that is considered by an investigator, who is a qualified physician, to be vaccine related.

Investigators are not obligated to actively seek AEs or SAEs 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 intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in [Table 4](#).

Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	<u>Reporting Time Period:</u> Consent to Randomization/ Allocation	<u>Reporting Time Period:</u> Randomization/ Allocation through Protocol-specified Follow-up Period	<u>Reporting Time Period:</u> After the Protocol- specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
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
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. - any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

NSAE=nonserious adverse event; SAE=serious adverse event

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated/randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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.

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

None.

8.4.7 Events of Clinical Interest

None.

8.5 Treatment of Overdose

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

Sponsor does not recommend specific treatment for an overdose.

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

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant's legally acceptable representative provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- DNA for future research

8.9 Visit Requirements

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

8.9.1 Screening

The screening visit or the last screening visit (for re-screening) should be on the same day of randomization and the first dose of vaccination. Potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

If possible, all Day 1 visit procedures should be performed on the day of consent. If date of Day 1 visit (and all procedures) is later than consent date, the interval between the date of consent and the date of the Day 1 visit should be no more than 14 days. If the interval is 15 days or longer, then the participant's legally acceptable representative must be reconsented.

8.9.2 Prerequisites for Vaccination Visits (Day 1, Month 2, and Month 6)

This section summarizes prerequisites for vaccination visits. See the inclusion/exclusion criteria for specific restrictions on Day 1 (see Section 5.1 and Section 5.2). At Month 2 (only for 3-dose boy arm) and Month 6 study vaccination visits, study personnel should verify by questioning the participant's legally acceptable representative and/or by examination that:

1. The participant has not had a fever (oral temperature $\geq 37.5^{\circ}\text{C}$) within the 24-hour period prior to the vaccination visit.
2. The participant has not received any systemic (oral or parenteral) corticosteroids in 14 days prior to any study vaccination visits.
3. The participant has not received a non-study inactivated or recombinant vaccine within 14 days prior to any study vaccination visit or a non-study live vaccine within 28 days prior to any study vaccination visit.

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

8.9.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study vaccinations but continue in the study will attend study visits per the SoA (Section 1.3). However, serum will not be collected at the Month 7 study visit or subsequent visits from participants who did not complete the specified study vaccination regimen.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Study Design Overview	A phase 3, open-label clinical study to evaluate the immunogenicity and safety of 9vHPV vaccine, in Japanese 9-15 boys and 9-14 girls of age
Treatment Assignment	Approximately 300 participants will be enrolled and allocated in a 1:1:1 ratio based on gender and age into the 3-dose [0,2,6 regimen] in 9 to 15 years old boys, 2-dose [0,6 regimen] in 9 to 14 years old boys and 2-dose [0,6 regimen] in 9 to 14 years old girls arms. Details are provided in Section 6.3.1.
Analysis Populations	Immunogenicity: Per-Protocol Immunogenicity (PPI) population Safety: All Participants as Treated (APaT) population
Primary Endpoint(s)	<ul style="list-style-type: none"> Seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 3 doses of the 9vHPV vaccine. Seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 2 doses of the 9vHPV vaccine.
Key Secondary Endpoints	<ul style="list-style-type: none"> Geometric mean titers (GMTs) to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 3 doses of the 9vHPV vaccine. GMTs to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 2 doses of the 9vHPV vaccine.
Statistical Methods for Key Immunogenicity Analyses	<p>The primary immunogenicity objective is estimation of the HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 seroconversion at 1 month post last dose (Month 7) following 3 doses and 2 doses of the 9vHPV vaccine. Seroconversion to a specific HPV type is defined as changing serostatus from seronegative at Day 1 to seropositive at 1 month post last dose (Month 7). Percent seroconversion will be evaluated by computing point estimates and constructing 95% confidence interval (CI) of the percent of participants who seroconvert at 1 month post last dose (Month 7). Calculation of the 95% CI of percent seroconversion is based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].</p> <p>The secondary objective is to estimate GMTs at 1 month post last dose (Month 7) for each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 following 3 doses and 2 doses of the 9vHPV vaccine. GMTs and corresponding 95% CI will be derived by taking the anti-logarithm of the mean and corresponding 95% CI of the mean of the log-transformed anti-HPV titers.</p>

Statistical Methods for Key Safety Analyses	Incidence of solicited injection-site AEs, systemic AEs, SAEs, and serious vaccine-related AEs will be summarized by study arm.
Interim Analyses	No interim analyses are planned in this study.
Multiplicity	Not applicable. The study is an estimation-only study.
Sample Size and Power	The study will enroll 300 participants (100 participants for each study arm) to receive V503. At least 95 participants evaluable per study arm will allow estimation of percent seroconversion that has a corresponding 95% CI with a half-width of about 3 percentage points, assuming true percent seroconversion of 99% and the discontinuation rate and exclusion from the HPV type-specific PPI population of at most 5%. In addition, at least 95 participants evaluable per study arm provides at least 0.99 probability to demonstrate that the point estimate of the percent seroconversion exceeds 90% for all of the 9 HPV types when the true percent seroconversion is 99%. At least 95 participants evaluable per study arm provides at least 0.88 probability to attain a lower limit of 95% CI of percent seroconversion equal to or more than 90% when the true percent seroconversion is at least 99%.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the designee/Clinical Biostatistics department of the Sponsor. This trial is being conducted as an open-label study, i.e., participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

First database lock will be executed when all girls aged 9 to 14 years old in the 2-dose arm have either completed the Month 7 visit (1 month post last dose) or discontinued from the study before that time to report on base phase analysis for this arm.

A second database lock will be executed at end-of-study to report on base phase analysis for the 2-dose and 3-dose arms in boys and on extension phase analysis for all study arms for safety and persistence of immune response.

Summaries of the primary and secondary immunogenicity endpoints will be reported in Integrated Summary of Immunogenicity reports where in addition to reporting the immunogenicity results in this study, the study results will be compared with immunogenicity results in studies of 16 to 26 year-old Japanese males and females who received 3 doses of the 9vHPV vaccine for the purpose of immunobridging efficacy in 16 to 26 year-old Japanese males and females to 9 to 15 year-old Japanese boys and girls. The results of the 2-dose arm in girls and the 2-dose and 3-dose arms in boys will be reported in two separate integrated Summary of Immunogenicity reports. The details about the analysis will be documented in a separate iSAP.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. The study is an estimation-only study. No hypothesis will be tested.

9.4 Analysis Endpoints

9.4.1 Immunogenicity Endpoints

The primary immunogenicity endpoints are seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 3 doses; and following 2 doses of the 9vHPV vaccine. Seroconversion is defined as changing serostatus from seronegative at Day 1 to seropositive at 1 month post last dose (Month 7). A participant with a cLIA titer at or above the serostatus cutoff for a given HPV type is considered seropositive for that HPV type.

The key secondary immunogenicity endpoints are cLIA geometric mean titers (GMTs) for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 3 doses; and following 2 doses of the 9vHPV vaccine. Exploratory endpoints include cLIA GMTs and seropositivity for each vaccine HPV type at Months 18 and 30 to assess persistence of immune responses.

9.4.2 Safety Endpoints

- Solicited injection-site AEs and elevated temperatures Days 1 through 5 post vaccination
- Systemic AEs, SAEs and Serious vaccine-related AEs Days 1 through 15 post vaccination
- SAEs and Serious vaccine-related AEs observed any time during the study

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

Per-Protocol Immunogenicity (PPI) Population

The PPI population will serve as the primary population for the analysis of immune response to each HPV-types. To be included in this population, participants must:

- (1) Have received all required vaccinations of 9vHPV vaccine with the correct dose within acceptable day ranges (see [Table 5](#)).
- (2) Have provided blood samples for serology testing within 21 to 49 days post last dose.
- (3) Be seronegative to the appropriate HPV type(s) at Day 1.

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

The final determination on protocol violations, which will be used for determining the PPI population, will be made prior to the database lock and will be documented in a separate memo.

Table 5 Acceptable Day Ranges for Vaccination Visits

Vaccination Dose	Protocol Specified Visit Window	Day Range for Inclusion in Statistical Analysis (Relative to Day 1 [†])
3-Dose [0,2,6 regimen]		
Dose 1	Day 1 [†]	0
Dose 2	Month 2 ± 3 weeks	36 to 84
Dose 3	Month 6 ± 4 weeks	148 to 218
2-Dose [0,6 regimen]		
Dose 1	Day 1 [†]	0
Dose 2	Month 6 ± 4 weeks	148 to 218
[†] Day 1 refers to the date when vaccination dose 1 was administered.		

Table 6 Acceptable Day Ranges for Collection of Serum Samples

Study Visit	Sample Type	Target Collection Day (Relative to Day 1) [†]	Day Range for Inclusion in Statistical Analysis (Relative to Day 1 [†])
Day 1	Serum	0	-14 to 0
Month 7	Serum	30 days post last dose	21 to 49 post last dose
Month 18	Serum	548	366 to 730
Month 30	Serum	913	731 to 1004
[†] Day 1 refers to the date when vaccination dose 1 was administered. For Month 7, indicated target collection/day range is relative to date of injection of last dose of 9vHPV vaccine.			

All 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 at least 1 vaccination.
- (2) Have provided serum samples with evaluable results.
- (3) Be seronegative to the appropriate HPV types at Day 1.

For each of the PPI and ANPS analysis populations:

- 1) To be included in the analysis population for HPV 6 or 11, participants must be seronegative to both HPV 6 and 11 at Day 1;
- 2) To be included in the analysis population for any other vaccine HPV type, participants must be seronegative at Day 1 only for the HPV type being analyzed.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all participants who received at least 1 dose of 9vHPV vaccine and have provided safety data at any time during the study. Participants will be included in the study arm corresponding to the study treatment they actually received for the analysis of safety data using the APaT population (i.e., 3 doses [0,2,6 regimen] or 2 doses [0,6 regimen] of 9vHPV vaccine). For participants who received only 1 dose of 9vHPV vaccine, or a participant allocated to the 3-dose regimen arm but received 2 doses that does not correspond to the [0,6 regimen], a safety profile listing will be created separately from the safety reports that will be provided for the 3-dose [0,2,6 regimen] and 2-dose [0,6 regimen] arms.

9.6 Statistical Methods

9.6.1 Statistical Methods for Immunogenicity Analyses

Estimation of percent seroconversion

Within a study arm, the point estimate of percent seroconversion is calculated as the percent of participants with evaluable serology result at 1 month post last dose (Month 7) who seroconvert at 1 month post last dose (Month 7), where seroconversion is as defined in Section 9.4.1. Calculation of the corresponding 95% CI is based on the exact binomial method proposed by Clopper and Pearson (1934).

Estimation of percent seropositivity

For each of the Months 18 and 30 time points, within a study arm, the point estimate of percent seropositivity for a given HPV type is calculated as the percent of participants with evaluable serology result with cLIA titer at or above the serostatus cutoff for the given HPV type. Calculation of the corresponding 95% CI is based on the exact binomial method proposed by Clopper and Pearson (1934).

Estimation of GMTs

Within a study arm, GMTs and corresponding 95% CI will be derived by taking the anti-logarithm of the mean and corresponding 95% CI (calculated based on the t-distribution) of the mean of the log-transformed anti-HPV titers. Anti-HPV titers reported as less than the LLOQ of the relevant anti-HPV type will be replaced by the half of the LLOQ in the log-transformation of anti-HPV titers.

Table 7 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
Seroconversion to each HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 3 doses of 9vHPV vaccine	P	Point estimate, 95% CI by exact binomial method	PPI	Observed data only
	S		ANPS	
Seroconversion to each HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 2 doses of 9vHPV vaccine	P	Point estimate, 95% CI by exact binomial method	PPI	Observed data only
	S		ANPS	
Secondary Endpoints				
GMTs to each HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 3 doses of 9vHPV vaccine	P	Point estimate and 95% CI	PPI	Observed data only
	S		ANPS	
GMTs to each HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 2 doses of 9vHPV vaccine	P	Point estimate and 95% CI	PPI	Observed data only
	S		ANPS	
Abbreviations: P = Primary, PPI = Per-protocol immunogenicity, S = Supportive, ANPS = all naïve participants with serology				

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs).

The analysis of safety results usually follows a tiered approach in the studies conducted by the Sponsor. However, this study has no comparison between study arms. Thus, the following summaries will be provided as described in [Table 8](#).

- Incidence is defined as (number of participants with the indicated endpoint divided by the total number of participants with follow-up over the relevant period)*100%.

- For the measured adverse events of redness and swelling, 0 to 1 inch will be categorized as mild intensity, >1 inch to 2 inches will be categorized as moderate intensity, and >2 inches will be categorized as severe intensity.

The specific events of interest in this study will be injection-site prompted adverse events on the VRC, such as pain/tenderness, swelling and redness/erythema occurring Day 1 through 5 following any vaccination, and elevated temperature ($\geq 37.5^{\circ}\text{C}$), from Day 1 through 5 following any vaccination.

Table 8 Analysis Strategy for Safety Parameters

Adverse Event Endpoint	Within study arm 95%CI	Follow-Up Period		
		After Any Vaccination Visit		Any Time During Study
		Day 1 to Day 5 [†]	Day 1 to Day 15 [†]	
Clinical AEs/vaccine-related AEs				
Any AEs/vaccine-related AEs			•	
Deaths				•
Injection-site AEs/vaccine-related AEs				
Injection-site AEs/vaccine-related AEs of pain/tenderness, swelling, and redness/erythema	•	•		
Other injection-site AEs/vaccine-related AEs	•	•		
Severe injection-site AEs [§] /vaccine-related AEs	•	•		
Number (%) of participants by maximum intensity rating, over all injection-site AEs [§] /vaccine-related AEs		•		
Number (%) of participants by maximum intensity rating, within each of the categories of injection-site AEs [§] /vaccine-related AEs		•		
Systemic AEs/vaccine-related AEs				
Any systemic AEs/vaccine-related AEs	•		•	
Number (%) of participants by maximum intensity rating, over all systemic AEs/vaccine-related AEs			•	
Temperatures				
Elevated temperatures [#]	•	•		
Maximum temperatures ^{††}		•		
AEs of Special Interest				
Serious AEs	•		•	•
Serious vaccine-related AEs	•		•	•
New medical conditions ^{‡‡}				•
Pregnancy outcomes				•
[†] The day of vaccination is counted as Day 1. Day 1 to Day 5 refers to the period within 4 days of a vaccination. Day 1 to Day 15 refers to the period within 14 days of a vaccination.				
[§] For the measured adverse events of redness and swelling 0 to 1 inch will be categorized as mild, >1 inch to 2 inches will be categorized as moderate and >2 inches will be categorized as severe.				
[#] Defined as maximum (over the follow-up period) temperature ≥37.5°C.				
^{††} Distribution of maximum temperatures over the relevant follow-up period.				
^{‡‡} Including new medical conditions considered potentially of an autoimmune nature.				
The exact binomial method proposed by Clopper and Pearson (1934).				
AEs = Adverse events; CI = Confidence interval				

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics and demographic variables

Baseline and demographic characteristics; prior and concomitant therapies; counts and percent of participants screened, enrolled, vaccinated and the primary reason for discontinuation; will be summarized in tabular format by study arm. No statistical hypothesis tests will be performed on these characteristics.

9.7 Interim Analyses

No interim analyses are planned in this study.

9.8 Multiplicity

Not applicable. The study is an estimation-only study.

9.9 Sample Size and Power Calculations

A total sample size of 300 participants will be enrolled. 100 participants will be enrolled in each study arm. When the discontinuation rate and exclusion from the HPV type-specific PPI population is at most 5%, at least 95 participants in each study arm will be evaluable for the analysis of immune response at 1 month post last dose (Month 7). In each arm, at least 95 participants evaluable per study arm will allow estimation of percent seroconversion that has a corresponding 95% CI with half-width of about 3 percentage points, assuming true percent seroconversion of 99%. In addition, at least 95 participants evaluable per study arm provides at least 0.99 probability to demonstrate that the point estimate of percent seroconversion exceeds 90% for all of 9 HPV types when the true percent seroconversion is 99%. At least 95 participants evaluable per study arm provides at least 0.88 probability to attain a lower limit of 95% CI of percent seroconversion equal to or more than 90% when the true percent seroconversion is at least 99%.

For the safety analysis, all participants are expected to be evaluable. If no SAE are observed among the 100 participants per study arm, this study will provide 95% confidence that the underlying percentage of participants with an SAE is <3.0% in each study arm.

The estimate and the half-width of the 95% confidence interval for the underlying percentage of participants with the adverse event given various hypothetical observed number of participants with an adverse event within the study arm are provided in [Table 9](#). These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934).

Table 9 Estimate of Incidence of Adverse Event and Half-width of 95% Confidence Interval Based on Hypothetical Number of Participants with Adverse Event among 100 Participants in the Study Arm

Hypothetical Number of Participants with Adverse Event	Estimate of Incidence	Half-width of 95% Confidence Interval [†]
1	1%	2.7%
2	2%	3.4%
4	4%	4.4%
8	8%	5.8%
16	16%	7.6%
32	32%	9.5%
[†] Based on the exact binomial method (Clopper and Pearson, 1934).		

9.10 Subgroup Analyses

No subgroup analyses are planned for this study.

9.11 Compliance (Medication Adherence)

Compliance is defined in this study as receipt of all scheduled study vaccinations. To summarize compliance, the numbers of participants who receive each vaccination will be tabulated. Compliance with the planned vaccination schedule (3-dose: Day 1, Month 2, Month 6, 2-dose: Day 1, Month 6) will be described by histograms of actual intervals between vaccinations relative to the expected interval.

9.12 Extent of Exposure

As indicated in Section 6.1, each study participant is planned to be administered 0.5 mL of 9vHPV vaccine at each vaccination visit (3-dose: Day 1, Month 2, Month 6, 2-dose: Day 1, Month 6). Thus, each participant is expected to be administered a total of 1.5 mL of 9vHPV vaccine over a 6-month duration for 3-dose 9 to 15 years old boys, 1.0 mL of 9vHPV vaccine over a 6-month duration for 2-dose 9 to 14 years old boys and 2-dose 9 to 14 years old girls, respectively.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 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.

10.1.2 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.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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 that 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.

10.1.3.1 Confidentiality of Data

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

10.1.3.2 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 to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3.3 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.

10.1.4 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.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the 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 study 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.

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, 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.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 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 or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- There are no protocol-specific requirements for safety laboratory testing.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- 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 intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting 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 intervention 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 intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant’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) that 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 1 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.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
 - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
 - Moderate: An event that causes sufficient discomfort to interfere 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 erythema/redness or swelling from the day of vaccination through Day 5 postvaccination will be evaluated by maximum size.

Assessment of causality

- Did the Sponsor’s product cause the AE?
- The determination of the likelihood that the Sponsor’s product caused the AE will be provided by an investigator who is a qualified physician. The investigator’s signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor’s product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor’s product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?
- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a vaccine-induced effect?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in the 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 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
 - Yes, there is a reasonable possibility of Sponsor's product relationship:
 - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship:
 - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 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.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
 - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
 - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

- Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

Not applicable.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.¹
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.²
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.²
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants' legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants' legal guardians on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant's legal guardians will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants or their legal guardians may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants or their legal guardians may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant and participant's legal guardian of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The

specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
9vHPV	9-valent human papillomavirus
AE	adverse event
ANPS	All Naïve Participants with Serology
APaT	All Participants as Treated
CI	confidence interval
β-hCG	β-human chorionic gonadotropin
cLIA	competitive Luminex Immunoassay
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EDC	electronic data collection
EMA	European Medicines Agency
FBR	future biomedical research
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
GMT	Geometric mean titer
HIV	human immunodeficiency virus
HPV	human papillomavirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IRT	interactive response technology
iSAP	integrated statistical analysis plan
IVIG	intravenous gamma globulin
mMU/mL	milli-Merck Units per milliliter
NSAE	nonserious adverse event
PE	Phycoerythrin
PK	pharmacokinetic
PPI	Per-Protocol Immunogenicity
qHPV	quadrivalent HPV
RNA	ribonucleic acid
RRP	Recurrent Respiratory Papillomatosis
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TNF-α	tumor necrosis factor-alpha
VLP	virus-like particle
VRC	vaccination report card
WHO	World Health Organization

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