Official Protocol Title:	A Phase 3, randomized, placebo-controlled clinical study to evaluate the efficacy, immunogenicity and safety of the 9vHPV vaccine in Japanese males, 16 to 26 years of age.
NCT number:	NCT04635423
Document Date:	24-Sep-2024

TITLE PAGE

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Protocol Title: A Phase 3, randomized, placebo-controlled clinical study to evaluate the efficacy, immunogenicity and safety of the 9vHPV vaccine in Japanese males, 16 to 26 years of age.

Protocol Number: 064-03

Compound Number: V503

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

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IND	Not applicable

Approval Date: 24 September 2024

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 3	24-SEP-2024	The overall rationale for this amendment is to add a database lock for the final efficacy analysis to account for cases that accrued after the data used for the primary efficacy analysis but before the final immunogenicity and safety assessments. The final database lock for the base study will occur after all immunogenicity and safety data of the base study are available.
Amendment 2	05-DEC-2023	The overall rationale for this amendment is to add an extension study to give participants in the placebo group a 3-dose series of the 9vHPV vaccine and give participants who did not complete 3-dose regimen of 9vHPV vaccine the opportunity to finish the series after completion of the base study.
Amendment 1	19-SEP-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA.
Original Protocol	13-AUG-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment:

The overall rationale for this amendment is to add a database lock for the final efficacy analysis to account for cases that accrued after the data used for the primary efficacy analysis but before the final immunogenicity and safety assessments. The final database lock for the base study will occur after all immunogenicity and safety data are available.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
4.1 Overall Design	Added the description of an additional database lock after the final efficacy sample assessment in the base study.	To conduct the final efficacy analysis earlier than the final database lock of the base study.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
8.5.4 Regulatory Reporting Requirements for SAE	Added note for EU reporting requirements.	To comply with EU CTR regulations.
9.1 Statistical Analysis Plan Summary	Added the description of an additional database lock after the final efficacy sample assessment in the base study.	To conduct the final efficacy analysis earlier than the final database lock of the base study.
9.2 Responsibility for Analyses/In-house Blinding	Added the description of an additional database lock after the final efficacy sample assessment in the base study.	Refer to Section 9.1 rationale.
9.6 Statistical Methods	Added the description of an additional database lock after the final efficacy sample assessment in the base study.	Refer to Section 9.1 rationale.
10.1.3 Data Protection	Added note on global privacy compliance.	To clarify adherence to global privacy compliance.
10.1.8 Data Quality Assurance	Added note for document retention period in the EU	Refer to Section 8.5.4 rationale.
Throughout Protocol	Minor administrative, formatting, editorial, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, randomized, placebo-controlled clinical study to evaluate the efficacy, immunogenicity and safety of the 9vHPV vaccine in Japanese males, 16 to 26 years of age.

Short Title: Phase 3 study for efficacy against anogenital persistent infection, immunogenicity, and safety of the 9vHPV vaccine in Japanese males

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The following objectives and endpoints will be evaluated in Japanese males, 16 to 26 years of age.

Primary Objective	**Primary Endpoint**
Objective: To demonstrate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 6/11/16/18-related anogenital (external genital and intra-anal) persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type. **Hypothesis:** Administration of a 3-dose regimen of the 9vHPV vaccine reduces the combined incidence of HPV 6/11/16/18-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo (The statistical criterion for success requires that the lower bound of the 2-sided 95% CI of vaccine efficacy is >0%).	HPV 6/11/16/18-related anogenital persistent infection
Objective: To evaluate the safety and tolerability of the 9vHPV vaccine.	-Solicited injection-site adverse events (AEs) -Systemic AEs -Serious adverse events (SAEs)

Secondary Objectives	Secondary Endpoints
Objective: To demonstrate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type. **Hypothesis:** Administration of a 3-dose regimen of the 9vHPV vaccine reduces the combined incidence of HPV 31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo (The statistical criterion for success requires that the lower bound of the 2-sided 95% CI of vaccine efficacy is >0%).	HPV 31/33/45/52/58-related anogenital persistent infection
Objective: To summarize antibody responses [Geometric Mean Titer (GMT) and percent seroconversion] to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7 in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type, by all participants, heterosexual males (HM) group and males who have sex with males (MSM) group, respectively.	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	Papilloma viral infection
Population	Japanese males, 16 to 26 years of age
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects Investigator Sponsor Outcomes Assessor

Estimated Duration of Study	The Sponsor estimates that the study will require approximately up to 7 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. The base study of this study is a case-driven study and primary efficacy analysis will be conducted after at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases are collected. After completion of the base study, the participants in the placebo group and participants who did not complete 3-dose regimen of 9vHPV vaccine will be offered an opportunity to start or complete a 3-dose series of 9vHPV vaccine in the extension study. 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.

Number of Participants:

Approximately 1050 participants will be randomized in 1:1 ratio to receive the 9vHPV vaccine or placebo. The targeted enrollment for MSM is approximately 10% of all participants.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Vaccination Regimen	Use
The 9vHPV vaccine	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	0.5 mL	IM	Day 1, Month 2, Month 6	Test Product
Placebo	Saline for injection	0.9% sodium chloride	0.5 mL	IM	Day 1, Month 2, Month 6	Placebo
The 9vHPV vaccine (Extension Study)	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	0.5 mL	IM	1 dose in Ext: Ext 1 OR 2 doses in Ext: Ext 1 and Month 4 in Ext	Test Product
Placebo (Extension Study)	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	0.5 mL	IM	Ext 1, Month 2 in Ext, Month 6 in Ext	Test Product

9vHPV = 9-valent human papillomavirus; IM = Intramuscular; VLP = virus-like particle

Other current or former name(s) or alias(es) for study intervention(s) are as follows: the 9vHPV vaccine, SILGARD®9, GARDASIL®9 and V503.

Total Number of Intervention Groups/Arms	2 intervention groups
Duration of Participation	Each participant will participate in the base study for up to 61 months from the time the participant (or their legally acceptable representative) provides documented informed consent through the final contact. Each participant will receive 3 doses of the 9vHPV vaccine or placebo intramuscularly at Day 1, Month 2, and Month 6. After the completion of vaccination, each participant will be followed every 6 months. This is a case-driven study, and participants will continue in the study until at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases are collected. After at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases have accrued, the initial database lock and unblinding will be performed and notified to the study sites. Following notification, participants remaining in the study (ie, who have not yet completed a Final Visit) will proceed to the Final Visit in the base study promptly (as shown in Section 1.3, and Section 8.12.1.4). Sponsor will notify the participants' vaccination assignment after the initial database lock. After unblinding the participants' vaccination assignment, eligible participants will be offered and consented to enter an extension study, which could last up to 9 months. Participants in the placebo group will receive a 3-dose series of the 9vHPV vaccine. Participants who did not complete a 3-dose series in the base study will be eligible to receive 1 to 2 doses of 9vHPV depending on the doses they had completed. Participants will have a safety phone call 1 month after their last dose in the extension study.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	Yes
Steering Committee	No

Study governance considerations are outlined in Appendix 1.

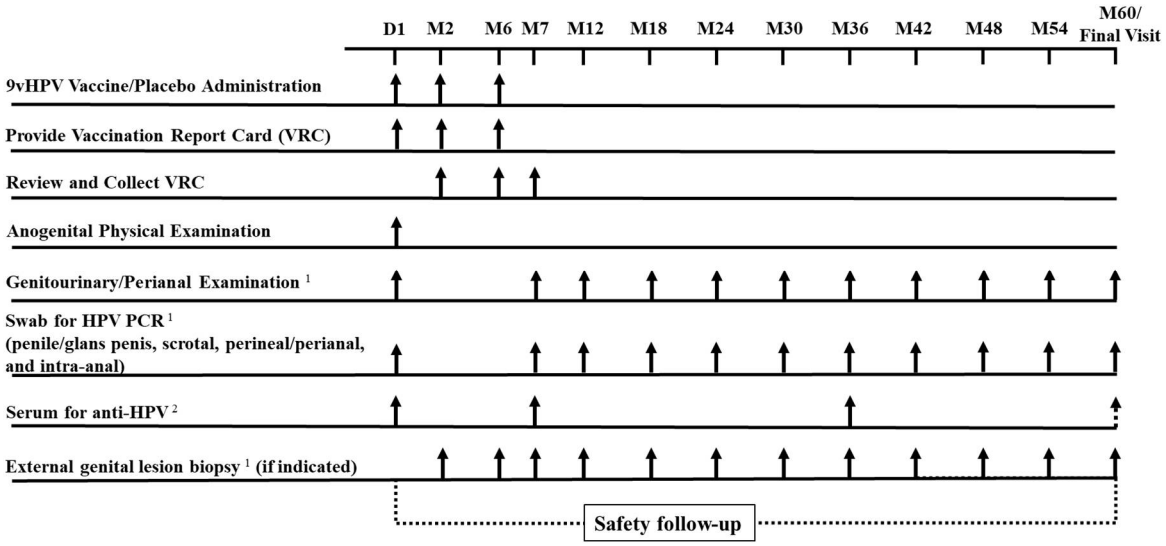
Study Accepts Healthy Participants: Yes

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 (Base Study) and Figure 2 (Extension Study).

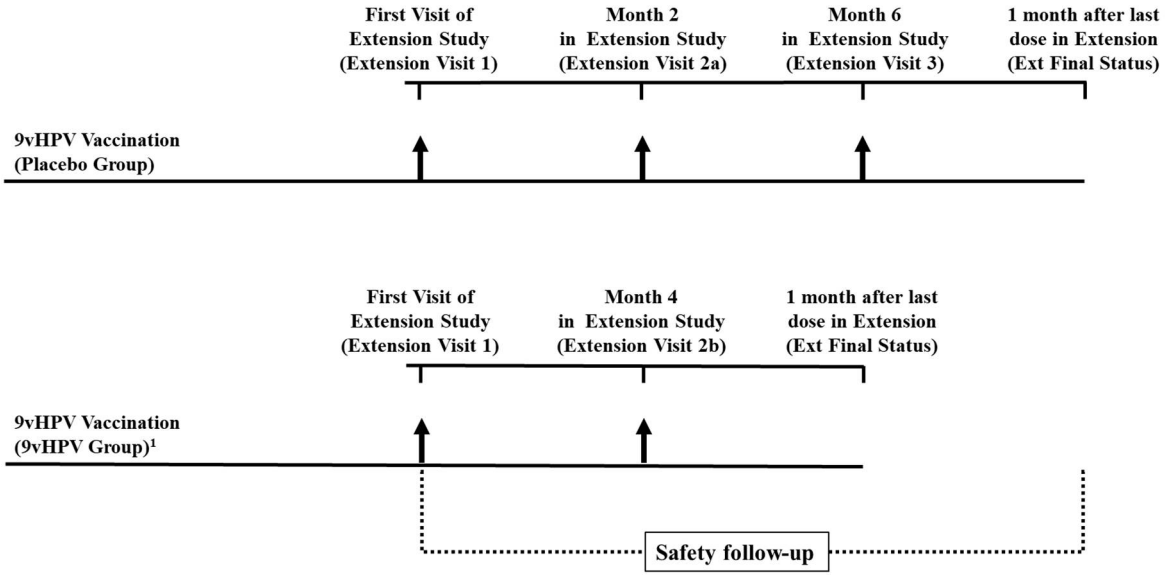
Figure 1 Study Design (Base Study)



9vHPV = 9-valent human papillomavirus; D = Day; HPV = human papillomavirus; M = Month; PCR = polymerase chain reaction
After at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases have accrued, initial database lock and unblinding will be performed and notified to the study sites. Following notification, participants remaining in the study (ie, who have not yet completed a Final Visit) will proceed to the Final Visit in the base study promptly. Under that scenario, participants who have not yet completed a Final Visit will complete the specified procedures in Final Visit in this Schedule of Activities. (See Section 1.3 and Section 8.12.1.4).

[1] After initial database lock and unblinding, examination and sample collection for efficacy assessment should not be conducted.
[2] Even after initial database lock and unblinding, serum sample will be collected. At the Final Visit, serum sample should be collected within the specific day ranges from Day 913 to Day 1277 only from the participant who have not yet completed Month 36.

Figure 2 Study Design (Extension Study)



9vHPV = 9-valent human papillomavirus

[1] Participants who did not complete the 3-dose regimen of 9vHPV vaccine in the base study will be eligible to receive the remaining doses from the series (ie, if they already received 2 doses in the base study, they will receive 1 dose in the extension study and a safety phone call 1 month after the last dose; if they already received 1 dose in base study, they will receive 2 doses which are 4 months apart in the extension study and a safety phone call 1 month after the last dose). For those who do not require a dose at the Extension Visit 2b, the visit will not be conducted.

1.3 Schedule of Activities

1.3.1 Scheduled Visits for Base Study

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	Notes
Scheduled Day/Month	**Day 1**	**Month**												
		2	**6**	**7**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60 (Final Visit)**	
Visit Window[1]		**± 3 Weeks**	**± 4 Weeks**	**3 to 7 Weeks Postdose 3**	**± 1 month**									To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Administrative Procedures														
Obtain Informed Consent	X													
Obtain Informed Consent for Future Biomedical Research	X													Participation in future biomedical research is optional and consent must be obtained before collection of blood (DNA) samples.
Review Inclusion/Exclusion Criteria	X													
Assign Participant Identification Card	X													
Collect Lifetime Medical History (includes substance usage)	X													Substances: Alcohol, tobacco
Update Medical History (new conditions not already recorded as medical history or AEs)		X	X	X	X	X	X	X	X	X	X	X	X	
Collect Lifetime Sexual History	X													
Collect Sexual Activity		X	X	X	X	X	X	X	X	X	X	X	X	Sexual activity will not be collected after initial database lock and unblinding.
Review Prior/Concomitant Medication and Non-study Vaccination Review	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 6.5 for prerequisites for medications and non-study vaccines

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	Notes
Scheduled Day/Month	**Day 1**	**Month**												
		2	**6**	**7**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60 (Final Visit)**	
Visit Window[1]		**± 3 Weeks**	**± 4 Weeks**	**3 to 7 Weeks Postdose 3**	**± 1 month**									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. Participants who have a fever (defined as an oral temperature of ≥37.5°C) within the 24-hour period prior to vaccination 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													
Anogenital Physical Examination	X													Prior to vaccination
Genitourinary examination for external genital lesions	X			X	X	X	X	X	X	X	X	X	X	Prior to vaccination on Day 1 Examination will not be required after initial database lock and unblinding.
Penile/glans penis file and wetted swab for HPV PCR	X			X	X	X	X	X	X	X	X	X	X	Prior to vaccination on Day 1 Sample should not be collected after initial database lock and unblinding.
Scrotal file and wetted swab for HPV PCR	X			X	X	X	X	X	X	X	X	X	X	Prior to vaccination on Day 1 Sample should not be collected after initial database lock and unblinding.
Perianal examination for external genital lesions	X			X	X	X	X	X	X	X	X	X	X	Prior to vaccination on Day 1 Examination will not be required after initial database lock and unblinding.

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	Notes
Scheduled Day/Month	Day 1	Month												
		2	6	7	12	18	24	30	36	42	48	54	60 (Final Visit)	
Visit Window[1]		± 3 Weeks	± 4 Weeks	3 to 7 Weeks Postdose 3	± 1 month									To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Perineal/perianal file and wetted swab for HPV PCR	X			X	X	X	X	X	X	X	X	X	X	Prior to vaccination on Day 1 Sample should not be collected after initial database lock and unblinding.
Intra-anal wetted swab for HPV PCR	X			X	X	X	X	X	X	X	X	X	X	Prior to vaccination on Day 1 Sample should not be collected after initial database lock and unblinding.
External genital lesion biopsy (if indicated)		X	X	X	X	X	X	X	X	X	X	X	X	Processed and analyzed at Central Laboratory Sample should not be collected after initial database lock and unblinding.
Sexually Transmitted Infection (STI) Testing (local laboratory testing, at the discretion of the investigator if clinically indicated)	X	X	X	X	X	X	X	X	X	X	X	X	X	Optional at any visit
Blood Sample Collection (Serum for anti-HPV)	X			X					X				(X)[2]	Prior to vaccination on Day 1 Sample should be collected even after initial database lock and unblinding.
Blood Sample Collection (DNA) for Future Biomedical Research	X													Prior to vaccination from enrolled participants only (optional).
Vaccine Allocation/Randomization	X													
9vHPV Vaccine/Placebo Administration	X	X	X											
30-minute postvaccination observation period	X	X	X											
Provide Vaccination Report Card (VRC)	X	X	X											See Section 8.4.4 for data collected in VRC.

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	Notes
Scheduled Day/Month	**Day 1**	**Month**												
		2	**6**	**7**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60 (Final Visit)**	
Visit Window[1]		**± 3 Weeks**	**± 4 Weeks**	**3 to 7 Weeks Postdose 3**	**± 1 month**									To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Review and Collect VRC		X	X	X										Telephone contacts after 15 days from Day 1, Month 2 and Month 6, respectively to remind the participants.
Monitor Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	

Once at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases have been observed, initial database lock and unblinding will be performed and notified to the study sites. Following notification, participants remaining in the study (ie, who have not yet completed a Final Visit) will proceed to a Final Visit in the base study promptly. Under that scenario, participants who have not yet completed a Final Visit will complete the specified procedures in Final Visit in this Schedule of Activities. Details are shown in Section 8.12.1.4.

[1] At or later than Visit 5, any visit outside of visit window must occur at least 4 months after the previous visit (ie, the minimum length of time between samples to be counted as a case of persistent infection, see Section 9.4.1). Regarding protocol study visit windows, the following situations require consultation between the investigator and the Sponsor and written documentation of the collaborative decision: the study site is considering skipping a visit.

[2] When the cases would accrue earlier, participants who have not yet completed Month 36 should schedule a Final Visit with collection of serum sample within the specific day ranges from Day 913 to Day 1277, if possible. At the Final Visit, serum sample should not be collected from the participants who have already completed Month 36 or outside of the day ranges from Day 913 to Day 1277.

1.3.2 Scheduled Visits for Study Extension (Placebo Group)

Visit Number	Extension Visit 1	Extension Visit 2a	Extension Visit 3	Ext Final Status	Notes
Scheduled Day/Month	**First Visit of Extension Study**	**2 (Extension)**	**6 (Extension)**	**1 month after last dose in Extension**	
Visit Window		**± 3 Weeks**	**± 4 Weeks**	**± 1 Week**	To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Obtain Informed Consent	X				
Review Inclusion/Exclusion Criteria	X				
Measure Oral Temperature	X	X	X		Prior to each vaccination. Participants who have a fever (defined as an oral temperature of ≥37.5°C) within the 24-hour period prior to vaccination must be rescheduled.
9vHPV Vaccine Administration	X	X	X		The first vaccination in the extension study is recommended to occur the same day as the Final Visit of base study, if possible.
30-minute postvaccination observation period	X	X	X		
SAEs and Deaths	X	X	X	X (Phone call)	SAEs and deaths, regardless of causality, will be reported from the time of first vaccination through 1 month after the participant's last vaccination in the extension study.

9vHPV = 9-valent human papillomavirus; SAE=serious adverse event

1.3.3 Scheduled Visits for Study Extension (9vHPV Group)

Visit Number	Extension Visit 1	Extension Visit 2b	Ext Final Status	Notes
Scheduled Day/Month	**First Visit of Extension Study**	**4 (Extension)**	**1 month after last dose in Extension**	For those who do not require a dose at the Extension Visit 2b, the visit will not be conducted.
Visit Window		**± 3 Weeks**	**± 1 Week**	To calculate visit windows, assume 1 month=30 days and 1 week=7 days
Obtain Informed Consent	X			
Review Inclusion/Exclusion Criteria	X			
Measure Oral Temperature	X	X		Prior to each vaccination. Participants who have a fever (defined as an oral temperature of ≥37.5°C) within the 24-hour period prior to vaccination must be rescheduled.
9vHPV Vaccine Administration [a]	X	X		The first vaccination in the extension study is recommended to occur the same day as the Final Visit of base study, if possible.
30-minute postvaccination observation period	X	X		
SAEs and Deaths	X	X	X (Phone call)	SAEs and deaths, regardless of causality, will be reported from the time of first vaccination through 1 month after the participant's last vaccination in the extension study.

9vHPV = 9-valent human papillomavirus; SAE=serious adverse event

[a] Participants who did not complete the 3-dose regimen of 9vHPV vaccine in the base study will be eligible to receive the remaining doses from the series (ie, if they already received 2 doses in the base study, they will receive 1 dose in the extension study and a safety phone call 1 month after the last dose; if they already received 1 dose in base study, they will receive 2 doses which are 4 months apart in the extension study and a safety phone call 1 month after the last dose).

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] [Stamataki, 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].

Global clinical studies have demonstrated that the quadrivalent HPV (qHPV) vaccine reduces the incidence of external genital and intra-anal persistent infection, anal precancers, and anogenital warts caused by HPV types 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]. The results of Protocol V501-122, a local Phase 3 study, demonstrated that qHPV vaccine also prevents external genital and intra-anal persistent infection caused by HPV types 6, 11, 16, and 18 in Japanese males [Mikamo H., et al 2019].

The 9vHPV vaccine was developed to cover the 4 HPV types included in the qHPV vaccine and an additional 5 high-risk HPV types (31, 33, 45, 52, 58). HPV 6 and 11 are responsible for approximately 90% of global 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, as of February 2020, is licensed in more than 80 countries or regions 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.

HPV vaccination contributes to reducing the burden of HPV diseases in males. The 9vHPV vaccine is approved to prevent vaccine type HPV-related genital warts and anal cancer and its precancers in males in other countries. In contrast to cervical cancer in females, there is no widespread screening program in any country for detection of HPV related anal cancers in males, making prophylactic vaccination is the only realistic preventive measure for HPV diseases 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. 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.

This study will 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 prevention of anal cancer and its precancerous or dysplastic lesions caused by 9vHPV types in both males and females, and genital warts in males in Japan. 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 Japan, the 9vHPV vaccine was approved for the prevention of cervical, vulvar, and vaginal cancers and precancers, and genital warts caused by 9-valent HPV types in women.

2.2.1.1 Disease Burden and Epidemiology for HPV-related anogenital disease

The average lifetime probability of acquiring HPV among those with at least 1 opposite sex partner is estimated to be greater than 80% [Chesson, H.W., et al 2014]. 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 is strongly correlated with the number of lifetime sexual partners [Xi, L.F. and Koutsky, L.A. 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, increasing the risk of exposure to the virus.

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 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.S., 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, 952 new anal cancer cases occurred in 2015 based on national cancer incidence data from the National Cancer Registration and Statistics Cancer Information Service of the National Cancer Research Center [National Cancer Center. 2015]. In addition, Daling et al. reported that HPVs were detected in 78.0% and 97.7% anal cancer of HM and MSM, respectively [Daling, J.R., et al 2004].

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

The qHPV vaccine was highly effective in preventing HPV 6, 11, 16, or 18-type related persistent infection and external genital lesions [genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN)] in male participants, 16-26 years old, and anal diseases (AIN/anal cancer) in MSM participants in a global Phase 3 study (V501-020). Long term follow-up data in 2 additional global studies (V501-020-21 and V501-018-11) showed the protective effectiveness of qHPV vaccine in boys and males, 9 to 26 years of age persisted for approximately 10 years after the first vaccination. Similarly, the results of Protocol V501-122 demonstrated that qHPV vaccine prevents persistent anogenital infections associated with HPV types 6, 11, 16 and 18 in Japanese males (16-26 years of age). qHPV vaccine was generally well-tolerated both in non-Japanese and Japanese males in these studies.

The efficacy, immunogenicity and safety of the 9vHPV vaccine (V503) was demonstrated in a global Phase 3 study in females (16-26 years old, including Japanese females) in Protocol V503-001. The 9vHPV vaccine prevented infection and disease caused by the vaccine type HPV and was generally well-tolerated [Joura, E.A., et al 2015] [Huh, W.K., et al 2017]. In

addition, an open-label, Japan local Phase 3 study was also conducted. The safety, tolerability, and immunogenicity of the 9vHPV vaccine in Japanese girls (9-15 years old) was demonstrated in Protocol V503-008 [Iwata, S., et al 2017]. At Month 7 (after 1 month post dose 3), 100% of the participants exhibited seroconversion for each type of HPV with a 3-dose regimen of the 9vHPV vaccine. The immunogenicity in this population was similar to that observed in Japanese females aged 16-26 years in V503-001.

2.2.2.2 On-going Clinical Studies in Japan

For the 9vHPV vaccine in males, 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. This study also includes Japanese adult males, 20 to 45 years of age. In addition, a local phase 3 study (Protocol V503-066) is also currently being conducted to evaluate the immunogenicity and safety of the 9vHPV vaccine following 3-dose in Japanese boys aged 9 to 15 years as well as that following 2-dose in Japanese boys and girls aged 9 to 14 years.

2.2.2.3 Real-world Evidence Studies

A recent study of a nationally representative sample of males and females in the USA found a reduction in the prevalence of HPV types 6/11/16/18 infections in genital sites among vaccinated participants that completed the National Health and Nutrition Examination Survey. There were a reduced prevalence of HPV types 6/11/16/18 infections at the genital site among vaccinated females (RR 0.2 [0.1 to 0.3]) and males (RR 0.7 [0.1 to 5.4]) compared with non-vaccinated participants [Brouwer, A.F., et al 2019].

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 AEs identified in previous studies and post marketing surveillance support a favorable benefit-risk for the 9vHPV vaccine in this study population.

Approximately 50% of participants receive placebo in the base study. After the base study is completed, recipients of placebo and participants who did not complete their 3-dose series of 9vHPV vaccine in the base study will be offered vaccination with the 9vHPV vaccine in an extension study as allowed by local regulations and IRBs.

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

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The following objectives and endpoints will be evaluated in Japanese males, 16 to 26 years of age.

Primary Objective	**Primary Endpoint**
Objective: To demonstrate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 6/11/16/18-related anogenital (external genital and intra-anal) persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type. **Hypothesis:** Administration of a 3-dose regimen of the 9vHPV vaccine reduces the combined incidence of HPV 6/11/16/18-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo (The statistical criterion for success requires that the lower bound of the 2-sided 95% CI of vaccine efficacy is >0%).	HPV 6/11/16/18-related anogenital persistent infection
Objective: To evaluate the safety and tolerability of the 9vHPV vaccine.	-Solicited injection-site adverse events (AEs) -Systemic AEs -Serious adverse events (SAEs)

Secondary Objectives	Secondary Endpoints
Objective: To demonstrate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type. **Hypothesis:** Administration of a 3-dose regimen of the 9vHPV vaccine reduces the combined incidence of HPV 31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo (The statistical criterion for success requires that the lower bound of the 2-sided 95% CI of vaccine efficacy is >0%).	HPV 31/33/45/52/58-related anogenital persistent infection
Objective: To summarize antibody responses [Geometric Mean Titer (GMT) and percent seroconversion] to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7 in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type, by all participants, heterosexual males (HM) group and males who have sex with males (MSM) group, respectively.	Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To evaluate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type.	HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection

Objective: To evaluate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 6/11/16/18/31/33/45/52/58-related genital warts, PIN, penile, perianal or perineal cancer compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type.	HPV 6/11/16/18/31/33/45/52/58-related genital warts, PIN, penile, perianal or perineal cancer
Objective: To evaluate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 6/11/16/18/31/33/45/52/58-related intra-anal persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type.	HPV 6/11/16/18/31/33/45/52/58-related intra-anal persistent infection
Objective: To evaluate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection detected in samples from three or more consecutive visits 6 months (± 1-month window) or longer apart (i.e., at least 12 months persistent infection) compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type.	HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection

4 STUDY DESIGN

4.1 Overall Design

Base Study

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind study of the 9vHPV vaccine (V503) in Japanese males, 16 to 26 years of age.

This study will evaluate the efficacy, immunogenicity and safety of the 9vHPV vaccine in Japanese males. In this study, approximately 1050 Japanese male participants (including a target enrollment of approximately 10% MSM) will be randomized in a 1:1 ratio with stratification by HM and MSM to receive 3 doses of either the 9vHPV vaccine or placebo (saline solution) on Day 1, Month 2, and Month 6.

Penile/glans penis, scrotal, perineal/perianal, and intra-anal samples will be collected by a wetted swab specimen for HPV PCR testing at Day 1, Month 7, 12, and every 6 months thereafter up to a maximum of approximately Month 60. These swabs will be tested for detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 by PCR assay. PCR analysis of the swabs will be used to identify participants who have an active HPV infection at enrollment and to determine persistent HPV infection endpoints.

A detailed genitourinary and perianal inspection will be performed at Day 1, Month 7, 12, and every 6 months thereafter up to a maximum of approximately Month 60. If a lesion observed at Day 1 is assessed to be possibly, probably, or definitely HPV-related or of unknown etiology, then the participant should be excluded from the study. All new (after Day 1) genitourinary and perianal lesions judged by the investigator to be possibly, probably, or definitely HPV-related, or any lesion whose etiology is not known will be biopsied. If multiple lesions are observed (after Day 1), then lesions of each representative morphology will be biopsied. If more than one anatomic location is affected, then a lesion from each location will be biopsied.

Tissue samples obtained from biopsy will be analyzed by HPV Thinsection PCR assay and by a consensus diagnosis from the HPV Vaccine Program Pathology Panel to determine clinical disease efficacy endpoints.

Blood samples will be collected immediately before vaccination on Day 1, Month 7, and Month 36 (or Final Visit) to evaluate HPV antibody responses.

Participants will be followed for solicited injection-site AEs Days 1 through Days 5 following each vaccination, and any other injection-site AEs and systemic AEs Days 1 through Days 15 following each vaccination. Any SAEs regardless of causality will be recorded from the time of randomization through 6 months postdose 3. Vaccine-related SAEs and deaths will be collected throughout the study. New medical conditions (defined as incident medical conditions occurring outside of 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.

The primary analysis is case driven. The database will be locked, and the primary analysis will be conducted after at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases have been observed in the base study. There is no interim analysis planned in this study. These efficacy results as well as immunogenicity and safety results based on data in the initial database lock for the primary analysis will be reported as the primary CSR. All participants will be unblinded after the primary efficacy analysis database lock. Once a participant is unblinded, no further efficacy samples will be collected from the participant.

Once at least 17 primary endpoint cases and at least 17 secondary efficacy endpoint cases are accrued, each participant will proceed to the Final Visit promptly without completing any other scheduled visits in order to complete the base study (as shown in Section 1.3, and Section 8.12.1.4). Additional database locks will be executed, including a second database lock after the completion of the final efficacy sample assessment for the purpose of the final efficacy analysis and a final database lock of the base study after the last participant's Final Visit in the base study for the final immunogenicity and safety analysis, respectively. Cumulative data collected from the initiation of the study will be summarized separately and a report will be written after each database lock. The base study will end after the last participant completes their Final Visit in the base study.

Extension Study

After accrual of at least 17 primary endpoint cases and at least 17 secondary efficacy endpoint cases in the base study have been achieved and the database has been locked for the primary efficacy analysis, participants will be unblinded to determine eligibility for subsequent vaccination with 9vHPV vaccine in the extension study.

The participants' vaccination group assignment in the base study will be communicated to the investigator by the Sponsor for the purpose of determining participant eligibility for receiving 9vHPV vaccine in the extension study. The investigator will be responsible for notifying each participant regarding his original vaccination group assignment and determining who is eligible to participate in the extension study. In the event that this communication results in the return of a participant who did not complete the base study (eg, lost to follow-up), this participant may be offered vaccine.

Eligible participants will be reconsented for the extension study and follow the procedures outlined in Section 1.3.2 and Section 1.3.3. If possible, it is recommended that the first vaccination in the extension study is administered on the same day as the Final Visit of the base study. Participants in the placebo group will receive a 3-dose series with the 9vHPV vaccine as allowed by local regulations and IRBs. Participants in the active group who did not complete the 3-dose series in the base study will be eligible to receive 1 to 2 doses in the extension study depending on the doses they had completed. SAEs and deaths will be collected throughout the extension study. Safety data from the extension study will be summarized in a separate report.

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

4.2 Scientific Rationale for Study Design

This study is designed to evaluate the 9vHPV vaccine efficacy against HPV 6/11/16/18-related anogenital persistent infection and HPV 31/33/45/52/58-related anogenital persistent infection, respectively. The qHPV vaccine efficacy findings associated with the 4 HPV types in V501-020 will be extrapolated to the 9vHPV vaccine, via the demonstration of the efficacy similarities against HPV type 6, 11, 16 or 18-related anogenital persistent infection in V501-122 with qHPV vaccine. Considering the comparison between this study data and previous study data (V501-122), 16 to 26 years old in both HM and MSM are selected as this study population in a manner consistent with Protocol V501-122. The enrollment of approximately 10% MSM participant will be targeted in this study. Please note “10%” is a target number considering the challenging nature of MSM enrollment in Japan from operational aspect. In addition, participants will be enrolled regardless of the history of circumcision. This study targeted young males with a maximum of 5 female (HM) and/or male (MSM) sexual partners in order to minimize the proportion of enrolled subjects who were HPV positive at baseline. In addition, in order to obtain a cohort with a reasonable risk of becoming infected after the vaccination series was completed, virgins were excluded from the study, with the exception of MSMs who identified themselves as a male who has had sex with males or must have engaged in oral sex with another male within the last year.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Efficacy endpoints based on precancerous lesions (high-grade intraepithelial dysplasia) were used in clinical studies with the qHPV and the 9vHPV vaccines to demonstrate protection from cervical, vulvar, vaginal, and anal cancers and precancers caused by vaccine HPV types. Results from efficacy clinical trials of the qHPV vaccine have shown that participants with HPV 16/18-related persistent infection were at a greater risk of HPV 16/18-related high-grade cervical dysplasia. In contrast, participants without persistent infection were unlikely to develop HPV 16/18-related high-grade cervical disease [Radley, D., et al 2016]. Similar results were observed in the pivotal study of the 9vHPV vaccine (Protocol V503-001) for the endpoints of HPV 31/33/45/52/58-related persistent infection and HPV 31/33/45/52/58-related high-grade disease (MSD unpublished data). This suggests that HPV 16/18/31/33/45/52/58-related persistent infection is appropriate as a surrogate endpoint for HPV 16/18/31/33/45/52/58-related high-grade cervical disease. Although HPV infection has been primarily studied in the context of cervical cancer, the results are considered applicable to other squamous epithelial cancers (including cancers of vulva, vagina, anal canal, oral cavity, pharynx, and larynx), that are susceptible to infection by high-risk HPV types [Gillison, M.L., et al 2012].

The primary efficacy endpoint is the incidence of HPV 6-, 11-, 16- or 18-related anogenital persistent infection. This endpoint was chosen based on the finding from two previous

studies of qHPV vaccine. One is the Japanese Phase 3 study that demonstrated the efficacy of qHPV vaccine against HPV 6-, 11-, 16- or 18-related anogenital persistent infection in Japanese males (Protocol V501-122). The other is the previous global Phase 3 study (V501-020) that qHPV vaccine showed prophylactic efficacy against HPV 6-, 11-, 16- or 18-related AIN and genital warts as well as HPV 6-, 11-, 16- or 18-related persistent infection in 16- to 26-year-old males, suggesting HPV related anogenital persistent infection is a predictor of HPV related anogenital diseases in males. For the purpose of bridging qHPV vaccine efficacy against HPV 6-, 11-, 16- or 18-related AIN and genital warts to 16- to 26-year-old Japanese males who received the 9vHPV vaccine, the incidence of HPV 6-, 11-, 16- or 18-related anogenital persistent infection was selected as the primary efficacy endpoint in this study as well as in V501-122.

As the secondary endpoint, the incidence of the other 5 types of HPV (31-, 33-, 45-, 52- or 58)-related anogenital persistent infection will also be assessed similarity with the 9vHPV vaccine efficacy finding associated with the 5 HPV types in V503-001 that was global Phase 3 study in 16- to 26-year-old females including Japanese females.

4.2.1.2 Immunogenicity Endpoints

Humoral immune responses to HPV vaccination will be evaluated based on previously established methods including MSD's Competitive Luminex Immunoassay (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 8.3 and Section 9.4.2.

4.2.1.3 Safety Endpoints

Safety assessments in this study are consistent with those used in previous studies of the 9vHPV vaccine and qHPV vaccine. In the base study, the paper vaccination report card (VRC) will be used to record AEs during the postvaccination periods. Details for the VRC are provided in Section 8.4.4.

Details on the safety endpoints evaluated in this study can be found in Section 8.4 and Section 9.4.3.

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

4.2.1.4 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.

4.2.2 Rationale for the Use of Placebo

In Japan at the start of the study, qHPV vaccine has been approved and marketed under the name of GARDASIL® only for females 9 years of age or older. As there is no active comparator for this male study in Japan, placebo (saline solution) will be included to demonstrate the vaccine efficacy and to compare the safety profile of the 9vHPV vaccine in the base study. Participants randomized in the placebo arm will receive placebo in the base study and those who are eligible will be offered a 3-dose series of 9vHPV vaccine in the extension study.

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 (SILGARD®9 in Japan, GARDASIL®9 in USA, EU, and other countries).

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their 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 (Section 7.3).

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

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Healthy male participants between the ages of 16 and 26 years (inclusive) will be enrolled in this study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

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

5.1.1 Base Study

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, from 16 years to 26 years of age inclusive, at the time of signing the informed consent.

Informed Consent

3. Provides written informed consent/assent for the study by the participant [or, for minor participants, if applicable, the parent/legal guardian (legally acceptable representative) and the participant]. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

4. 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.

5. Can read, understand, and complete the VRC.
6. *Agrees to refrain from sexual activity (including vaginal and anal penetration and any genital contact) for 48 hours prior to any scheduled visit that includes sample collection, to avoid detection of viral DNA which has been deposited in the male genital area during sexual intercourse and is not the result of ongoing infection.
7. a) For HM: Participants must be a heterosexual male, who has had exclusively female sexual partners, and has 1 to 5 lifetime female sexual partners at the time of enrollment.

   b) For MSM: Participants must identify themselves as a male who has sex with males, must have engaged in either insertive or receptive anal intercourse or oral sex with another male sexual partner within the last year, and have 0 to 5 lifetime male and/or female sexual partners at the time of enrollment.

   For protocol purposes, a female sexual partner is defined as a female with whom the participant has engaged in vaginal intercourse. For protocol purposes, a male sexual partner is defined as a male with whom the participant has engaged in insertive or receptive anal intercourse.

5.1.2 Extension Study

After initial database lock and unblinding a participant's vaccination group assignment in the base study, the participant will be eligible for inclusion in the extension study if the participant still meets Inclusion Criteria #1 and #4, and:

8. Was in the placebo group during the base study; or was in the 9vHPV vaccine group and did not complete the vaccination series in the base study.
9. Provides documented informed consent for the extension study.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

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

5.2.1 Base Study

Medical Conditions

1. Has a history of HPV-related anal lesion (anal intraepithelial neoplasia, anal condyloma or anal cancer) or HPV-related head and neck cancer.
2. Has a history of or clinical evidence at the Day 1 external genital examination of HPV-related external lesion (genital warts, penile/perianal/perineal intraepithelial neoplasia, or penile cancer).

3. Has clinical evidence at the Day 1 external genital examination of gross genital lesion suggesting sexually transmitted disease.
4. *Has a fever (defined as oral temperature ≥37.5°C) within the 24-hour period prior to the Day 1 visit
5. Has a history of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention.
6. 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.
7. Has known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
8. 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.
9. Has a history of splenectomy.
10. 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.
11. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the 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.

Prior/Concomitant Therapy

12. 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 he 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 high-dose corticosteroids (≥20 mg/day of prednisone 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.
13. 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 [Benesis™]) or blood-derived product other than IVIG.
14. *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.

15. 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

16. Is concurrently enrolled in other clinical studies of investigational agents or studies involving collection of genital specimens.

Diagnostic Assessments

None.

Other Exclusions

17. *Has engaged in sexual activity within 48 hours prior to Day 1 (this may result in the detection of viral DNA that has been deposited in the male genital area during sexual intercourse and is not the result of ongoing infection).

    Sexual activity is defined as:

- Penile penetrative vaginal intercourse with female partner
- Penile penetrative or receptive anal intercourse with male or female partner
- Any oral/genital contact, or genital/genital contact

18. *Has shaved their genital region and/or applied any post-shave lotion or lubricants within 24 hours prior to the visit.
19. 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.
20. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.2.2 Extension Study

The participant must be excluded from the extension study if the participant meets Exclusion Criteria #4*, #5, #6, #7, #10, #16, or #19.

5.3 Lifestyle Considerations

5.3.1 Activity Restrictions

Participants will refrain from sexual activity (including vaginal and anal penetration and any genital contact, stated in 5.2 Exclusion Criteria) for 48 hours prior to any scheduled visit that includes efficacy sample collection.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently 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(s)**	**Dosage Level(s)**	**Route of Administration**	**Vaccination Regimen**	**Use**	**IMP or NIMP/ AxMP**	**Sourcing**
The 9vHPV vaccine	Experimental	V503 (9vHPV vaccine)	Biological /Vaccine	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	Test Product	IMP	Provided centrally by Sponsor
Placebo	Placebo Comparator	Saline for injection	Biological /Vaccine	Solution	0.9% sodium chloride	0.5 mL	IM	Day 1, Month 2, Month 6	Placebo	IMP	Provided Centrally by Sponsor
The 9vHPV vaccine (Extension Study)	Experimental	V503 (9vHPV vaccine)	Biological /Vaccine	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	1 dose in Ext: Ext 1 OR 2 doses in Ext: Ext 1 and Month 4 in Ext	Test Product	IMP	Provided Centrally by Sponsor
Placebo (Extension Study)	Experimental	V503 (9vHPV vaccine)	Biological /Vaccine	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	Ext 1, Month 2 in Ext, Month 6 in Ext	Test Product	IMP	Provided Centrally by Sponsor

9vHPV = 9-valent human papillomavirus; AXMP = Auxiliary Medicinal Product; HPV = human papillomavirus; IM = Intramuscular; VLP = virus-like particle.
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 on 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.

6.1.1 Drug Device Combination Product/Combination Medicinal Product

In the extension study, combination medicinal product(s) (MSD marketed/MSD investigation medicinal product and medical device or non-MSD marketed/non-MSD investigational product and medical device) provided for use in this study are GARDASIL®9 syringes. Refer to Appendix 4 for instruction on reporting events associated with these combination medicinal products.

Instructions for combination medicinal product use are provided separately.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3. Information on preparation and administration of study vaccine and placebo is provided in Section 6.3.3 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

Intervention randomization of the base study will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive the 9vHPV vaccine or placebo.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. HM or MSM

Even though randomization will be stratified by HM and MSM, the test of the primary and secondary efficacy hypotheses will not be stratified by HM and MSM. Stratification is intended to support immunogenicity analysis within HM and MSM, to avoid unbalanced allocation between the vaccination groups particularly in the MSM cohort.

6.3.3 Blinding

In the base study, a double-blinding technique will be used. the 9vHPV vaccine (V503) and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in clinical evaluation of the participants are unaware of the intervention assignments.

After accrual of at least 17 primary endpoint cases and at least 17 secondary efficacy endpoint cases in the base study have been achieved and the database has been locked for the primary efficacy analysis, vaccination assignment will be unblinded for all participants. The participants' vaccination group assignment in the base study will be communicated to the investigator by the Sponsor for the purpose of determining participant eligibility for receiving 9vHPV vaccine in the extension study. By receiving the vaccination allocation for the participants, the relevant investigator, study-site personnel, and the participant will be unblinded to study vaccination assignment. After this point of time, only the central laboratory personnel and the pathology panel will remain blinded to the primary vaccination group assignment.

See Section 8.1.11 for a description of the method of unblinding a participant during the study should such action be warranted.

In the extension study, administration of the 9vHPV vaccine will be conducted as open label; 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

In the base study, 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 during the base study:

- 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 8.12.1.2).
- 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 base study.

Use of prior and concomitant medications/vaccination should be recorded for the base study as described in Section 8.1.6.

In the extension study, dosage or interval of vaccinations for concomitant therapy or other vaccination will not be specified, but will be in accordance with the local approved label for each drug or vaccine and judgement by the investigators.

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 after the end of the study. After the base study is completed, recipients of placebo and participants who did not complete their 3-dose series of 9vHPV vaccine in the base study will be offered vaccination with the 9vHPV vaccine in the extension study as allowed by local regulations and IRBs.

6.8 Clinical Supplies Disclosure

The base study is blinded but supplies are provided as open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the intervention randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

Not applicable.

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 before completion of the protocol-specified vaccination regimen will continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

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 8.12.3.

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 that, 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 8.12.3 for those procedures to be completed at each specified visit.

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 FBR, 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 used for screening or baseline purposes provided the procedures meet 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. 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 38.5 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 2 Blood Collection Volumes

	Day 1	**Month 7**	**Month 36 (or Final Visit)**
Anti-HPV Immunogenicity Testing	10 mL	10 mL	10 mL
Blood (DNA) for Future Biomedical Research	8.5 mL	-	-
Total Volume	18.5 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 (or their legally acceptable representative) prior to participating in this clinical study or FBR. 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.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

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

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or 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 FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

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 provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study 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) in the base study, the participant's lifetime medical history of genitourinary or HPV-related diagnoses will be collected. Other 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 postvaccination and not considered SAEs) will be collected throughout the base study. In the extension study, any new medical history will not be collected.

8.1.5 Sexual History, Demographics, Substance Use

A sexual history will be obtained by the investigator or qualified designee. At Visit 1 (Day 1), the participant's lifetime number of female and/or male sexual partners and age of first sexual intercourse will be collected. After Visit 1, the participant's sexual activity including the number of new females and/or males with which the participant engaged in sexual intercourse (for females, insertive vaginal intercourse; for males insertive or receptive anal intercourse) will be collected throughout the base study. In the extension study, any sexual activity will not be collected.

Other documentation, such as lifetime sexual history, demographics, and substance use (alcohol and tobacco) 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 of the base study. 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. During the base study, prior and concomitant medicines 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 during the study.

8.1.6.2 Concomitant Medications

During the base study, 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. The non-study HPV vaccine must be recorded in the extension study, if used.

Participants may receive allergen desensitization therapy and tuberculin skin testing while participating in the base 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 before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any individual 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 8.12.1.1.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.9 Study Intervention Administration

8.1.9.1 Study Intervention Administration in Base Study

Study vaccine should be prepared and administered by the *Unblinded* Study Personnel who are not involved in clinical evaluation of the participants.

Preparation of Study Vaccine/Placebo by Unblinded Study Personnel

The study vaccine and placebo must be stored at 2.0°C to 8.0°C. Do NOT freeze the study vaccine/placebo. Protect the study vaccine/placebo 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 the vial between the palms of both hands for 30 seconds before withdrawing the 0.5 ml dose of vaccine from the single-dose vial using a sterile needle and syringe. **The study vaccine should be a whitish, semi-translucent suspension when thoroughly mixed. The normal saline placebo should be a clear, colorless liquid.** If the appearance of vaccine or placebo is otherwise, do not administer, and contact the Sponsor immediately.

The *Unblinded* Study Personnel will wrap the prepared syringe with the nontransparent label provided by the Sponsor to mask the difference in appearance between vaccine and placebo. Adequate treatment provision, including epinephrine and equipment for maintaining an airway should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

Study Vaccine Administration by Unblinded Personnel

Study vaccines should be administered by the designated unblinded physician at Day 1, Month 2, and Month 6. At each vaccination visit, participants will receive the 9vHPV vaccine or placebo 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 a 90° angle into the muscle tissue using a needle long enough to ensure intramuscular deposition of study vaccine. The study vaccine should be administered in the deltoid muscle using preferably a 1.0 mL syringe (the largest allowable size is a 3.0 mL syringe) with the following needle length and gauge specifications:

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

Observing Participants After Vaccination by Blinded Personnel

Unblinded study personnel should not have contact with participants for any study-related procedures/assessments after administration of study vaccines, which includes all safety follow-up procedures. All participants will be observed by *Blinded* 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.

All safety, efficacy, and immunogenicity assessments will be conducted by blinded personnel, and the participant will be blinded to the study vaccine received. Vaccination information, such as Component Identification Number and time of vaccination, must be recorded on the appropriate eCRF as per the Data Entry Guidelines.

8.1.9.2 Study Intervention Administration in Extension Study

In the extension study, preparation and administration of the 9vHPV vaccine will be conducted as open label. Study vaccine should be prepared and administered by appropriately qualified members of the Study Personnel.

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 study vaccine will be supplied as a prefilled syringe. The syringe should be shaken before use.

Attach the appropriate needle (as recommended by the product label) by twisting in a clockwise direction until the needle fits securely on the syringe. The followings are needle length and gauge specifications:

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

Administer the entire dose as an intramuscular injection per standard protocol.

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 should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

Study Vaccine Administration

At each vaccination visit in the extension study, participants will receive 9vHPV vaccine as a 0.5 mL intramuscular injection as specified in Section 1.3.2 and Section 1.3.3. The first vaccination in the extension study is recommended to occur the same day as the Final Visit of the base study, if possible. 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 be administered at a 90° angle into the muscle tissue using a needle long enough to ensure intramuscular deposition of study vaccine. The study vaccine should be administered in the deltoid muscle.

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.

8.1.9.3 Timing of Dose Administration

In the base study, the first dose of study vaccine or placebo will be administered at Day 1, which should be the day of randomization. The second and third (final) doses of study vaccine or placebo will be administered at Month 2 (± 3 weeks) and Month 6 (± 4 weeks), respectively (Section 1.3).

In the extension study, the 3 doses of the 9vHPV vaccine will be administered at the first visit of the extension study (Extension Visit 1) and at 2 months and 6 months after Extension Visit 1 for the participants in the placebo group (Section 1.3.2). For the participants who did not complete the 3-dose regimen of 9vHPV vaccine in the base study, the remaining doses from the series (i.e., if they already received 2 doses in the base study, they will receive 1 dose in the extension study; if they already received 1 dose in base study, they will receive 2 doses which are 4 months apart in the extension study) will be provided (Section 1.3.3).

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the 3-dose of vaccination regimen should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

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 3 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 may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the 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 FBR 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 of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before 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.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the 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

The base study is blinded. Participants will be unblinded after the primary efficacy analysis database lock to determine eligibility for participation in the extension study.

The following is applicable for the base study:

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity grade of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

The Sponsor will remain blinded to participant vaccination allocations until the required number of cases of the primary and the secondary efficacy endpoint have been observed and the database is unblinded for the primary analyses of efficacy.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

The extension study is unblinded. Participants will be unblinded throughout the extension study.

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.

8.1.13 Optional Testing for Sexually Transmitted Infections

Local laboratory testing for sexually transmitted infections (STIs) including chlamydia, gonorrhea, herpes simplex virus (HSV), syphilis, hepatitis B, and HIV may be performed at any visit during the base study at the discretion of the investigator if clinically indicated. Abnormal results should be captured as New Medical History at the next visit. In addition, per the exclusion criteria for this study, known HIV-positive participants should not be enrolled in the study.

Any participant who tests positive for an STI during the study will not be discontinued from the trial and may participate in all study procedures. These participants will be referred for appropriate counseling and treatment outside of the context of the protocol.

8.1.14 Sexual Activity

At every scheduled visit from Visit 2 through the Final Visit in the base study, participants will be asked questions regarding sexual activity since last visit. Details such as the date of last sexual intercourse, number of new sexual partners and total number of sexual partners, etc. will be recorded in the appropriate eCRF.

Sexual activity of participant is defined as:

- Penile penetrative vaginal intercourse with female partner

- Penile penetrative or receptive anal intercourse with male or female partner
- Any oral/genital contact, or genital/genital contact

If a participant has engaged in sexual activity 48 hours prior to visit that includes efficacy sample collection, then the visit will be rescheduled to a later time when this criterion is not met. See Section 8.12.1.3 for prerequisites for sample collection. Sexual activity will not be collected after participants are unblinded.

8.2 Genital Examination and Efficacy Assessments (Base Study)

8.2.1 Anogenital Physical Examination

An anogenital physical examination will be performed on Day 1 of the base study prior to the external genital lesion examination. A physical examination details will be documented in the participant's chart and any medical conditions including will be documented in the data collection system. If a lesion observed at Day 1 meets the exclusion criterion 1, then the participant should be excluded from the study.

8.2.2 External Genital Examination

In the base study, the external genital lesion examination should be completed prior to external genital swab collection, and prior to vaccination on Day 1. If a lesion observed at Day 1 meets the exclusion criteria 2 or 3, then the participant should be excluded from the study.

Equipment

The minimal equipment needed to perform the genital lesion inspection includes:

- Good light source
- Magnifying apparatus (hand-held magnifying glass of 4x to 5x power)
- Nonsterile gloves
- Optional: colposcope at low power magnification (2x to 4x)

8.2.2.1 Procedure for Penile and Scrotal Examination

1. The participant should be lying supine on the examination table.
2. The examiner should inquire as to whether the participant has shaved their genital region and/or applied any post-shave lotion or lubricants within 24 hours prior to the visit.
3. The examiner should inquire as to whether the participant has noticed any bumps or lesions or unusual symptoms (eg, itching, dyspareunia, or dysuria). Begin with the inspection of the penile shaft, glans penis and urethral meatus, noting and recording

evidence of abnormalities, including any abnormalities of the skin, rashes, minor lacerations, or bruises, etc.

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

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

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

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

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

8.2.2.2 Procedure for Perineal/Perianal Examination

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

2. The examiner should inquire as to whether the participant has noticed any bumps or lesions or unusual symptoms (eg, itching, dyspareunia).

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

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

5. The examiner should spread the contiguous skin using his/her thumbs and note the condition of the anus.

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

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

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

8.2.3 Efficacy Assessments

In the base study, penile/glans penis, scrotal, perineal/perianal, and intra-anal swabs will be tested for detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 by

PCR assay. PCR analysis of the swabs will be used to determine persistent HPV infection endpoints.

In addition, all new (after Day 1) genitourinary and perianal lesions judged by the investigator to be possibly, probably, or definitely HPV-related, or any lesion whose etiology is not known will be biopsied. Tissue samples obtained from biopsy will be analyzed by HPV Thinsection PCR assay (detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and by a consensus diagnosis from the HPV Vaccine Program Pathology Panel to determine clinical disease efficacy endpoints.

Once a participant is unblinded, no further efficacy samples should be collected from the participant.

8.2.3.1 Collection of Swabs for HPV PCR

After the completion of external genital lesion examination, one penile/glans swab, one scrotal swab, one perineal/perianal swab, and one intra-anal swab will be collected.

Specimen collection supplies provided by the Sponsor/Central Laboratory must be used. Details regarding sample handling are provided in the laboratory manual.

8.2.3.1.1 Penile/Glans Penis File and Wetted Swab for HPV PCR

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

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

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

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

5. Discard the file in a Biohazard Sharps container.

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

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

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

8.2.3.1.2 Scrotal File and Wetted Swab for HPV PCR

1. The participant should be lying supine on the examination table. As same as the penile/glans penis sampling, remove the nail file from the packaging; remove the swab from the packaging, then twist the top off of the sterile saline ampule and wet the entire head of the swab with the sterile saline. Only one file and one swab are to be used in the scrotal sampling.

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

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

4. Discard the file in a Biohazard Sharps container.

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

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

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

8.2.3.1.3 Perineal/Perianal File and Wetted Swab for HPV PCR

1. The participant should lie on his left lateral side with his knees tucked up towards his chest or in the prone knee-chest position that allows comfortable access for examination. As same as the penile/glans penis sampling, remove the nail file from the packaging. Remove the swab from the packaging, then twist the top off of the sterile saline ampule. Only one file and one swab are to be used in the perineal/perianal sampling.

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

3. Discard the file in a Biohazard Sharps container.

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

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

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

8.2.3.1.4 Intra-anal Wetted Swab for HPV PCR

1. As same as the perineal/perianal sampling, the participant should lie on his left lateral side with his knees tucked up towards his chest or in the prone knee-chest position that allows comfortable access for examination. Remove the swab from the packaging, then twist the top off of the sterile saline ampule. Only one swab is to be used in the intra-anal sampling.

2. Using the non-dominant hand, the examiner should spread the buttocks to better visualize the anus. The swab should be held in the dominant hand, and once at the

entrance to the anus, the contiguous skin should be spread and the swab should be inserted into the anus as far as it will go until resistance is met (generally 5-6 cm), swabbing the inside of the anal canal in a 360º rotating motion 2 to 3 times.

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

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

5. Place the appropriate label for the Intra-anal Sample on the STM vial.

8.2.3.2 External Genital Lesion Biopsy

8.2.3.2.1 External Genital Lesion Biopsy at Study Site

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

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

- The location and anatomical area of each biopsied lesion should be identified and noted (as per the lab kit requisition supplied by the Sponsor and should also be recorded in the appropriate eCRF).

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

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

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

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

- To promote hemostasis, apply gentle pressure. Styptic may be used. For larger areas, a single interrupted suture may be used. Electrocauterization is to be avoided, but the decision is left to the discretion of the practitioner. Silver nitrate is to be avoided, as it is reported to be more caustic and painful to the participant.

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

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

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

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

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

Thinsection microtomy biopsy specimens will be tested for detection of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. In addition to this testing, specimens may be tested for other HPV types.

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

8.2.3.2.2 Preparation and Disposition of Thin Sections from Tissue Specimens

The following procedures will be performed at the Sponsor-designated central laboratory. The procedures will be performed by an experienced, qualified histotechnologist according to the Central Laboratory's Standard Operating Procedure. The histotechnologist will assure that the microtome and work areas are clean and free of contaminants. All Thinsection microtomy for PCR will be performed at a time when all other routine work has been completed, so that potential contaminations can be minimized. Prior to sectioning each block, a new blade will be installed in the microtome. The blade will only be positioned so that it is at the left margin of the blade surface. Technicians sectioning study blocks will utilize "biologically clean" gloves while handling the blocks (new gloves for each block). First, the histotechnologist will face the block by removing two 4-micron sections from the face of the block. These sections will be discarded. Using sterile plastic forceps, the next two 4-micron paraffin sections are collected and floated in a water bath for the preparation of one hematoxylin & eosin (H&E) slide (Slide 1, with 2 sections).

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

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

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

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

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

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

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

8.2.3.2.3 Specimens Taken Outside the Context of the Study

Tissue biopsies collected outside the context of the study are strongly discouraged. "Outside the context of the study" is defined as processing of samples at a local laboratory rather than

through the Sponsor-designated Central Laboratory. If a participant undergoes a biopsy outside the context of the study, all efforts will be made to obtain the operative report, local pathology report, diagnostic slides (for tissue biopsies), tissue block for slide preparation, PCR analysis and pathology panel review.

8.2.3.3 HPV DNA PCR Assay

The HPV PCR Assay developed and published by MSD [Else, E. A., et al 2011][Roberts, C.C., et al 2011] is a multiplexed real-time type-specific PCR assay. The PCR assay has been used in previous efficacy studies that supported the licensure of GARDASIL® and GARDASIL®9/SILGARD®9. The PCR assay is validated for the detection of HPV DNA of 14 HPV types, including the 12 HPV types that have been recognized as oncogenic by the International Agency for Research on Cancer (including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) [Bouvard, V., et al 2009] and the low-risk types HPV 6 and 11.

HPV vaccine types 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be analyzed using this type-specific multiplex (L1, E6, and E7 gene detection) PCR assay. HPV types 35, 39, 51, 56, and 59 will be detected using a duplex (E6 and E7 gene detection) PCR assay using the preparation method described below.

Specimens are received and prepared for multiplex PCR using a DNA purification method (Qiagen Technology Kit). Multiplex PCR (based on real-time fluorescent PCR) allows the simultaneous detection of 3 gene products (L1, E6, and E7) for a given HPV type in 1 reaction. The HPV type-specific primer pairs based on the published HPV L1, E6, and E7 sequences, are used to specifically amplify a portion of each gene simultaneously. The specific amplicons are detected in real-time by fluorescently labeled oligonucleotide probes. The gene-specific oligonucleotide probes are each labeled with a different fluorescent label, and the fluorescent emission is captured during PCR cycling. After analysis of the raw fluorescent data by the real-time PCR instrument software, a threshold cycle (Ct), which represents the PCR cycle at which an increase in reporter fluorescence above a baseline signal can first be detected, is determined. Each gene-specific assay (ie, gene-specific dye layer) is considered positive if the Ct is <45 cycles. A gene-specific assay is considered negative if the Ct = "No Ct". A sample is called positive when 2 or 3 genes are positive or when the same single gene scores positive on consecutive tests. The assay has been validated for swab and tissue specimens.

8.3 Immunogenicity Assessments (Base Study)

8.3.1 Blood Sample Collection for Serum Anti-HPV Antibody Testing

In the base study, 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 at 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, and Month 36 (or Final Visit) 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 and hypotheses, 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.

8.3.2 Competitive Luminex Immunoassay

The 9-valent HPV 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 in the base study. The testing will be performed by Q Squared Solutions (California, USA).

For the 9-valent HPV 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/ml (mMU/mL).

The assay was validated at Q Squared Solutions. Validation evaluated precision, linearity, LLOQ, ULOQ, 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 of the base study 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 of the base study if the participant's anti-HPV titer, as assessed by cLIA, is less than the corresponding serostatus cutoff for that HPV type.

8.4 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.

8.4.1 Physical Examinations

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

Height and weight will be recorded on Day 1 of the base study 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.

8.4.2 Oral Temperature Measurements

In the base study, oral temperature will be assessed before study vaccine is administered on Day 1, Month 2, and Month 6 visits. If the participant has a fever (defined as an oral temperature of ≥37.5°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 ≥37.5°C), then an AE of "fever" must be documented in the eCRF.

In the extension study, oral temperature will be assessed before 9vHPV vaccine is administered at the visits specified in Section 1.3.2 and Section 1.3.3 of the SoA.

8.4.3 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).

8.4.4 Vaccination Report Card

Base Study:

The investigator or delegate will train the participant 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. Participants should be informed to contact the investigator immediately in the event of a hospitalization or visit to another physician.

Participants will use the VRC to document the following information:

- Oral temperatures measured Day 1 (day of vaccination) through Day 5 postvaccination.
  - Participants will record 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 ≥37.5°C), the AE of "fever" must be documented in the appropriate eCRF.
- Solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) Day 1 through Day 5 postvaccination.
- Any other injection-site or systemic AEs Day 1 through Day 15 postvaccination.
- Concomitant medications and non-study vaccinations 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 will be conducted after 15 days postvaccination.

All participants 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 at Visit 2 (Month 2), Visit 3 (Month 6), and Visit 4 (Month 7). For the AEs outlined above, the investigator will use the information provided by the participant 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, participants 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.

Extension Study:

A VRC will not be utilized for participants enrolled in the extension study and NSAEs will not be collected. SAEs and death will be collected from the first dose of vaccination until 1 month after the last dose.

8.4.5 Postvaccination Observation Period (30 Minutes)

In both the base study and study extension, 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.

8.5 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 need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.5.3. 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.

8.5.1 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 provides documented informed consent, but before 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.

Base Study:

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

Extension Study:

SAEs and death will be collected from the first dose of vaccination until 1 month after the last dose.

Base Study and Extension Study:

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

- A death that occurs before the participant completing the study, but outside the 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 the investigator 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 3.

Table 3 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	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
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.

8.5.2 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.

8.5.3 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 cancer and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In

addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.5.4 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 toward 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 SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.5.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since participants are males and partner pregnancy/lactation information are not applicable.

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

None.

8.5.7 Events of Clinical Interest

None.

8.6 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 more than the number of doses of study vaccine specified in the protocol 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.

8.7 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.8 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- DNA for future research

8.11 Health Economics Medical Resource Utilization and Health Economics

Health Economics OR Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

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

8.12.1 Visit Requirements in Base Study

8.12.1.1 Screening Visit

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 must be reconsented.

8.12.1.2 Prerequisites for Vaccination Visit (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 and Month 6 study vaccination visits, study personnel should verify by questioning the participant and/or by examination that:

1. The participant has not had a fever (oral temperature ≥37.5°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 the Month 2 and Month 6 study vaccination visits.

3. The participant has not received a non-study inactivated or recombinant vaccine within 14 days prior to 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.

8.12.1.3 Prerequisites for Anogenital Sample Collection Visits

See the inclusion/exclusion criteria for specific restrictions on Day 1 (see Section 5.1 and Section 5.2). For visits that include collection of study specimens, the site study personnel should verify by questioning the participant that he had not engaged in sexual activity within 48 hours nor shaved their genital region and/or applied any post-shave lotion or lubricants within 24 hours prior to any visit that includes collection of swabs, and/or biopsies specimens. See section 8.1.14 for details regarding documentation of sexual activity. If the participant does not meet the requirements listed above, the study visit should be re-scheduled.

8.12.1.4 Early Termination Procedures

Once at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases have been observed, initial database lock and unblinding will be performed and notified to the study sites. Following notification, participants remaining in the study (ie, who have not yet completed a Final Visit) will proceed to a Final Visit in the base study promptly. Under that scenario, participants who have not yet completed a Final Visit will complete the specified procedures in Final Visit in this Schedule of Activities.

Participants who have not yet completed Month 36 should schedule a Final Visit with collection of serum sample within the specific day ranges from Day 913 to Day 1277 (within the acceptable ranges for collection of serum sample, see Section 9.5.2), if possible. At the Final Visit, serum sample should not be collected from the participants who have already completed Month 36 or outside of the day ranges from Day 913 to Day 1277.

If the Sponsor elects to terminate earlier under this scenario, the limited procedures shown in the SoA (Section 1.3) will be conducted at the final visit as follows; update medical history,

review prior/concomitant medication and non-study vaccination review, monitor AEs, and blood sample collection for serum for anti-HPV (only for the participants who have not yet completed Month 36). Refer to Section 8.1.4, 8.1.6, 8.3.1 and 8.5, respectively, for the details of each procedure.

8.12.2 Visit Requirements in Extension Study

8.12.2.1 Prerequisites for Vaccination Visit (Extension Visit 1, Extension Visit 2a/2b, and Extension Visit 3)

This section summarizes prerequisites for vaccination visits in the extension study. See the inclusion/exclusion criteria for specific restrictions on Extension Visit 1 (see Section 5.1.2 and Section 5.2.2). At Extension Visit 2a/2b, and Extension Visit 3, study personnel should verify by questioning the participant and/or by examination that:

1. The participant has not had a fever (oral temperature ≥37.5°C) within the 24-hour period prior to the vaccination visit.

If the participant does not meet the requirements listed above, the study visit should be re-scheduled.

8.12.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Participants who discontinue study vaccinations but continue in the study will attend study visits per the SoA including sampling of swabs, and/or biopsies specimens (Section 1.3) in the base study. However, serum will not be collected at the Month 7 study visit or subsequent visits from participants who did not complete the 3-dose study vaccination regimen.

9 KEY STATISTICAL CONSIDERATIONS

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

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12. The same analysis plan for analysis populations and methods without hypothesis testing will be applied to evaluate decreasing of selected efficacy and immunogenicity endpoints from the first database lock for primary analysis, by using data up to the end-of-base-study (the database lock after the completion of the final efficacy sample assessment for the final efficacy analysis and after the last participant's Final Visit in the base study for the final immunogenicity and safety analysis). Descriptive analysis of selected safety endpoints will be reported in an end-of-base-study report and an extension study report.

Study Design Overview	A Phase 3, randomized, placebo-controlled clinical study to evaluate the efficacy, immunogenicity and safety of the 9vHPV vaccine in Japanese males, 16 to 26 years of age.
Treatment Assignment	All enrolled participants will be randomized in a 1:1 ratio to the 9vHPV vaccine group or placebo group.
Analysis Populations	Efficacy: Pre-Protocol Efficacy (PPE) population Immunogenicity: Per-Protocol Immunogenicity (PPI) population Safety: All Participants as Treated (APaT) population
Primary Endpoint	Efficacy: HPV 6/11/16/18-related anogenital persistent infection
Key Secondary Endpoints	Efficacy: HPV 31/33/45/52/58-related anogenital persistent infection Immunogenicity: • GMTs to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post last dose (Month 7). • Seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post last dose (Month 7).

Statistical Methods for Efficacy Analyses	The primary efficacy hypothesis will be evaluated by comparing the 9vHPV vaccine with placebo with respect to the primary efficacy endpoint. The p-value for testing the hypothesis that vaccine efficacy (VE) is greater than 0% as well as 95% confidence interval (CI) for VE will be provided using the exact binomial method proposed by Chan and Bohidar (1998) [Chan, I. S. F. and Bohidar, N. R. 1998]. The statistical criterion for success requires that the lower bound of the 2-sided 95% CI for VE against the primary efficacy endpoint is greater than 0%. The secondary efficacy hypothesis will be evaluated by comparing the 9vHPV vaccine with placebo with respect to the secondary efficacy endpoint based on the same method to be used in testing the primary efficacy hypothesis. The statistical criterion for success requires that the lower bound of the 2-sided 95% CI for VE against the secondary efficacy is greater than 0%.
Statistical Methods for Immunogenicity Analyses	The secondary immunogenicity objective will be addressed by summarizing antibody titer responses measured using cLIA at Month 7. The GMTs and the corresponding 95% CIs will be estimated based on the t-distribution for HPV types of 6, 11, 16, 18, 31, 33, 45, 52, and 58. Point estimates and the corresponding 95% CIs of percent seroconversion will be provided using the exact binomial method of Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934] for HPV types of 6, 11, 16, 18, 31, 33, 45, 52, and 58, for all participants, HM group and MSM group, respectively.
Statistical Methods for Key Safety Analyses	There are no Tier 1 AEs identified in this study. For Tier-2 AEs, 95% CIs will be provided for between-treatment differences in the percentage of participants with events using the methods proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	No interim analyses are planned in this study.
Multiplicity	The overall type 1 error rate associated with testing the primary and secondary efficacy hypotheses will be controlled to not exceed 0.025 (1-sided) by a fixed sequence procedure. The secondary efficacy hypothesis will be tested only if the primary efficacy hypothesis is successfully demonstrated.

Sample Size and Power	Testing the primary efficacy hypothesis with 17 total cases has 94% power to demonstrate that the efficacy of the 9vHPV vaccine compared to placebo is greater than 0% at 1-sided type 1 error rate ≤ 0.025 if the underlying true VE against the primary efficacy endpoint is at least 85%. Testing the secondary efficacy hypothesis with 17 total cases has also 94% power to demonstrate that the efficacy of the 9vHPV vaccine compared to placebo is greater than 0% at an overall 1-sided type 1 error rate ≤ 0.025 if the underlying true VE against the secondary endpoint is at least 85%. A total of approximately 1050 participants are needed to be enrolled in order to accumulate approximately 17 total primary endpoint cases and at least 17 total secondary efficacy endpoint cases within 56 months from the time the first study participant signs the ICF.

9.2 Responsibility for Analyses/In-house Blinding

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

The base study will be conducted as a double-blind study under in-house blinding procedures. The official database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. The first database lock will be executed, and a study report will be written reporting of the test of the primary and secondary efficacy hypotheses when at least 17 confirmed cases for each primary endpoint and secondary endpoint have been accumulated. After the first database lock for primary analysis, data for immunogenicity and safety endpoints will continue to be collected, and additional database locks will be executed, including a second database lock for the final efficacy analysis after the completion of the final sample assessment for efficacy in the base study and a final database lock of the base study for the final immunogenicity and safety analysis after the last participant's Final Visit in the base study. A report will be written after each database lock. Participants will be unblinded after the initial database lock to determine eligibility for participation in the extension study.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an IRT system.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3. Data in the first database lock will be used for hypothesis testing.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary efficacy endpoint

HPV 6/11/16/18-related anogenital persistent infection is defined to have occurred if any of the following occurs:

- The participant is positive by an HPV PCR assay (type 6, 11, 16, or 18) to at least 1 common gene for the given vaccine HPV type in anogenital or biopsy samples collected in two or more consecutive visits 6 months (± 1-month window) apart (The minimum length of time between samples for a participant to be counted as a case of persistent infection is 4 months); OR
- The participant has Pathology Panel consensus diagnosis of genital warts, PIN, penile, perianal or perineal cancer AND detection of HPV 6, 11, 16 or 18 by Thinsection PCR in an adjacent section of the same biopsy block AND is PCR positive for the same HPV type to at least 1 common gene in the sample obtained at a separate adjacent visit with regardless of visit interval, prior to or following the biopsy showing HPV disease.

Secondary efficacy endpoint

HPV 31/33/45/52/58-related anogenital persistent infection is defined to have occurred if any of the following occurs:

- The participant is positive by an HPV PCR assay (type 31, 33, 45, 52 or 58) to at least 1 common gene for the given vaccine HPV type in anogenital or biopsy samples collected in two or more consecutive visits 6 months (± 1-month window) apart (The minimum length of time between samples for a participant to be counted as a case of persistent infection is 4 months); OR
- The participant has Pathology Panel consensus diagnosis of genital warts, PIN, penile, perianal or perineal cancer AND detection of HPV 31, 33, 45, 52 or 58 by Thinsection PCR in an adjacent section of the same biopsy block AND is PCR positive for the same HPV type to at least 1 common gene in the sample obtained at a separate adjacent visit with regardless of visit interval, prior to or following the biopsy showing HPV disease.

Exploratory efficacy endpoints

- HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart.
- HPV 6/11/16/18/31/33/45/52/58-related genital warts, PIN, penile, perianal or perineal cancer

- HPV 6/11/16/18/31/33/45/52/58-related intra-anal persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart.
- HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection detected in samples from three or more consecutive visits 6 months (± 1-month window) or longer apart (i.e., at least 12 months persistent infection)

These endpoints will be also evaluated for each HPV types.

9.4.2 Immunogenicity Endpoints

GMT to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post last dose (Month 7) based on cLIA using serum samples.

Seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post last dose (Month 7) based on cLIA using serum samples. Seroconversion is defined as changing a participant's serostatus from seronegative at Day 1 to seropositive at 1 month post last dose (Month 7). A participant with anti-HPV cLIA titer at or above the serostatus cutoff of the cLIA for a given HPV type is considered seropositive for that HPV type.

9.4.3 Safety Endpoints

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

9.5 Analysis Populations

In efficacy and immunogenicity analysis populations, participants are analyzed in the vaccination group to which they were randomized (i.e., as-randomized). In safety analysis population, participants are analyzed according to the vaccination regimen actually received (i.e., as-treated).

9.5.1 Efficacy Analysis Populations

Per-Protocol Efficacy (PPE) Population

The PPE population will serve as the primary population for the analysis of efficacy in this study. To be included in the per-protocol population, participants must:

1. Have received all 3 vaccinations with the correct dose of the correct clinical material within 1 year.
2. Have Month 7 swab samples collected within 14 to 72 days post dose 3 with non-missing PCR result.

3. Be seronegative to the appropriate HPV type(s) at baseline and PCR-negative to the appropriate HPV type(s) on all swabs and biopsies (if collected) from baseline through Month 7.
4. Have no other protocol violations that could interfere with the evaluation of efficacy.

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

HPV Type-Specific Naïve (HN-TS) Population

The HN-TS population will serve as a supportive population for the analysis of efficacy in this study. To be included in the HN-TS population, participants must:

1. Have received at least 1 vaccination,
2. Be seronegative and PCR-negative to appropriate HPV type(s) at Day 1.

Participants who receive incorrect clinical material or an incorrect dose of vaccine will be included in the vaccination group to which they were randomized. Protocol violations that could interfere with the evaluation of efficacy will not cause participants to be excluded from the HN-TS population.

For each of the PPE and HN-TS analysis populations, to be included in the analysis population with respect to either HPV type 6 or 11, participants must be HPV-negative at the relevant time point(s) for both HPV 6 and 11. To be included in the analysis populations with respect to any other vaccine HPV type, participants need to be HPV-negative at the relevant time point(s) only for the HPV type under evaluation.

In the PPE population, efficacy endpoints are counted starting after Month 7 (after 1 month post dose 3). In the HN-TS population, efficacy endpoints are counted starting after Day 1.

9.5.2 Immunogenicity Analysis Populations

Per-Protocol Immunogenicity (PPI) Population

The PPI population will serve as the primary population for the analysis of immunogenicity in this study. To be included in this population, participants must satisfy all the criteria for the PPE population, and additionally must:

1. Have received all vaccinations within acceptable day ranges (see Table 4)
2. Have provided blood samples for serology testing within the acceptable day range (see Table 5)

All Naïve Participants with Serology (ANPS)

A supportive analysis of immunogenicity will be conducted on the ANPS 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 at Day 1 and PCR-negative from Day 1 through Month 7 to the appropriate HPV type(s).

Participants who receive incorrect clinical material or an incorrect dose of vaccine will be included in the analysis in the group to which they were randomized.

Table 4 Acceptable Day Ranges for Vaccination Visits

Dose of the 9vHPV Vaccine Scheduled for Injection	Protocol Specified Visit Window	Day Range for Inclusion in Statistical Analysis (Relative to Day 1†)
Dose 1	Day 1†	0
Dose 2	Month 2 ± 3 weeks	36 to 84
Dose 3	Month 6 ± 4 weeks	148 to 218
† Day 1 refers to the date when dose 1 of the 9vHPV vaccine is injected.		

Table 5 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 dose 3	21 to 49 post dose 3
Month 36	Serum	1095	913 to 1277
† Day 1 refers to the date when dose 1 of the 9vHPV vaccine is injected. For Month 7, indicated target collection/day range is relative to date of injection of dose 3 of the 9vHPV vaccine.			

9.5.3 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of the 9vHPV vaccine or placebo and have provided safety data at any time during the study. Participants will be included in the treatment group corresponding to the study treatment they actually received (i.e., 3 doses of vaccine or 3 doses of placebo). For participants who received injections of vaccine and placebo (i.e., cross-treated participants) corresponding to a regimen that does not correspond to any of the protocol-defined vaccination groups (i.e., not 3 doses of vaccine nor 3 doses of placebo), a safety profile listing will be created separate from the safety reports that will be provided for the protocol-defined vaccination groups.

9.6 Statistical Methods

Statistical methods for efficacy and immunogenicity analyses are described in Section 9.6.1 and Section 9.6.2, respectively. The same analysis plan for analysis populations and methods without hypothesis testing will be applied to evaluate decreasing of selected efficacy and immunogenicity endpoints from the first database lock for primary analysis, by using data up to the end-of-base-study (the database lock after the completion of the final efficacy sample assessment for the final efficacy analysis and after the last participant's Final Visit in the base study for the final immunogenicity and safety analysis). Safety analysis approaches are described in Section 9.6.3. Selected safety endpoints will be summarized separately using descriptive methods for Tier 3 events in an end-of-base-study report. Only SAE/death will be summarized separately using descriptive methods in an extension study report. Methods related to exploratory objectives will be further described in the sSAP.

9.6.1 Statistical Methods for Efficacy Analyses

For each of the primary and secondary efficacy objectives, the hypothesis that VE is greater than 0% will be tested.

The null and alternative hypotheses to be tested are:

$$H_0: VE \leq 0\%$$
$$H_1: VE > 0\%;$$

where VE is defined as:

$$VE = 100\% * \{1-(Rv/Rp)\}$$

and Rv and Rp are the incidence rates of the relevant efficacy endpoint in the 9vHPV vaccine and placebo groups, respectively. VE is equivalent to the percent reduction in the risk of becoming a case of an efficacy endpoint in the 9vHPV vaccine group relative to the risk in the placebo group. The incidence rate Rv is defined as Rv = Cv/Tv, where Cv = the count of the relevant efficacy endpoint cases in the vaccine group and Tv = total person-years of follow-up for efficacy in the vaccine group. The incidence rate Rp is defined similarly.

The hypothesis that VE is greater than 0% will be tested by constructing a 100*(1−α) % CI for VE with respect to the relevant efficacy endpoint, denoted as (VE_L, VE_U). The test of hypothesis will be declared successful if VE_L >0%.

Generally, the 100*(1−α) % CI for VE, (VE_L, VE_U), will be computed as follows. Under the assumption that Rv and Rp are the means of independent Poisson processes, and given that there is a total of n = Cv + Cp efficacy endpoint cases observed across 2 vaccination groups, then the number of efficacy cases Cv in the 9vHPV vaccine group is distributed as Binomial(n,π), where the binomial probability π is defined as:

$$\pi = TvRv/(TvRv+TpRp)$$

The probability π is a person-years-adjusted estimate of the probability that a particular participant who became a case of the relevant efficacy endpoint belongs to the 9vHPV vaccine group. The lower bound of the 100*(1–α) % exact CI for the probability π is obtained by searching for the proportion π_L such that the probability of observing Cv or more efficacy endpoint cases out of n total efficacy cases is ≤α/2. Similarly, the upper bound of the 100*(1–α)% exact CI for the probability π is obtained by searching for the proportion π_U such that the probability of observing Cv or fewer efficacy endpoint cases out of n total efficacy cases is ≤α/2 [Chan, I. S. F. and Bohidar, N. R. 1998]. VE_L and VE_U are then calculated from π_L and π_U as follows:

$$VE_L = 100\%*\{1-\pi_U\,(1+\theta)\}/(1-\pi_U);$$
$$VE_U = 100\%*\{1-\pi_L\,(1+\theta)\}/(1-\pi_L);$$

where θ = Tp/Tv is the ratio of the total person-years of follow-up for efficacy in the placebo group over the 9vHPV vaccine group.

The efficacy analyses strategy are summarized in Table 6.

Table 6 Analysis Strategy for Efficacy Variable

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Efficacy Hypothesis				
HPV 6/11/16/18-related anogenital persistent infection	P	Point estimate, 95% CI and p-value by exact method	PPE	Observed data only
	S	Point estimate and 95% CI by exact method	HN-TS	Observed data only
Secondary Efficacy Hypothesis				
HPV 31/33/45/52/58-related anogenital persistent infection	P	Point estimate, 95% CI and p-value by exact method	PPE	Observed data only
	S	Point estimate and 95% CI by exact method	HN-TS	Observed data only
Abbreviations: HN-TS=HPV Type-Specific Naïve, P=Primary, PPE=Per-Protocol Efficacy, S=Supportive				

9.6.2 Statistical Methods for Immunogenicity Analyses

9.6.2.1 Estimation of GMTs

Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody GMT and the corresponding 2-sided 95% CI will be evaluated at 1 month post last dose (Month 7) by vaccine group. For this purpose, the mean and corresponding 95% CI of the natural logarithm of the anti-HPV titers will be calculated and exponentiated to generate the GMT and the corresponding 95% CI. The 95% CI of the mean of the natural logarithm of anti-HPV titers will be constructed based on the t-distribution. Reverse cumulative distribution (RCD) plots will be provided for graphical representation of distributions of HPV titers at Month 7.

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 numerical computation of GMT.

9.6.2.2 Estimation of Percent Seroconversion

The percent seroconversion with respect to anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58, at Month 7 will be evaluated by computing point estimates and corresponding 2-sided 95% CIs by vaccine group. Calculation of the 95% CI of percent seroconversion will be based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

9.6.3 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements. The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) are either pre-specified as “Tier 1” endpoints or will be classified as belonging to “Tier 2” or “Tier 3” based on the observed proportions of participants with an event. The safety analysis strategy is summarized in Table 7.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol based on the global safety data on the 9vHPV vaccine.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with corresponding 95% CIs provided for the differences in the proportion of participants with events (using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]). Membership in Tier 2 requires that at least 1% of participants in any treatment group exhibit the event.

In addition to individual events that occur in at least 1% of participants in any treatment group, the broad AE categories consisting of the proportion of participants with SAEs during

Days 1 through 15 postvaccination, vaccine-related SAEs observed any time during the study, and elevated temperatures (≥37.5°C) will be considered Tier 2 endpoints. The proportion of participants with solicited injection-site AEs (pain/tenderness, swelling, and redness) and severe injection-site AEs during Days 1 through 5 postvaccination will also be included in Tier 2 endpoints. Detailed endpoints and day ranges are summarized in Table 7.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates (counts and percentages) by vaccination group are provided for Tier 3 safety parameters. Safety analyses will be based on the observed data (i.e., with no imputation of missing data).

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint [a]	95% CI for Comparison of 9vHPV to Placebo	Descriptive Statistics
Tier 2	Injection-site pain/tenderness, swelling, and redness during Days 1 through 5 postvaccination	X	X
	Other injection-site AEs (incidence ≥1% of participants in either group) during Days 1 through 5 postvaccination	X	X
	Severe injection-site AEs [b] during Days 1 through 5 postvaccination	X	X
	Systemic AEs (incidence ≥1% of participants in either group) during Days 1 through 15 postvaccination	X	X
	Elevated temperatures [c] during Days 1 through 5 postvaccination	X	X
	SAEs during Days 1 through 15 postvaccination	X	X
	Serious vaccine-related AEs observed any time during the study	X	X
Tier 3	AEs by SOC		X
	Maximum intensity rating for each category of injection-site AEs		X
	Maximum intensity rating, over all systemic AEs		X
	Maximum temperatures		X
	New medical conditions		X

Abbreviations: AE=adverse event, SAE=serious adverse event, SOC=System Organ Class
(a) The day of vaccination is counted as Day 1. Day ranges for endpoints are as follows: injection-site AEs and maximum temperatures Days 1 through 5 postvaccination; systemic AEs Days 1 through 15 postvaccination.
(b) For the injection-site redness and swelling 0 to 2.5 cm (0 to 1 inch) will be categorized as mild, >2.5 to 5 cm (>1 inch to 2 inches) will be categorized as moderate, and >5 cm (>2 inches) will be categorized as severe.
(c) Defined as maximum (over the follow-up period) temperature ≥37.5°C.
Note: X = indicated summary statistic will be provided.

9.6.4 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 vaccine group. 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

The overall type 1 error rate associated with testing the primary and secondary efficacy hypotheses will be controlled by a fixed sequence procedure. When at least 17 cases of the primary endpoint and at least 17 cases of the secondary endpoint have been observed, the primary efficacy hypothesis will be tested at a 1-sided type 1 error rate ≤ 0.025, as discussed in Section 9.9.1. The secondary efficacy hypothesis will be tested at a 1-sided type 1 error rate ≤ 0.025 only if the primary efficacy hypothesis is successfully demonstrated.

9.9 Sample Size and Power Calculations

This is an event-driven study and the planned sample size is approximately 1050 participants.

9.9.1 Sample Size and Power for Testing the Primary Efficacy Hypothesis

With a 1:1 randomization between the 2 arms, the decision rule displayed in Table 8 for testing the primary efficacy hypothesis of VE >0% at a total of 17 cases will have 1-sided type 1 error rate ≤ 0.025 and power has 94% if the true VE is at least 85% (see Table 8). Type 1 error rate and power calculations were done based on the method proposed by Chan and Bohidar (1998) [Chan, I. S. F. and Bohidar, N. R. 1998]. Table 8 also displays the decision rule that will be used if the primary efficacy hypothesis is tested with total cases greater than 17.

Table 8 Decision Rule and Corresponding Type 1 Error rate and Power for Testing the Primary Efficacy Hypothesis

Analysis Time Point	Total Cases	Critical Case Split		Type 1 Error rate	True Vaccine Efficacy (VE)				
		Vaccine	Placebo		75%	80%	85%	90%	95%
					Power (%)				
Final	17	4	13	0.0245	76	86	94	98	>99
	18	4	14	0.0154	72	83	92	98	>99
	19	4	15	0.0096	67	80	91	98	>99
	20	5	15	0.0207	80	90	96	99	>99
	21	5	16	0.0133	77	88	95	99	>99
	22	5	17	0.0085	73	85	94	99	>99
	23	6	17	0.0173	84	93	98	>99	>99
	24	6	18	0.0113	81	91	97	>99	>99
	25	7	18	0.0216	89	96	99	>99	>99

A total of approximately 1050 participants are needed to be enrolled in order to accumulate approximately 17 total primary endpoint cases within 56 months from the time the first study participant signs the ICF based on the following assumptions. Assumption is based on V501-122:

- 14 months enrollment;
- Exclusion rate from PPE analysis is approximately 15%;
- Attrition rate is approximately 5% per year;
- Annual incidence rate for the primary efficacy endpoint is 1.9% per year;
- True VE is 85%.

9.9.2 Sample Size and Power for Testing the Secondary Efficacy Hypothesis

Table 8 also displays the decision rule that will be used for testing the secondary efficacy hypothesis with 17 or more total cases. The testing of the secondary efficacy hypothesis of VE >0% at 17 total cases will have 1-sided type 1 error rate ≤ 0.025 and power has 94% if the true VE is at least 85% (see Table 8).

A total of approximately 1050 participants are needed to be enrolled in order to accumulate at least 17 total secondary endpoint cases at the time of accumulation of at least 17 primary efficacy cases, i.e., within 56 months from the time the first study participant signs the ICF, when the annual incidence rate of the secondary efficacy endpoint is 2.0% per year and true VE is equal to 85% (based on the same enrollment duration, attrition, and exclusions from the PPE population assumed in Section 9.9.1.

9.9.3 Sample Size and Power for Safety Analysis

The probability of observing at least one SAE in this study depends on the number of participants vaccinated and the underlying percentage of participants with SAE in the study population. If the underlying incidence of SAE is 0.5%, there is a 93% chance of observing at least one SAE among 525 participants in the 9vHPV vaccine group. If no adverse experiences are observed among the 525 participants in the 9vHPV vaccine group, this study will provide 95% confidence that the underlying percentage of participants with an SAE is <0.6%.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the point and 95% CI estimates of VE for the primary, the secondary efficacy and the exploratory endpoint will be provided by Age, Sexual Orientation, Smoking, Lifetime Sexual Partners, Presence of Other HPV Types.

Both for HM and MSM subgroups analyses will be performed for following endpoints.

Efficacy:

- HPV 6/11/16/18-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart
- HPV 31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart
- HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart
- HPV 6/11/16/18/31/33/45/52/58-related genital warts, PIN, penile, perianal or perineal cancer
- HPV 6/11/16/18/31/33/45/52/58-related intra-anal persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart
- HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection detected in samples from three or more consecutive visits 6 months (± 1-month window) or longer apart (i.e., at least 12 months persistent infection)

Immunogenicity:

- GMT to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7
- Seroconversion to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered the 9vHPV or placebo.

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 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 their 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, frequently 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 their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

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 before 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 Committees Structure

10.1.4.1 Clinical Adjudication Committee (CAC)

A CAC, the HPV Vaccine Program Pathology Panel in this study, will evaluate the potential genital warts, PIN, penile, perianal or perineal cancer for the purposes of confirming them. The HPV Vaccine Program Pathology Panel will be responsible for providing the definitive pathologic diagnoses of external genital lesion biopsies for study purposes (not for medical management). Slides from external genital lesion biopsies will be evaluated by HPV Vaccine Program Pathology Panel. The HPV Vaccine Program Pathology Panel will prepare reports on each tissue specimen without knowing the vaccination groups of the participants. A separate guideline that details the HPV Vaccine Program Pathology Panel process has been approved by the HPV Vaccine Program Pathology Panel.

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

10.1.5 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 ICMJE authorship requirements.

10.1.6 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.

10.1.7 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, ICH 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.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 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 (eg, EU CTR: 25 years after the end of the study). 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.

10.1.9 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.

10.1.10 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 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 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 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 preexisting 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.5.6 for protocol-specific exceptions.

10.3.3 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 preexisting condition that has not worsened is not an SAE.) A preexisting 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.

10.3.4 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.

10.3.5 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 assess the intensity of 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 with a legally acceptable representative: awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies with a legally acceptable representative: 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 used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies with a legally acceptable representative: 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 study intervention cause the AE?

- The determination of the likelihood that the study intervention 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 initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based on the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? 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 reexposed to the study intervention 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; (2) the study is a single-dose vaccine study; or (3) study intervention(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 STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION 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 study intervention 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 their 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 study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- 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 their 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.

10.3.6 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 8.5.1 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 email 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: Combination Medicinal Products: Complaints, Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

The recording and follow-up procedures described in the protocol apply to combination medicinal products as described below. For purposes of this section, combination medicinal products in scope for device information collection include combination medicinal products as listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

10.4.1 Definitions

Medical Device – Devices, etc, (other than regenerative medicine products) intended for use in the diagnosis, treatment, or prevention of disease in humans or animals, or intended to affect the structure or functions of the body of humans or animals.

Combination Medicinal Product – The products to be manufactured and marketed as a single drug, medical device, or regenerative medical product by combining two or more different type of drugs, medical devices or processed cells that are presumed to fall under the category of drugs, medical devices, or regenerative medical products if it is distributed alone.

Malfunction – When the device constituent part of a combination medicinal product, as described in the protocol, has quality, safety, or performance issue, such as damage or failure in operation, regardless of the stage of design, delivery, storage, or use.

Serious Adverse Event Due to Malfunction – A SAE occurring in a participant and/or the associated person in a clinical trial caused by, or suspected to be caused by, the use of the device constituent part of the combination medicinal product, as described in the protocol.

Malfunction That May Lead to Serious Adverse Events – Any malfunction of a device constituent part of a combination medicinal product, as described in the protocol, which might have led to the death of a participant and/or the associated person or to a serious deterioration in their state of health. “Which might have led to” means there is the possibility that death or a serious deterioration might have occurred in a participant and/or the associated person, although no event has occurred.

10.4.2 Recording, Assessing Causality, and Follow-up of Complaints, PQCs/Malfunctions

Recording

- When a Complaint, PQC/malfunction occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- AEs occurring during the study will be recorded in the participant's medical records (or equivalent), in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions in the data entry guidelines (or equivalent). Device constituent part of drug-device combination product/combination medicinal product information (regardless of participants or associated persons) will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.5.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor.
- It is important that the investigator provides an assessment of causality (relationship to the medical device) at the time of the initial report.
- Malfunction, which may lead to SAEs, will be reported to the Sponsor within 5 calendar days of learning of the information via a paper reporting form.

Assessing Causality

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes should also be considered and investigated, such as underlying disease(s), concomitant therapy, and other risk factors as well as the temporal relationship of the event to study intervention administration.

Follow-up

- The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

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[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.10 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[3, 4]

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 or 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 on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant 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[3, 4]

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 is 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 that 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[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using 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[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the 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 study use only. If specimens were collected from study participants specifically for FBR, 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 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 before 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.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the 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[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the 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 used 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[3, 4]

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[3, 4]

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[3, 4]

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[3, 4]

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.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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
AIN	Anal intraepithelial neoplasia
ANPS	All Naïve Participants with Serology
APaT	All Participants as Treated
CI	confidence interval
cLIA	competitive Luminex Immunoassay
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic Case Report Form
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
H&E	hematoxylin & eosin
HIV	human immunodeficiency virus
HM	heterosexual males
HN-TS	HPV Type-Specific Naïve
HPV	human papillomavirus
HSV	herpes simplex virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors

Abbreviation	Expanded Term
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
IVIG	intravenous gamma globulin
LLOQ	lower limit of quantitation
mMU/mL	milli-Merck Units per milliliter
MSM	males who have sex with males
PCR	polymerase chain reaction
PIN	penile/perianal/perineal intraepithelial neoplasia
PK	pharmacokinetic
PPE	Per-Protocol Efficacy
PPI	Per-Protocol Immunogenicity
PQC	product quality complaint
qHPV	quadrivalent HPV
RCD	reverse cumulative distribution
RNA	ribonucleic acid
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental statistical analysis plan
STI	Sexually Transmitted Infection
SUSAR	suspected unexpected serious adverse reaction
TNF-α	tumor necrosis factor-alpha
ULOQ	upper limit of quantitation
VE	vaccine efficacy
VLP	virus-like particle
VRC	vaccination report card

11 REFERENCES

[Alemany, L., et al 2014]	Alemany L, Saunier M, Tinoco L, et al. Large contribution of human papillomavirus in vaginal neoplastic lesions: a worldwide study in 597 samples. Eur J Cancer. 2014;50:2846-54.
[Alemany, L., et al 2015]	Alemany L, Saunier M, Alvarado-Cabrero I, et al. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. Int J Cancer. 2015;136:98-107.
[Aubin, F., et al 2008]	Aubin F, Prétet JL, Jacquard AC, et al. Human papillomavirus genotype distribution in external acuminata condylomata: a Large French National Study (EDiTH IV). Clin Infect Dis. 2008;47:610-5.
[Baseman, J.G., et al 2005]	Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol. 2005;32 Suppl 1:S16-24.
[Blomberg, M., et al 2012]	Blomberg M, Friis S, Munk C, et al. Genital warts and risk of cancer: a Danish study of nearly 50000 patients with genital warts. J Infect Dis. 2012;205:1544-53.
[Bouvard, V., et al 2009]	Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. Special Report: Policy; A review of human carcinogens-Part B: biological agents. Lancet 2009;10:321-2.
[Brouwer, A.F., et al 2019]	Brouwer AF, Eisenberg MC, Carey TE, et al. Multisite HPV infections in the United States (NHANES 2003-2014): an overview and synthesis. Prev Med. 2019;123:288-98.
[Centers for Disease Control and Prevention 2015]	Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. 13th ed. Hamborsky J, Kroger A, Wolfe S, editors. Washington (DC): Department of Health and Human Services (HHS); c2015. Chapter 6, Vaccine administration; p.79-106.
[Chan, I. S. F. and Bohidar, N. R. 1998]	Chan ISF, Bohidar NR. Exact power and sample size for vaccine efficacy studies. Commun Statist-Theory Meth. 1998;27:1305-22.
[Chan, P.K.S., et al 2009]	Chan PKS, Luk ACS, Luk TNM, et al. Distribution of human papillomavirus types in anogenital warts of men. J Clin Virol. 2009;44:111-4.

[Chesson, H.W., et al 2014]	Chesson HW, Dunne EF, Hariri S, et al. The estimated lifetime probability of acquiring human papillomavirus in the United States. Sex Transm Dis. 2014;41:660-4.
[Chuang, T.Y., et al 1984]	Chuang TY, Perry HO, Kurland LT, et al. Condyloma acuminatum in Rochester, Minn, 1950-1978.II. Anaplasias and unfavorable outcomes. Arch Dermatol. 1984;120:476-83.
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404-13.
[Daling, J.R., et al 2004]	Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer. 2004;101:270-80.
[de Martel, C., et al 2017]	de Martel C, Plummer M, Vignat J, et al. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017;141:664-70.
[de Sanjosé, S., et al 2013]	de Sanjosé S, Alemany L, Ordi J, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. Eur J Cancer. 2013;49:3450-61.
[de Sanjosé, S., et al 2019]	de Sanjosé S, Serrano B, Tous S, et al. Burden of Human Papillomavirus (HPV)-Related Cancers Attributable to HPVs 6/11/16/18/31/33/45/52 and 58. JNCI Cancer Spectr. 2019;2:pky045.
[De Vuyst H., et al 2009]	De Vuyst H, Clifford GM, Nascimento MC, et al. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer. 2009;124:1626-36.
[Else, E. A., et al 2011]	Else EA, Swoyer R, Zhang Y, Taddeo FJ, Bryan JT, Lawson J, et al. Comparison of real-time multiplex human papillomavirus (HPV) PCR assays with INNO-LiPA HPV genotyping extra assay. J Clin Microbiol. 2011 May;49(5):1907-12.
[Ferris, D.G., et al 2017]	Ferris DG, Samakoses R, Block SL, et al. 4-Valent Human Papillomavirus (4vHPV) Vaccine in Preadolescents and Adolescents After 10 Years. Pediatrics. 2017;140:e20163947.

[Forman, D., et al 2012] Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30 Suppl 5:F12-23.

[Garland, S.M., et al 2009] Garland SM, Steben M, Sings HL, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect Dis. 2009;199:805-14.

[Gillison, M.L., et al 2012] Gillison ML, Alemany L, Snijders PJF, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine. 2012;30 Suppl 5:F34-54.

[Giuliano, A.R., et al 2011] Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011;364:401-11.

[Herfs, M., et al 2018] Herfs M, Roncarati P, Koopmansch B, et al. A dualistic model of primary anal canal adenocarcinoma with distinct cellular origins, etiologies, inflammatory microenvironments and mutational signatures: implications for personalised medicine. Br J Cancer. 2018;118:1302-12.

[Huh, W.K., et al 2017] Huh WK, Joura EA, Giuliano AR, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. Lancet. 2017;390:2143-59.

[Iwata, S., et al 2017] Iwata S, Murata S, Han SR, et al. Safety and Immunogenicity of a 9-Valent Human Papillomavirus Vaccine Administered to 9- to 15-Year-Old Japanese Girls. Jpn J Infect Dis. 2017;70:368-73.

[Joura, E.A., et al 2015] Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372:711-23.

[Koutsky, L. 1997] Koutsky L. Epidemiology of genital human papillomavirus infection. Am J Med. 1997;102:3-8.

[Lacey, C.J.N., et al 2006] Lacey CJN, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine. 2006;24 Suppl 3:S3/35-41.

[Madkan, V.K., et al 2007]	Madkan VK, Cook-Norris RH, Steadman MC, et al. The oncogenic potential of human papillomaviruses: a review on the role of host genetics and environmental cofactors. Br J Dermatol. 2007;157:228-41.
[MHLW. 2019]	MHLW. Annual number of reported sexually transmitted diseases (STD) by sex. Available from: https://www.mhlw.go.jp/topics/2005/04/tp0411-1.html
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4:213-26.
[Mikamo H., et al 2019]	Mikamo H, Yamagishi Y, Murata S, et al. Efficacy, safety, and immunogenicity of a quadrivalent HPV vaccine in Japanese men: A randomized, Phase 3, placebo-controlled study. Vaccine. 2019;37:1651-8.
[National Cancer Center. 2015]	Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan (Monitoring of Cancer Incidence in Japan (MCIJ)). Available from: https://ganjoho.jp/data/reg_stat/statistics/dl/cancer_incidence47pref(2014-2015).xls
[NIID. 2018]	National Institute of Infectious Diseases. Annual report on infectious disease outbreak trends. Available from: https://www.niid.go.jp/niid/images/idwr/ydata/2018/Syuukei/Syu_12_1.xlsx
[Oriel, J.D. 1971]	Oriel JD. Natural history of genital warts. Brit J Vener Dis. 1971;47:1-13.
[Paavonen, J. 2007]	Paavonen J. Human papillomavirus infection and the development of cervical cancer and related genital neoplasias. Int J Infect Dis. 2007;11 Suppl 2:S3-9.
[Palefsky, J.M., et al 2011]	Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365:1576-85.
[Pitisuttithum, P., et al 2015]	Pitisuttithum P, Velicer C, Luxembourg A. 9-Valent HPV vaccine for cancers, pre-cancers and genital warts related to HPV. Expert Rev Vaccines. 2015;14:1405-19.
[Radley, D., et al 2016]	Radley D, Saah A, Stanley M. Persistent infection with human papillomavirus 16 or 18 is strongly linked with high-grade cervical disease. Hum Vaccin Immunother. 2016;12:768-72.

[Roberts, C.C., et al 2011]	Roberts CC, Swoyer R, Bryan JT, et al. Comparison of real-time multiplex human papillomavirus (HPV) PCR assays with the linear array HPV genotyping PCR assay and influence of DNA extraction method on HPV detection. J Clin Microbiol. 2011;49:1899-906.
[Roberts, C., et al 2014]	Roberts C, Green T, Hess E, et al. Development of a human papillomavirus competitive luminex immunoassay for 9 HPV types. Hum Vaccin Immunother. 2014;10:2168-74.
[Serrano, B., et al 2012]	Serrano B, Alemany L, Tous S, et al. Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. Infect Agent Cancer. 2012;7:38.
[Stamataki, S., et al 2007]	Stamataki S, Nikolopoulos TP, Korres S, et al. Juvenile recurrent respiratory papillomatosis: still a mystery disease with difficult management. Head Neck. 2007;29:155-62.
[Stone, K.M. 1995]	Stone KM. Human papillomavirus infection and genital warts: update on epidemiology and treatment. Clin Infect Dis. 1995;20 Suppl 1:S91-7.
[Valvo, F., et al 2019]	Valvo F, Ciurlia E, Avuzzi B, et al. Cancer of the anal region. Crit Rev Oncol Hematol. 2019;135:115-27.
[Xi, L.F. and Koutsky, L.A. 1997]	Xi LF, Koutsky LA. Epidemiology of genital human papillomavirus infections. Bull Inst Pasteur. 1997;95:161-78.
[Yanofsky, V.R., et al 2012]	Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol. 2012;5:25-36.