Official Protocol Title:	A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9vHPV and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age
NCT number:	NCT05119855
Document Date:	15-Feb-2023

TITLE PAGE

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Protocol Title: A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9vHPV and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age

Protocol Number: 076-03

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):

NCT	NCT05119855
EU CT	Not applicable
EudraCT	2021-003591-13
JAPIC-CT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	13447

Approval Date: 15 February 2023

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	15-FEB-2023	The primary purpose of this amendment is to change from a hypothesis testing study to an estimation study design due to early closure of enrollment.
Amendment 2	12-JUL-2022	The primary reason for this amendment is to allow enrollment of participants with SARS-CoV-2 infection >90 days prior to enrollment.
Amendment 1	15-DEC-2021	The primary reasons for this amendment are to change the age range for study participants to 9 to 11 years of age and to change the dose (volume) of the mRNA-1273 vaccine to 50 µg (0.25 mL) to reflect emerging clinical data for the mRNA-1273 vaccine.
Original Protocol	09-AUG-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment: The primary purpose of this amendment is to change from a hypothesis testing study to an estimation study design due to early closure of enrollment.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1 Synopsis Section 1.2 Schema Section 3 Hypotheses, Objective, and Endpoints Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 9.1 Statistical Analysis Plan Summary Section 9.3 Hypotheses/Estimation Section 9.6.1 Statistical Methods for Immunogenicity Analyses Section 9.8 Multiplicity Section 9.9 Sample Size and Power Calculations Section 9.10 Subgroup Analyses	• Changed the study design from comparative, hypothesis testing to estimation. • Changed the expected enrollment from approximately 400 to approximately 160 participants. • Changed study duration from approximately 12 months to approximately 21 months.	In the setting of the evolving COVID-19 pandemic setting, enrollment has been slower than anticipated. Additionally, the mRNA-1273 vaccine clinical supply will not be available after 1Q2023 to support further enrollment. Therefore, enrollment will conclude with an expected enrollment of approximately 160 participants and the planned analyses will be converted to descriptive data summaries.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Title Page	Added NCT number.	Include additional study identifier.
Section 1.1 Synopsis	Updated indication from "Prevention of persistent infection and disease caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58" to "Papilloma viral infection".	Align with MedDRA preferred terminology.
Section 1.1 Synopsis Section 6.1 Study Intervention(s) Administered	• Additional intervention information from Table 1 included in Synopsis. • Dose Formation: "Sterile Suspension" changed to "Suspension". • Use: "Experimental" changed to "Test Product".	Clarification and to align with global regulatory requirements.
Section 4.4 Beginning and End-of-Study Definition	Replaced example for lost to follow-up and added reference to the respective section.	Clarification.
	Added text to define the European Economic Area (EEA).	To align with global regulatory requirements.
Section 8.1.10.1 Withdrawal From Future Biomedical Research Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Updated Sponsor contact email address for future biomedical research.	New email address.
Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Changed "Sponsor's product" to "study intervention" and emergency room to emergency department.	To harmonize terminology.

Section Number and Name	Description of Change	Brief Rationale
Throughout Document	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.
	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9vHPV and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age

Short Title: Safety and Immunogenicity of 9vHPV Vaccine Coadministered With mRNA-1273 SARS-CoV-2 Vaccine

Acronym: None

Hypotheses, Objectives, and Endpoints:

The following objectives and endpoints will be evaluated in boys and girls 9 to 11 years of age.

Primary Objectives	Primary Endpoints
• **Objective 1:** To evaluate the GMTs of antibodies to each of the 9vHPV vaccine types at 4 weeks Postdose 2 of a 2-dose regimen of 9vHPV vaccine, when the first dose of a 2-dose regimen of 9vHPV vaccine is administered concomitantly or nonconcomitantly with a first dose of a 2-dose regimen of mRNA-1273 vaccine.	• Serum antibody titers at 4 weeks Postdose 2 of 9vHPV vaccine measured by cLIA to each of the 9vHPV vaccine types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58)
• **Objective 2:** To evaluate the GMCs of SARS-CoV-2 spike protein-specific binding antibody at 4 weeks Postdose 2 of a 2-dose regimen of mRNA-1273 vaccine, when the first dose of a 2-dose regimen of mRNA-1273 vaccine is administered concomitantly or nonconcomitantly with a first dose of a 2-dose regimen of 9vHPV vaccine.	• Serum antibody concentrations at 4 weeks Postdose 2 of mRNA-1273 vaccine measured by ECL assay specific to the SARS-CoV-2 spike protein

• **Objective 3:** To evaluate the safety and tolerability of 2-dose regimens of 9vHPV and mRNA-1273 vaccines where the first dose of each vaccine is administered concomitantly.	• Solicited injection-site AEs • Solicited systemic AEs • SAEs • Vaccine-related SAEs
Secondary Objectives	**Secondary Endpoints**
• **Objective:** For each of the Concomitant and Nonconcomitant Groups, to estimate percent seroconversion to each of the 9vHPV vaccine types at 4 weeks Postdose 2 induced by a 2-dose regimen of 9vHPV vaccine.	• Serum antibody titers at 4 weeks Postdose 2 of 9vHPV vaccine measured by cLIA to each of the 9vHPV vaccine types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58)
• **Objective:** For each of the Concomitant and Nonconcomitant Groups, to estimate percent seroresponse at 4 weeks Postdose 2 induced by a 2-dose regimen of mRNA-1273 vaccine.	• Serum antibody concentrations at 4 weeks Postdose 2 of mRNA-1273 vaccine measured by ECL assay specific to the SARS-CoV-2 spike protein

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Papilloma viral infection
Population	Boys and girls 9 to 11 years of age
Study Type	Interventional
Intervention Model	Parallel This is a multi site study Concomitant administrations
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding

Estimated Duration of Study	The Sponsor estimates that the study will require approximately 21 months from the time the first participant (or their legally acceptable representative) provides documented informed consent/assent until the last participant's last study-related contact. 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 160 participants will be enrolled into the study.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Concomitant Group	mRNA-1273 vaccine	mRNA* 50 µg per dose	0.25 mL per dose	IM	Single dose at Day 1 and Month 1	Test Product
Concomitant Group	9vHPV vaccine	HPV6/11/16/18/31/33/ 45/52/58 L1 VLP: 30/40/60/40/20/20/20/ 20/20 mcg per dose	0.5 mL per dose	IM	Single dose at Day 1 and Month 6	Test Product
Nonconcomitant Group	mRNA-1273 vaccine	mRNA* 50 µg per dose	0.25 mL per dose	IM	Single dose at Day 1 and Month 1	Test Product
Nonconcomitant Group	9vHPV vaccine	HPV6/11/16/18/31/33/ 45/52/58 L1 VLP: 30/40/60/40/20/20/20/ 20/20 mcg per dose	0.5 mL per dose	IM	Single dose at Month 2 and Month 8	Test Product

HPV=human papillomavirus; IM=intramuscular; IMP=Investigational Medicinal Product; mL=milliliter; mRNA=messenger ribonucleic acid; NIMP/AxMP=noninvestigational/auxiliary medicinal product; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

The classification of IMP and NIMP/AxMP 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 and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

* mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 virus (Moderna Inc., Cambridge, MA)

Other current or former name(s) or alias(es) for study intervention(s) are as follows: Moderna COVID-19 vaccine and mRNA-1273 SARS-CoV-2 vaccine for mRNA-1273 vaccine; GARDASIL®9 and V503 for 9vHPV vaccine.

Total Number of Intervention Groups/Arms	2 intervention groups
Duration of Participation	Each participant will participate in the study for approximately 7 or 9 months from the time the participant provides documented informed consent/assent through the final contact.

Study Governance Committees:

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

There are no governance committees in this study.

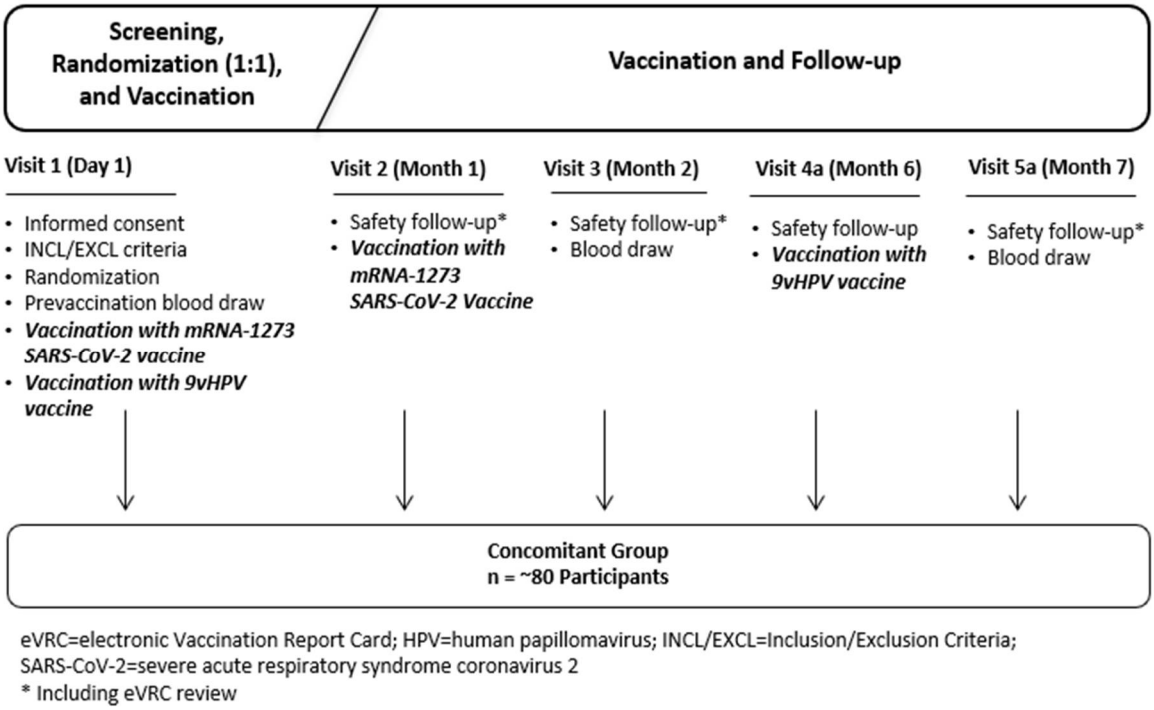
Study Accepts Healthy Participants: Yes

A list of abbreviations is in Appendix 8.

1.2 Schema

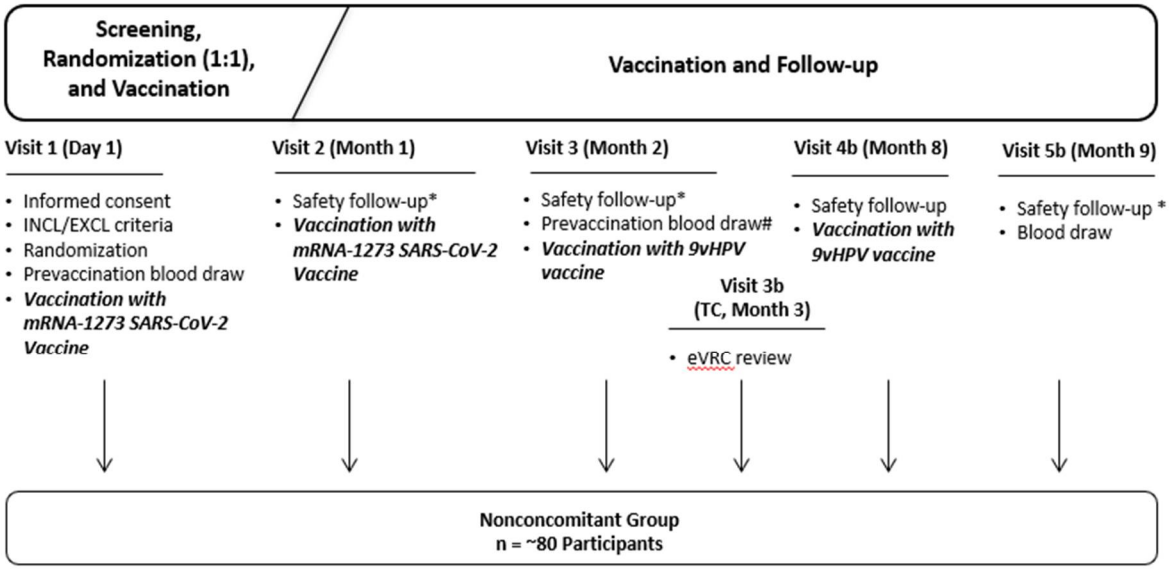
The main features of the study design are depicted in Figure 1 for Concomitant Group and Figure 2 for Nonconcomitant Group.

Figure 1 Study Design for Concomitant Group



eVRC=electronic Vaccination Report Card; HPV=human papillomavirus; INCL/EXCL=Inclusion/Exclusion Criteria; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
* Including eVRC review

Figure 2 Study Design for Nonconcomitant Group



eVRC=electronic Vaccination Report Card; HPV=human papillomavirus; INCL/EXCL=Inclusion/Exclusion Criteria; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; TC=telephone contact
* Including eVRC review
# Prevaccination blood draw for baseline anti-HPV antibody testing and SARS-CoV-2 Spike protein-specific binding antibody testing Postdose 2 of mRNA-1273 SARS-CoV-2 vaccine

1.3 Schedule of Activities

1.3.1 Scheduled Visits for Concomitant Group

Study Period	**Intervention and Follow-up**					**Notes**
Visit Number	**1**	**2**	**3**	**4a**	**5a**	
Scheduled Time	**Day 1**	**Month 1**	**Month 2**	**Month 6**	**Month 7**	
Visit Window[a]		**28 to 42 days after Visit 1**	**28 to 42 days after Visit 2**	**6 months after Day 1 ±4 weeks**	**28 to 49 days after Visit 4a**	**To calculate visit windows, assume 1 month = 30 days and 1 week = 7 days.**
Administrative and General Procedures						
Obtain Informed Consent/Assent	X					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, then the participant must be reconsented.
Obtain Informed Consent/Assent for Future Biomedical Research	X					Participation in future biomedical research is optional and consent/assent must be obtained before collection of blood (DNA) samples.
Review Inclusion/Exclusion Criteria	X					
Assign Participant Identification Card	X					
Collect Medical History	X					See Section 8.1.4 for details.
Collect Demographics	X					
Review Prior/Concomitant Medication and Nonstudy Vaccination	X	X	X	X	X	See Section 8.1.6 for details.
Clinical Procedures and Assessments						
Measure Oral Temperature	X	X		X		Oral temperature should be measured prior to vaccination. If the participant has a fever within the 24-hour period prior to a vaccination visit, the visit should be rescheduled until after the fever has resolved (Section 5.2).
Record Height and Weight	X					Height and weight will be recorded on Day 1 before vaccination.
Perform Physical Examination	X					Performed at Day 1 to assess inclusion/exclusion criteria. After Day 1, a physical examination is optional.

Study Period	**Intervention and Follow-up**					**Notes**
Visit Number	**1**	**2**	**3**	**4a**	**5a**	
Scheduled Time	**Day 1**	**Month 1**	**Month 2**	**Month 6**	**Month 7**	
Visit Window[a]		**28 to 42 days after Visit 1**	**28 to 42 days after Visit 2**	**6 months after Day 1 ±4 weeks**	**28 to 49 days after Visit 4a**	**To calculate visit windows, assume 1 month = 30 days and 1 week = 7 days.**
Laboratory Procedures and Assessments						
Perform Pregnancy Testing, Serum or Urine (required for all females)	X	X		X		The serum pregnancy test or urine pregnancy test must be sensitive to at least 25 mIU/mL β-hCG and performed prior to vaccination. Results must be negative prior to vaccination (Section 8.3.6).
Collect Blood Sample (Serum for anti-HPV Antibodies)	X				X	Serum must be collected before vaccination. Serum (including retention serum) must be shipped as specified by the Sponsor or central laboratory.
Collect Blood Sample (Serum for SARS-CoV-2 Spike Protein-specific Binding Antibody)	X		X			
Collect Blood (DNA) for Future Biomedical Research	X					Sample will be collected from randomized participants who provided consent for future biomedical research. Sample should be obtained before vaccine is administered on Day 1 or at a later date as soon as informed consent is obtained. Participation in future biomedical research is optional.
Randomization, Vaccine Administration, and Safety Procedures/Assessments						
Vaccine Allocation/Randomization	X					
Provide or Configure Electronic Device for eVRC Data Collection	X					Study personnel will train the participant on the use of the device for eVRC data collection.
Administer mRNA-1273 SARS-CoV-2 Vaccine (**Right Arm**)	X	X				
Administer 9vHPV Vaccine (**Left Arm**)	X			X		
30-minute Postvaccination Observation Period	X	X		X		
Review eVRC Data With Participant		X	X		X	
Collect Electronic Device From Participant					X	For participants who were provided an electronic device.

Study Period	**Intervention and Follow-up**					**Notes**
Visit Number	**1**	**2**	**3**	**4a**	**5a**	
Scheduled Time	**Day 1**	**Month 1**	**Month 2**	**Month 6**	**Month 7**	
Visit Window[a]		**28 to 42 days after Visit 1**	**28 to 42 days after Visit 2**	**6 months after Day 1 ±4 weeks**	**28 to 49 days after Visit 4a**	**To calculate visit windows, assume 1 month = 30 days and 1 week = 7 days.**
Monitor AEs	X	X	X	X	X	See Section 8.4.1 for details on the timing and frequency of AE monitoring.

AE=adverse event; β-hCG=β-human chorionic gonadotropin; DNA=deoxyribonucleic acid; eVRC=electronic Vaccination Report Card; HPV=human papillomavirus; mIU=milli international units; mL=milliliter; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

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

1.3.2 Scheduled Visits for Nonconcomitant Group

Study Period	**Intervention and Follow-up**						**Notes**
Visit Number	**1**	**2**	**3**	**3b (TC)**	**4b**	**5b**	
Scheduled Time	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 8**	**Month 9**	
Visit Window[a]		**28 to 42 days after Visit 1**	**28 to 42 days after Visit 2**	**29 to 35 days after Visit 3**	**6 months after Visit 3 ±4 weeks**	**28 to 49 days after Visit 4b**	**To calculate visit windows, assume 1 month=30 days and 1 week=7 days.**
Administrative and General Procedures							
Obtain Informed Consent/Assent	X						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, then the participant must be reconsented.
Obtain Informed Consent/Assent for Future Biomedical Research	X						Participation in future biomedical research is optional and consent/assent must be obtained before collection of blood (DNA) samples.
Review Inclusion/Exclusion Criteria	X						
Assign Participant Identification Card	X						
Collect Medical History	X						See Section 8.1.4 for details.
Collect Demographics	X						
Review Prior/Concomitant Medication and Nonstudy Vaccination	X	X	X	X	X	X	See Section 8.1.6 for details.
Clinical Procedures and Assessments							
Measure Oral Temperature	X	X	X		X		Oral temperature should be measured prior to vaccination. If the participant has a fever within the 24-hour period prior to a vaccination visit, the visit should be rescheduled until after the fever has resolved (Section 5.2).
Record Height and Weight	X						Height and weight will be recorded on Day 1 before vaccination.

Study Period	**Intervention and Follow-up**						**Notes**
Visit Number	**1**	**2**	**3**	**3b (TC)**	**4b**	**5b**	
Scheduled Time	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 8**	**Month 9**	
Visit Window[a]		**28 to 42 days after Visit 1**	**28 to 42 days after Visit 2**	**29 to 35 days after Visit 3**	**6 months after Visit 3 ±4 weeks**	**28 to 49 days after Visit 4b**	**To calculate visit windows, assume 1 month=30 days and 1 week=7 days.**
Perform Physical Examination	X						Performed at Day 1 to assess inclusion/exclusion criteria. After Day 1, a physical examination is optional.
Laboratory Procedures and Assessments							
Perform Pregnancy Testing, Serum or Urine (required for all females)	X	X	X		X		The serum pregnancy test or urine pregnancy test must be sensitive to at least 25 mIU/mL β-hCG and performed prior to vaccination. Results must be negative prior to vaccination (Section 8.3.6).
Collect Blood Sample (Serum for anti-HPV Antibodies)			X			X	Serum must be collected before vaccination. Serum (including retention serum) must be shipped as specified by the Sponsor or central laboratory.
Collect Blood Sample (Serum for SARS-CoV-2 Spike Protein-specific Binding Antibody)	X		X				
Collect Blood (DNA) for Future Biomedical Research	X						Sample will be collected from randomized participants who provided consent for future biomedical research. Sample should be obtained before vaccine is administered on Day 1 or at a later date as soon as informed consent is obtained. Participation in future biomedical research is optional.
Randomization, Vaccine Administration, and Safety Procedures/Assessments							
Vaccine Allocation/Randomization	X						
Provide or Configure Electronic Device for eVRC Data Collection	X						Study personnel will train the participant on the use of the device for eVRC data collection.
Administer mRNA-1273 SARS-CoV-2 Vaccine (**Right Arm**)	X	X					

Study Period	**Intervention and Follow-up**						**Notes**
Visit Number	**1**	**2**	**3**	**3b (TC)**	**4b**	**5b**	
Scheduled Time	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 8**	**Month 9**	
Visit Window[a]		**28 to 42 days after Visit 1**	**28 to 42 days after Visit 2**	**29 to 35 days after Visit 3**	**6 months after Visit 3 ±4 weeks**	**28 to 49 days after Visit 4b**	**To calculate visit windows, assume 1 month=30 days and 1 week=7 days.**
Administer 9vHPV Vaccine (**Left Arm**)			X		X		
30-minute Postvaccination Observation Period	X	X	X		X		
Review eVRC Data With Participant		X	X	X		X	
Collect Electronic Device From Participant						X	For participants who were provided an electronic device.
Monitor AEs	X	X	X	X	X	X	See Section 8.4.1 for details on the timing and frequency of AE monitoring.

AE=adverse event; β-hCG= β-human chorionic gonadotropin; DNA=deoxyribonucleic acid; eVRC=electronic Vaccination Report Card; HPV=human papillomavirus; mIU=milli international units; mL=milliliter; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; TC=telephone contact

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

2 INTRODUCTION

The 9-valent HPV vaccine was initially licensed as a 3-dose vaccination series and was subsequently approved for 2-dose regimens in individuals 9 to 14 years of age (the main target population for vaccination) in many countries. The WHO and the US ACIP changed their recommendations in 2014 and 2016, respectively, to include 2-dose regimens for individuals 9 to 14 years of age [World Health Organization 2014] [Meites, E., et al 2016].

The mRNA-1273 SARS-CoV-2 vaccine (Moderna Inc., Cambridge, MA) has been studied in children 6 to 11 years of age (mRNA-1273-P204; NCT04796896). The interim analysis from the study showed a robust neutralizing antibody response after 2 doses of mRNA-1273 vaccine at the 50-µg dose level with a favorable safety profile [Moderna, Inc. 2021], which was the basis for an expanded EUA for primary vaccination series in individuals 6 to 11 years of age [O'Shaughnessy, J. A. 2022].

2.1 Study Rationale

Licensure and recommendation of 2-dose regimens of the 9vHPV vaccine were based on a clinical study (Protocol V503-010; NCT01984697), which demonstrated that 2 doses of the 9vHPV vaccine administered either 6 or 12 months apart in boys and girls 9 to 14 years of age elicited noninferior GMTs to the 9 vaccine-targeted HPV types at 4 weeks after the last dose compared with a standard 3-dose regimen (administered at Day 1, Month 2, and Month 6) in young women 16 to 26 years of age [Iversen, O. E. 2016].

The initial EUA in December 2020 of a 2-dose regimen of the mRNA-1273 vaccine at the 100-µg dose level for persons >18 years of age was based on a clinical study (mRNA-1273-P301; NCT04470427), which demonstrated clinical efficacy in preventing symptomatic, laboratory-confirmed COVID-19 infection with an acceptable safety profile [Baden, L. R., et al 2021]. A further clinical study (mRNA-1273-P204; NCT04796896) demonstrated strong immune response in children 6 to 11 years of age [Moderna, Inc. 2021]. The SARS-CoV-2-neutralizing antibody geometric mean ratio comparing the response in children 6 to 11 years of age to the response in young adults from the mRNA-1273-P301 clinical study was 1.5 (95% Cl: 1.3, 1.8), with a seroresponse rate of 99.3%. The mRNA-1273 vaccine was generally well tolerated in children 6 to 11 years of age with a safety and tolerability profile generally consistent with the mRNA-1273-P301 clinical study. The mRNA-1273 vaccine is authorized for use for active immunization as a primary series (50 µg dose) to prevent COVID-19 illness in individuals 6 to 11 years of age under an EUA [O'Shaughnessy, J. A. 2022].

Previous studies have demonstrated that the concomitant use of the 9vHPV vaccine with other vaccines (ie, meningococcal, poliomyelitis, diphtheria, tetanus, and pertussis) routinely administered in this age group was well tolerated and did not interfere with antibody responses to any of the vaccines concomitantly administered [Kosalaraksa, P., et al 2015] [Schilling, A., et al 2015]. Concomitant administration of vaccines in this age group may help minimize the number of vaccination visits required and improve implementation of vaccination programs; however, there are no data available for mRNA COVID-19 vaccines coadministered with other vaccines. A study designed to rigorously assess the safety and

immunogenicity of coadministration of the first doses of a 2-dose 9vHPV vaccine and a 2-dose mRNA-1273 vaccine is needed.

There are currently limited data available for SARS-CoV-2 vaccines coadministered with other vaccines in adult populations [Lazarus, R., et al 2021], but to date, no coadministration data for an mRNA COVID-19 vaccine has been generated in pediatric populations. The ACIP has not recommended against coadministration of mRNA COVID-19 vaccines with other routine vaccinations but noted the lack of current data and called for studies to generate safety and immunogenicity data on coadministration [Wallace, M., et al 2021].

The current study will evaluate the safety and immunogenicity of 2-dose regimens of 9vHPV and mRNA-1273 vaccines where the first dose of each vaccine are administered concomitantly in boys and girls 9 to 11 years of age, compared with nonconcomitant administration of the 2 vaccines.

2.2 Background

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

Refer to the approved labeling and EUA prescribing information for detailed background information on mRNA-1273 vaccine.

2.2.1 Pharmaceutical and Therapeutic Background

The 9vHPV vaccine is an aluminum-adjuvanted recombinant protein vaccine prepared from the highly purified 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 disease caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The mRNA-1273 vaccine is based on a platform of nucleoside-modified mRNA encoding the pre-fusion stabilized spike glycoprotein of SARS-CoV-2 virus. The mRNA-1273 vaccine is indicated for active immunization as a primary series to prevent COVID-19 illness caused by SARS-CoV-2 in individuals 18 years of age and older. The mRNA-1273 vaccine was also authorized for use under an EUA as a first booster dose in individuals 18 years of age and older who have completed primary COVID-19 vaccination and as a second booster dose in individuals 50 years of age and older and adults 18 years of age and older with certain immunocompromising conditions. The mRNA-1273 vaccine (50 μg dose) is authorized for use for active immunization as a primary series to prevent COVID-19 illness in individuals 6 to 11 years of age under an EUA [O'Shaughnessy, J. A. 2022].

2.2.2 Preclinical and Clinical Studies

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

Refer to the approved labeling, the EUA, and the clinical study (mRNA-1273-P204; NCT04796896) in boys and girls 6 to 11 years of age for clinical study experience with the mRNA-1273 vaccine [Moderna, Inc. 2021] [O'Shaughnessy, J. A. 2022].

2.3 Benefit/Risk Assessment

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

A 2-dose schedule with a 6- to 12-month interval between doses is approved for HPV vaccines and recommended in many countries for individuals 9 to 14 years of age [World Health Organization 2017] [Meites, E., et al 2016]. This study is designed to enroll individuals before they age out of the recommended target population for 2-dose schedules and to enable completion of a 2-dose vaccine series before increased risk of exposure to HPV. In this study, all participants will receive 2 doses of the 9vHPV vaccine 6 months apart.

The 9vHPV vaccine has been shown to be efficacious in preventing persistent anogenital HPV infection and disease associated with 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 to risk analysis for the 9vHPV vaccine in the study population.

All participants will also receive a 2-dose regimen of mRNA-1273 vaccine. The frequency, severity, and magnitude of AEs identified in a previous clinical study support a favorable benefit to risk analysis for the mRNA-1273 vaccine in all studied populations. The mRNA-1273 vaccine has been shown to be efficacious in preventing COVID-19 illness in adolescents and adults. In the setting of an ongoing pandemic with increasing numbers of adults completing COVID-19 vaccination, preadolescents and young adolescents specifically represent a growing proportion of new COVID-19 cases reported to the US CDC and have been shown to contribute to household transmission [Lessler, J., et al 2021]. Individuals <18 years of age are estimated to account for approximately 20% of COVID-19 cases in all regions of the US, with growing recognition that primary vaccination series in this population will increasingly include preadolescents and young adolescents who were previously infected [Cull, B. 2022]. In the setting of continued SARS-CoV-2 pandemic transmission, a population seronegative for SARS-CoV-2 may be challenging to recruit and enroll.

Though there are currently no published data on evidence of immunogenicity and safety of SARS-CoV-2 vaccination in pediatric individuals with prior SARS-CoV-2 infection, current CDC guidance recommends vaccination after recovery from acute illness in individuals >6 months old and continues to recommend coadministration with other vaccines without respect to prior SARS-CoV-2 infection status [Centers for Disease Control and Prevention 2022].

Approximately 50% of participants will receive the first dose of mRNA-1273 vaccine concomitantly with 9vHPV vaccine.

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

The following objectives and endpoints will be evaluated in boys and girls 9 to 11 years of age.

Primary Objective	**Primary Endpoint**
• **Objective 1:** To evaluate the GMTs of antibodies to each of the 9vHPV vaccine types at 4 weeks Postdose 2 of a 2-dose regimen of 9vHPV vaccine, when the first dose of a 2-dose regimen of 9vHPV vaccine is administered concomitantly or nonconcomitantly with a first dose of a 2-dose regimen of mRNA-1273 vaccine.	• Serum antibody titers at 4 weeks Postdose 2 of 9vHPV vaccine measured by cLIA to each of the 9vHPV vaccine types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58)
• **Objective 2:** To evaluate the GMCs of SARS-CoV-2 spike protein-specific binding antibody at 4 weeks Postdose 2 of a 2-dose regimen of mRNA-1273 vaccine, when the first dose of a 2-dose regimen of mRNA-1273 vaccine is administered concomitantly or nonconcomitantly with a first dose of a 2-dose regimen of 9vHPV vaccine.	• Serum antibody concentrations at 4 weeks Postdose 2 of mRNA-1273 vaccine measured by ECL assay specific to the SARS-CoV-2 spike protein
• **Objective 3:** To evaluate the safety and tolerability of 2-dose regimens of 9vHPV and mRNA-1273 vaccines where the first dose of each vaccine is administered concomitantly.	• Solicited injection-site AEs • Solicited systemic AEs • SAEs • Vaccine-related SAEs
Secondary Objectives	**Secondary Endpoints**
• **Objective:** For each of the Concomitant and Nonconcomitant Groups, to estimate percent seroconversion to each of the 9vHPV vaccine types at 4 weeks Postdose 2 induced by a 2-dose regimen of 9vHPV vaccine.	• Serum antibody titers at 4 weeks Postdose 2 of 9vHPV vaccine measured by cLIA to each of the 9vHPV vaccine types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58)

• **Objective:** For each of the Concomitant and Nonconcomitant Groups, to estimate percent seroresponse at 4 weeks Postdose 2 induced by a 2-dose regimen of mRNA-1273 vaccine.	• Serum antibody concentrations at 4 weeks Postdose 2 of mRNA-1273 vaccine measured by ECL assay specific to the SARS-CoV-2 spike protein

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, open-label, multicenter study to evaluate the safety and immunogenicity of a 2-dose regimen of 9vHPV vaccine, where the first dose is administered concomitantly with a first dose of a 2-dose regimen of mRNA-1273 vaccine versus nonconcomitant administration of 9vHPV and mRNA-1273 vaccines in boys and girls 9 to 11 years of age. Approximately 160 participants will be randomly assigned in a 1:1 ratio to 1 of the following groups:

Concomitant Group: Participants will receive their first dose of 9vHPV vaccine and first dose of mRNA-1273 vaccine on Day 1; they will then receive their second dose of mRNA-1273 vaccine at Month 1 and their second dose of 9vHPV vaccine at Month 6.

Nonconcomitant Group: Participants will receive their first and second doses of mRNA-1273 vaccine on Day 1 and at Month 1, respectively; they will then receive their first and second doses of 9vHPV vaccine at Months 2 and 8, respectively.

Blood samples for immunogenicity assays will be collected prior to the first dose of each vaccine and 4 weeks Postdose 2 of each vaccine.

After completion of immunogenicity testing to evaluate the study objectives, all leftover serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. For study participants who provided consent for future biomedical research, leftover sera from the study will be deidentified and may be used for other purposes such as the development and/or validation of HPV assays or biomarker development after completion of all study-related immunogenicity testing (Section 8.9).

Participants will be followed for local and systemic AEs from Day 1 through Day 28 following each vaccination (see Section 8.4.1). Information for all AEs resulting in discontinuation from study, MAAEs (see Section 10.3.1), and SAEs, regardless of whether the events are considered to be vaccine-related by the investigator, will be collected from the time consent is signed through completion of participation in the study (see Section 8.4.1).

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 was originally designed to have a target enrollment of 400 boys and girls for sufficient power to test hypotheses to demonstrate noninferior immunogenicity of 9vHPV vaccine and mRNA-1273 in the Concomitant Group versus the Nonconcomitant Group. In the setting of the evolving COVID-19 pandemic setting, enrollment has been slower than anticipated. Additionally, the mRNA-1273 vaccine clinical supply will not be available after 1Q2023 to support further enrollment. Therefore, enrollment will conclude in 1Q2023, with expected enrollment of approximately 160 boys and girls 9 to 11 years of age. Participants

will be randomized in an open-label manner to receive 2 preventative vaccinations: 9vHPV and mRNA-1273 vaccines. The study design will allow evaluation of safety and immunogenicity when the first dose of these 2 vaccines are administered concomitantly compared with nonconcomitant administration of the 2 vaccines. The 2-dose series for 9vHPV vaccine is licensed in this age group to be administered 6 to 12 months apart. The 2-dose series for the mRNA-1273 vaccine is administered 28 days apart. As the timing of the 2-dose series differs between the 2 vaccines, this study will generate data to inform coadministration of the first dose of each vaccine. Overall, this design is similar to that used in previous coadministration studies (NCT00988884, NCT01073293) of the 9vHPV vaccine, including coadministration with meningococcal, poliomyelitis, diphtheria, tetanus, and pertussis vaccines [Kosalaraksa, P., et al 2015] [Schilling, A., et al 2015].

Efficacy of the 9vHPV vaccine was demonstrated in a clinical study in young women 16 to 26 years of age who received 3 doses of vaccine [Joura, E. A., et al 2015] [Huh, W . K., et al 2017] [Giuliano, A. R., et al 2019]. Clinical efficacy of HPV vaccines cannot be directly assessed in young adolescents because of limited exposure to HPV. Therefore, efficacy results in young women were extrapolated to pre- and young adolescents receiving a 3-dose regimen based on immunogenicity bridging [Van Damme, P., et al 2015]. The licensure and recommendation of 2-dose regimens of 9vHPV vaccine was based on the demonstration of noninferior immunogenicity at 1 month after the last dose in girls and boys 9 to 14 years of age who received 2 doses compared with young women 16 to 26 years of age who received 3 doses [Iversen, O. E. 2016]. Because the incidence of HPV infection has been demonstrated to peak soon after onset of sexual activity, and HPV prevalence has been highly correlated with the number of recent and lifetime genital sex partners, young adolescents are an appropriate group in which to implement HPV vaccination [Kjaer, S. K., et al 2001] [Malagon, T., et al 2019].

Efficacy of the mRNA-1273 vaccine was demonstrated in a clinical study in participants ≥18 years of age who received 2 doses administered 28 days apart [Baden, L. R., et al 2021]. A subsequent study in boys and girls 6 to 11 years of age demonstrated strong immune response compared with the young adult vaccine recipients[Moderna, Inc. 2021]. In the setting of a global pandemic, preadolescents and young adolescents are an appropriate group in which to implement COVID-19 vaccination as widespread vaccination is a critical tool during pandemic conditions. Continued COVID-19 vaccination programs, including these age groups, will likely continue to be important after transition from pandemic to endemic conditions for SARS-CoV-2.

Given that the 9vHPV vaccine is currently recommended in individuals 9 to 14 years of age [Meites, E., et al 2016], and that an mRNA COVID-19 vaccine currently has EUA for individuals 6 to 11 years of age, concomitant administration of these vaccines in the study population may help facilitate implementation of vaccine recommendations. The development of a combined immunization strategy may lead to better compliance for each of these vaccines, which is critical in the setting of an ongoing pandemic, and specifically to the goal of maintenance of routine vaccination for preventable diseases in a prolonged COVID-19 pandemic setting. In the context of the ongoing COVID-19 pandemic, participants in the Nonconcomitant Group will receive the mRNA-1273 vaccine first before initiation of the 9vHPV vaccine.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

Humoral immune responses to 9vHPV vaccination will be evaluated based on the previously established cLIA [Roberts, C., et al 2014]. Serum may also be tested using the HPV9 IgG LIA [Opalka, D., et al 2010]. These assays are consistent with those in the previous studies that supported the licensure of the 9vHPV vaccine.

Immune responses to mRNA-1273 vaccine will be measured by ECL assay specific to the SARS-CoV-2 spike protein, consistent with those in the Phase 3 studies evaluating the mRNA-1273 vaccine.

Details on the immunogenicity assessments and endpoints evaluated in this study can be found in Section 8.2 and Section 9.4.1, respectively.

4.2.1.2 Safety Endpoints

Detailed safety information will be collected for all participants on an eVRC, with time points optimized based on the expected timing of local and systemic reactions to vaccination (see Section 8.4.9). The eVRC used to record AEs during the postvaccination periods, as defined in Section 8.3.3, is structured as recommended in the final US FDA Patient-Reported Outcome Guidance [U.S. Food and Drug Administration 2009].

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

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

4.2.1.3 Pharmacokinetic Endpoints

No pharmacokinetic endpoints will be evaluated in this study.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints will be evaluated in this study.

4.2.1.5 Planned Exploratory Biomarker Research

Exploratory biomarker research is not planned for this study.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent/assent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

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/assented 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 that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator

This is an open-label study, and all participants will receive a 2-dose regimen of 9vHPV vaccine and a 2-dose regimen of mRNA-1273 vaccine. As the main objective of the study is to compare the safety and immunogenicity in participants who receive the first dose of the 2 vaccines concomitantly versus participants who receive the 2 vaccines nonconcomitantly, no comparator vaccine or placebo is required as part of the study design.

4.3 Justification for Dose

The 9vHPV vaccine administered as a 2-dose regimen in the study population is consistent with the approved dosing and product labeling of GARDASIL®9 (US, EU, and other countries).

The mRNA-1273 vaccine administered as a 2-dose regimen in the study population is consistent with the dosing regimen in the mRNA-1273-P204 (NCT04796896) study conducted in participants 6 to 11 years of age.

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/assent. The overall study ends when the last participant completes the last study-related contact, withdraws consent/assent, 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.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

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.

In the event that ≥2 participants experience myocarditis and/or pericarditis per the CDC case definition (Section 10.3.1), all further doses of mRNA-1273 vaccine for participants enrolled in the study must be discontinued, and the Sponsor will stop study enrollment. For participants already enrolled, dosing with 9vHPV vaccine as well as all laboratory and safety procedures and assessments may continue.

5 STUDY POPULATION

Healthy male and female participants between the ages of 9 and 11 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Is a healthy individual who meets all inclusion criteria and none of the exclusion criteria defined in this section.

Demographics

2. Is male or female, from 9 years to 11 years of age inclusive, at the time of signing the informed consent/assent.

3. Has not yet had coitarche and does not plan on becoming sexually active during the vaccination period.

Informed Consent/Assent

4. Participant or participant's legally acceptable representative understands the study procedures, alternate treatments available, and risks involved with the study and voluntarily agrees to participate by providing documented informed consent. As appropriate based on local guidelines, the participant will also provide documented informed assent for the study. The participant or the participant's legally acceptable representative may also provide assent/consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

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

6. Participant or participant's legally acceptable representative can read, understand, and complete the eVRC.

5.2 Exclusion Criteria

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

Medical Conditions

1. *Has a fever (defined as oral temperature ≥100.0° F or ≥37.8° C) within the 24-hour period prior to the Day 1 visit.

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

3. Is allergic to any component of the 9vHPV or mRNA-1273 vaccine, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from 9vHPV vaccine and other vaccines]). For this exclusion criterion, an allergy to vaccine components is defined as an allergic reaction that met the criteria for severe AEs or SAEs defined in Appendix 3.

4. Has a condition that is a contraindication to vaccination as indicated in the package insert of 9vHPV vaccine or EUA prescribing information of mRNA-1273 vaccine.

5. Has known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

6. Is currently immunocompromised or has been diagnosed as having congenital or acquired immunodeficiency, HIV infection, lymphoma, leukemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, or other autoimmune condition.

7. Has a history of splenectomy.

8. Has a history of myocarditis and/or pericarditis.

9. Is, at the time of signing informed consent/assent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence at the discretion of the investigator. Alcohol abusers are defined as those who drink despite recurrent social, interpersonal, and/or legal problems because of alcohol use.

10. Has a history of a positive test for HPV.

11. Has a history of a clinical or microbiological diagnosis of COVID-19, ≤90 days prior to Day 1 visit or history of MIS-C at any time prior to Day 1 visit.

12. (Female participants only) Is pregnant as determined by a serum pregnancy test or urine pregnancy test that is sensitive to at least 25 mIU/mL β-hCG.

13. Has a history or current evidence of any condition, therapy, laboratory 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 judgment of investigator.

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

Prior/Concomitant Therapy

14. Has received within 12 months prior to enrollment, is receiving, or plans to receive during the study, the following immunosuppressive therapies: radiation therapy, cyclophosphamide, azathioprine, methotrexate, any chemotherapy, cyclosporin, leflunomide (Arava™), TNF-α antagonists, monoclonal antibody therapies (including rituximab [Rituxan™]), IVIG, antilymphocyte sera, or other therapy known to interfere with the immune response. Regarding systemic corticosteroids, a participant will be excluded if he/she is currently receiving steroid therapy, has recently (defined as within 2 weeks of Day 1 vaccination) received such therapy, or has received 2 or more courses of corticosteroids 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.

15. Has received within the 3 months prior to the Day 1 vaccination, is receiving, or plans to receive during the study, any immune globulin product (including RhoGAM™ [Ortho-Clinical Diagnostics]) or blood-derived product.

16. *Has received inactivated or recombinant vaccines within 14 days prior to Day 1 vaccination or receipt of live vaccines within 21 days prior to Day 1 vaccination (Note: If there is local requirement for the longer period between receipt of live vaccines and study vaccine, then it should follow local regulatory requirement.)

Prior/Concurrent Clinical Study Experience

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

18. Has previously received a marketed or investigational HPV vaccine.

19. Has previously received a marketed or investigational COVID-19 vaccine.

20. Has participated in a clinical study for any HPV vaccine or any COVID-19 vaccine (receiving either active agent or placebo).

Diagnostic Assessments

None.

Other Exclusions

21. 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.

22. 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.

* For items denoted with an asterisk, if the exclusion criterion is met, then the Day 1 visit may be rescheduled for a time when the criterion is not met.

5.3 Lifestyle Considerations

There are no lifestyle restrictions for participants in this study.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently enrolled 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.

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 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 Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Concomitant Group	Experi-mental	mRNA-1273 vaccine	Biological/ Vaccine	Suspension	mRNA* 50 µg per dose	0.25 mL per dose	IM	Single dose at Day 1 and Month 1	Test Product	IMP	Central or local
Concomitant Group	Experi-mental	9vHPV vaccine	Biological/ Vaccine	Suspension	HPV6/11/16/18/ 31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/ 20/20/20 mcg per dose	0.5 mL per dose	IM	Single dose at Day 1 and Month 6	Test Product	IMP	Central
Nonconcomitant Group	Experi-mental	mRNA-1273 vaccine	Biological/ Vaccine	Suspension	mRNA* 50 µg per dose	0.25 mL per dose	IM	Single dose at Day 1 and Month 1	Test Product	IMP	Central or local
Nonconcomitant Group	Experi-mental	9vHPV vaccine	Biological/ Vaccine	Suspension	HPV6/11/16/18/ 31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/ 20/20/20 mcg per dose	0.5 mL per dose	IM	Single dose at Month 2 and Month 8	Test Product	IMP	Central

HPV=human papillomavirus; IM=intramuscular; IMP=Investigational Medicinal Product; mL=milliliter; mRNA=messenger ribonucleic acid; NIMP/AxMP=noninvestigational/auxiliary medicinal product; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

The classification of IMP and NIMP/AxMP 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 and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

* mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 virus (Moderna Inc., Cambridge, MA)

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 Medical Devices

Drug-device combination product(s), which is/are legally marketed and provided for use in this study are: GARDASIL®9 syringes. Refer to Section 8.4.8 and Appendix 4 for reporting events associated with these devices.

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.

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 allocation/randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to the Concomitant Group and Nonconcomitant Group, respectively.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

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

Listed below are specific restrictions for concomitant therapy or vaccination:

- See the exclusion criteria for specific restrictions for prior and concomitant medications at Day 1 (Section 5.2).

- If possible, participants should not receive "special medications" (eg, corticosteroids, immunosuppressives, immune globulins, and blood products) from Day 1 through 1 month after the completion of vaccination regimen, nonstudy inactivated or recombinant vaccines from 14 days prior to each study vaccination through 14 days after each study vaccination, or nonstudy live vaccines from 21 days prior to each study vaccination through 14 days after each study vaccination.

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

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

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

No dose modification is allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

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 still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

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 8.11.3.

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.

- **For mRNA-1273 vaccine only:** The participant experiences 1 or more of the following AEs assessed as clearly related to the mRNA-1273 vaccine after receiving the first dose: multisystem inflammatory syndrome in children, myocarditis, pericarditis, anaphylaxis, or generalized urticaria. In this case, the second dose of the mRNA-1273 vaccine must be discontinued.

    - **Note:** In addition to the stopping rule above, in the event that ≥2 participants experience myocarditis and/or pericarditis per the CDC case definition (Section 10.3.1), then all further doses of mRNA-1273 vaccine for participants enrolled in the study must be discontinued (Section 4.4.1).

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places 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 8.11.3 for those procedures to be completed at each specified visit.

Discontinuation from mRNA-1273 vaccine or 9vHPV vaccine is "permanent." Once a participant is discontinued from a study intervention, they shall not be allowed to restart the same study intervention; however, the participant may be administered the other study intervention as scheduled.

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/assent 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/assent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

- The maximum amount of blood collected from each participant over the duration of the study will not exceed 30.5 mL (Table 2 for Concomitant Group and Table 3 for Nonconcomitant Group).

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

Table 2 Approximate Blood Volumes Drawn by Study Visit and by Sample Types – Concomitant Group

Study Visit	**Visit 1 (Day 1)**	**Visit 2 (Month 1)**	**Visit 3 (Month 2)**	**Visit 4a (Month 6)**	**Visit 5a (Month 7)**
Parameter	**Approximate Blood Volume (mL)**				
Anti-HPV Immunogenicity Testing	6 mL	NA	NA	NA	6 mL
SARS-CoV-2 Spike Protein-specific Binding Antibody	5 mL	NA	5 mL	NA	NA
Blood (DNA) for FBR[a]	8.5 mL	NA	NA	NA	NA

DNA=deoxyribonucleic acid; FBR=Future Biomedical Research; HPV=human papillomavirus; mL=milliliter; NA=not applicable; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

[a] Sample should be obtained before vaccine is administered on Day 1 or at a later date as soon as informed consent for future biomedical research is obtained.

Table 3 Approximate Blood Volumes Drawn by Study Visit and by Sample Types – Nonconcomitant Group

Study Visit	**Visit 1 (Day 1)**	**Visit 2 (Month 1)**	**Visit 3 (Month 2)**	**Visit 4b (Month 8)**	**Visit 5b (Month 9)**
Parameter	**Approximate Blood Volume (mL)**				
Anti-HPV Immunogenicity Testing	NA	NA	6 mL	NA	6 mL
SARS-CoV-2 Spike Protein-specific Binding Antibody	5 mL	NA	5 mL	NA	NA
Blood (DNA) for FBR[a]	8.5 mL	NA	NA	NA	NA

DNA=deoxyribonucleic acid; FBR=Future Biomedical Research; HPV=human papillomavirus; mL=milliliter; NA=not applicable; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

[a] Sample should be obtained before vaccine is administered on Day 1 or at a later date as soon as informed consent for future biomedical research is obtained.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent/assent 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/assent is in place.

8.1.1.1 General Informed Consent/Assent

Informed consent/assent given by the participant or their legally acceptable representative must be documented on a consent/assent 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/assent discussion.

A copy of the signed and dated informed consent/assent 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/assent form or addendum to the original consent/assent 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/assent form.

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

8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent/assent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent/assent before performing any procedure related to FBR. A copy of the informed consent/assent 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/assent. 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 or qualified designee.

At the Day 1 visit, the participant's medical history for the year prior to Day 1 and any other medically relevant history in the opinion of the investigator, including history of HPV-related and COVID-related diagnoses, will be obtained by the investigator or qualified designee.

8.1.5 Demographics

Demographics will be collected in the data collection system, as discussed in the eCRF entry guidelines.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

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

- Any analgesic or antipyretic medication taken on the day of vaccination prior to vaccination.

- "Special medications" (corticosteroids, immunosuppressive therapies as defined in the exclusion criteria, immune globulins, and blood-derived products) from 3 days prior to Day 1 through 1 month after completion of the vaccination regimen.

- "Other medications" from 3 days prior to each study vaccination through 14 days after each study vaccination.

- "Nonstudy inactivated or recombinant vaccines" from 14 days prior to each study vaccination through 14 days after each study vaccination.

- "Nonstudy live vaccines" from 21 days prior to each study vaccination through 14 days after each study vaccination.

8.1.6.2 Concomitant Medications

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

For a specific case where a participant mistakenly receives any nonstudy HPV or COVID-19 vaccine, the nonstudy HPV or COVID-19 vaccine must be reported in the eCRF, regardless of when the nonstudy HPV or COVID-19 vaccine was received.

Any analgesic or antipyretic medication will be recorded on the eVRC (see Section 8.3.3) and appropriate eVRC.

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

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.8 Assignment of Treatment/Randomization Number

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

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

8.1.9 Study Intervention Administration

Study vaccines should be prepared and administered by appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance.

Adequate treatment provisions should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

Preparation of Study Vaccine by Study Personnel

9vHPV Vaccine

The 9vHPV vaccine must be stored at 2.0°C to 8.0°C (35.6°F to 46.4°F). 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. Administer the entire dose as an intramuscular injection.

mRNA-1273 Vaccine

The mRNA-1273 multiple-dose vials contain a frozen suspension that does not contain a preservative and are stored at -50°C to -15°C (-58°F to 5°F). It must be thawed prior to administration. Remove the required number of vial(s) from storage and thaw each vial before use following the instructions below.

If provided as a 5.5 mL vial: Thaw in refrigerated conditions between 2° to 8°C for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering. Alternatively, thaw at room temperature between 15° to 25°C for 1 hour.

If provided as a 7.5 mL vial: Thaw in refrigerated conditions between 2° to 8°C for 3 hours. Let each vial stand at room temperature for 15 minutes before administering. Alternatively, thaw at room temperature between 15° to 25°C for 1 hour and 30 minutes.

After thawing, do not refreeze. Swirl vial gently after thawing and between each withdrawal. Do not shake. Do not dilute the vaccine. The mRNA-1273 is a white to off-white suspension. It may contain white or translucent product-related particulates. Visually inspect the vial for other particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Record the date and time of first use on the vial label. The maximum number of doses that may be extracted from either vial presentation should not exceed 20 doses. Do not puncture the vial stopper more than 20 times. If the vial stopper has been punctured 20 times, discard the vial and contents. Discard vial after 12 hours. Do not refreeze.

Study Vaccine Administration

Study vaccine will be administered as specified in Section 1.3. At each vaccination visit, participants will receive a single dose of 9vHPV vaccine (0.5 mL) and/or mRNA-1273 vaccine (0.25 mL) as an intramuscular injection. For all participants (Concomitant and Nonconcomitant Groups), the 9vHPV vaccine should be administered in the deltoid muscle of the left arm and the mRNA-1273 vaccine should be administered in the deltoid muscle of the right arm. The deltoid muscle of the assigned arm is the preferred site of vaccination. Injections should not be given within 2 cm of a tattoo, scar, or skin deformation. If the assigned deltoid does not meet criteria for injection, then the vaccination intended for that deltoid should be administered in the ipsilateral thigh. 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 using prefilled syringe for 9vHPV vaccine or a 1.0 mL syringe for mRNA-1273 vaccine 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)

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, time of vaccination, and the arms the vaccines are administered, must be recorded on the appropriate eCRF as per the data entry guidelines.

8.1.9.1 Timing of Dose Administration

The first dose of study vaccine will be administered at Day 1, which should be the day of enrollment. Subsequent doses will be administered as specified in Section 1.3.

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 the 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 and rescreened.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the vaccination regimen should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who discontinue either study vaccine may receive the other study vaccine.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the review of safety data 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/assent for FBR. Participants may withdraw consent/assent 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/assent 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

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

8.1.12 Calibration of Equipment

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

8.2 Immunogenicity Assessments

8.2.1 SARS-CoV-2 Spike Protein-specific Binding Antibody Measured by ECL Assay

PPD VSD in Richmond, VA, has developed and validated an ECL Method for the Detection of SARS-CoV-2 Spike, Nucleocapsid, and Receptor Binding Domain antibodies in human serum. The assay is based on the Meso-Scale Discovery technology, which employs disposable multispot microtiter plates. The validation study established the assay operating characteristics, evaluated the precision and ruggedness, and assessed the dilutional linearity, selectivity, and relative accuracy of the SARS-CoV-2 antigens. The SARS-CoV-2 ECL assay met the prespecified acceptance criteria and is considered validated with regard to precision, ruggedness, relative accuracy, dilutional linearity, specificity, and selectivity.

8.2.2 Antibody to 9vHPV Vaccine Types Measured by 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 [Roberts, C., et al 2014]. The purpose of the assay is to detect these HPV antibodies before and after vaccination with the 9vHPV vaccine. The testing will be performed by Q Squared Solutions (California, USA).

For the 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 compete with an individual's serum antibodies for binding to the neutralizing epitopes of the VLPs. The fluorescent signal from the R-Phycoerythrin-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 9 HPV vaccine types. A standard curve for each HPV vaccine type is calculated using a weighted 4 parameter logistic curve fit. Results are expressed as mMU/mL.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard on Day 1 to determine whether the participant meets eligibility criteria for enrollment.

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

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

8.3.2 Oral Temperature Measurement

Oral temperature will be assessed at each vaccination visit prior to the administration of study vaccine. If the participant has a fever (defined as an oral temperature of ≥100.0° F or ≥37.8° C) within the 24-hour period prior to receiving a study vaccination, the participant should not receive the study vaccine, and the vaccination visit should be rescheduled until after the fever has resolved.

Postvaccination, if an oral temperature indicates a fever (defined as an oral temperature of ≥37.8° C or ≥100.0° F), then an AE of "fever" must be documented in the eCRF.

8.3.3 Electronic Vaccination Report Card

The eVRC was developed to be administered electronically via a hand-held device. This item was structured as recommended in the final Food and Drug Administration Patient-Reported

Outcome Guidance [U.S. Food and Drug Administration 2009]. Participants will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC. The investigator or delegate will train the participant in the use of the eVRC at Visit 1 (Day 1). The investigator or delegate will review the data captured on the eVRC with the participant at specific visits as described in Section 1.3.

Temperatures, injection-site reactions, solicited complaints, other complaints or illnesses, and concomitant medications or vaccinations will be recorded on the eVRC by the participant. All participants will be expected to bring the eVRC to the study site at specific visits as described in Section 1.3. Participants should be informed to contact the investigator immediately in the event of a hospitalization or visit to another physician.

The participant/participant's legally acceptable representative will use the eVRC to document the following information:

- Oral body temperatures measured Day 1 (day of vaccination) through Day 7 postvaccination
- Left arm (postvaccination with 9vHPV vaccine): Solicited injection-site AEs (Section 8.4.9.1) Day 1 through Day 7 postvaccination
- Right arm (postvaccination with mRNA-1273 vaccine): Solicited injection-site AEs (Section 8.4.9.1) Day 1 through Day 7 postvaccination
- Solicited systemic AEs (Section 8.4.9.1) Day 1 through Day 7 postvaccination
- Any other injection-site or systemic AEs (Section 8.4.9.2) Day 1 through Day 28 postvaccination
- Concomitant medications (including analgesic or antipyretic medication) and nonstudy vaccinations Day 1 through Day 28 postvaccination

For the AEs outlined above, the investigator will use the information provided by the participant both on the eVRC, and verbally at the time of eVRC review, to apply the appropriate assessment of causality as described in Appendix 3.

8.3.4 Postvaccination Observation Period (30 Minutes)

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

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6 Pregnancy Testing

All female participants will have a serum or urine pregnancy test (sensitive to at least 25 mIU/mL β-hCG) performed at each vaccination visit as outlined in Section 1.3 per the manufacturer's instructions and based on local requirements. All materials used for serum and/or urine pregnancy testing will be provided by the study sites.

The pregnancy test results must be obtained prior to each study vaccination (on the day the participant is vaccinated). Any participant found to be pregnant at Day 1 will not be enrolled in the study. For randomized participants who become pregnant after receiving study vaccinations, study visits and vaccinations will be paused until resolution of the pregnancy (eg, term, elective termination, spontaneous abortion). For participants found to be pregnant before the second dose of mRNA-1273 vaccine, no further dosing with mRNA-1273 vaccine should be administered and participants should be asked to remain in the study for safety follow-up. Study visits and study vaccination with 9vHPV vaccine in pregnant participants will be handled as described in Table 4.

Table 4 Guidelines for Pregnant Participants: Managing Study Visits and Study Vaccinations for 9vHPV Vaccine

Time When Pregnancy is Detected	**Action**
Day 1 (before first vaccination)	Do not enroll.
Between First and Second Doses of 9vHPV Vaccine	• No scheduled visits until resolution of the pregnancy (eg, term, elective termination, spontaneous abortion). • The second dose of 9vHPV vaccine should be administered at least 4 weeks after resolution of pregnancy and after normalization of β-hCG levels. • A blood sample should be collected 4 weeks Postdose 2 of 9vHPV vaccine. Scheduling of subsequent blood draws will be managed on a case-by-case basis.
After Vaccination Visits	• Continue with scheduled study visits during the pregnancy. • Safety follow-up will be conducted after resolution of the pregnancy (eg, term, elective termination, spontaneous abortion).
β-hCG=β-human chorionic gonadotropin; HPV=human papillomavirus	

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

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

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

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

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

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

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

All AEs that occur from the time of allocation/randomization through 28 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 28 days thereafter, must be reported by the investigator. All MAAEs, SAEs, and other reportable safety events that occur from the time of allocation/randomization throughout the duration of the individual's participation in the study, must be reported by the investigator, regardless of whether the events are considered to be vaccine-related by the investigator.

In this study, myocarditis and pericarditis are always considered to be SAEs that meet the "Other important medical events" criteria detailed in Section 10.3.2 (the investigator should also assess whether other criteria might apply). Definitions of myocarditis and pericarditis are provided in Section 10.3.1.

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 5.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 5 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent/Assent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting 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

Type of Event	**Reporting Period: Consent/Assent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. – any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	There are no ECIs for this study.			
ECI (do not require regulatory reporting)	There are no ECIs for this study.			
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

ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, 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.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities 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.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

This is not applicable to this study.

8.4.7 Events of Clinical Interest

There are no ECIs for this study.

8.4.8 Medical Device and Drug–Device Combination Products – PQCs/Malfunctions

The method of documenting and reporting of such events (complaints associated with medical devices including PQCs/malfunctions) will occur as below and in Appendix 4.

To fulfill regulatory reporting obligations worldwide, medical device information associated with AEs will be collected and reported to the Sponsor in the same time frame as AEs per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines.

PQCs/malfunctions including those that involve a participant or any user/associated person must be reported to the Sponsor. Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities about certain safety information relating to medical devices and drug-device combination products being used in clinical studies.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality between the AE and the medical device or device constituent of combination product.

8.4.9 Adverse Events on the VRC

Participants will use an eVRC to report solicited and unsolicited AEs.

The definitions of solicited and unsolicited AEs can be found in Appendix 3.

8.4.9.1 Solicited Adverse Event

Solicited AEs for this study are summarized in Table 6.

Table 6 Solicited Adverse Events

Type of Solicited Adverse Event	Predefined Solicited Adverse Events (Preferred Term)	Solicited Time Period
Injection Site	**Left arm (postvaccination with 9vHPV vaccine)** • Injection-site pain/tenderness • Injection-site swelling • Injection-site redness (erythema) **Right arm (postvaccination with mRNA-1273 vaccine)** • Injection-site pain/tenderness • Injection-site swelling • Injection-site redness (erythema) • Underarm gland swelling or tenderness (lymphadenopathy)	Day 1 to Day 7 postvaccination
Systemic	• Headache • Fatigue • Muscle aches all over the body (myalgia) • Joint aches in several joints (arthralgia) • Nausea • Vomiting • Chills	Day 1 to Day 7 postvaccination

All solicited injection-site AEs will be considered related to study intervention.

In addition, the investigator will review all solicited AEs for the following:

- Is the event a symptom of another diagnosis?
- Is the event ongoing at the end of the solicited period?
- Does the event meet serious criteria?

A solicited AE that meets any of the above criteria must also be reported on the appropriate eCRF as specified in the data entry guidelines.

8.4.9.2 Unsolicited Adverse Events

Unsolicited AEs for this study are events that are 1) not predefined in Table 6, or 2) predefined in Table 6 but reported at any time outside the solicited time period.

As detailed in Section 8.4, the investigator will assess unsolicited AEs that meet the definition of an AE or SAE with respect to seriousness, intensity, and causality.

8.5 Treatment of Overdose

In this study, an overdose is defined as a participant receiving >1 dose of any individual study vaccine in a 24-hour period or >2 doses of any individual study vaccine throughout the study.

Sponsor does not recommend specific treatment for an overdose.

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

All reports of overdose must be reported by the investigator within 5 calendar days to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Future Biomedical Research Sample Collection

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

- DNA for future research
- Leftover main study serum from anti-HPV antibody testing stored for future research
- Leftover main study serum from SARS-CoV-2 spike protein-specific binding antibody testing stored for future research

8.10 Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening

The Screening Visit or the last Screening Visit (for rescreening) should be on the same day of enrollment and the first dose of vaccination. Potential participants will be evaluated to determine that they fulfill the entry requirements as provided in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

8.11.2 Intervention and Follow-up Periods

Requirements during the intervention and follow-up periods are outlined in Section 1.3.

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

Participants who discontinue study vaccination but continue in the study will attend study visits as provided in Section 1.3; however, serum will not be collected.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to final database lock, changes are made to primary 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 nonconfirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in an sSAP and referenced in the CSR for the study. Posthoc 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.

Study Design Overview	A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9vHPV and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age
Treatment Assignment	Study participants will be randomized in a 1:1 ratio between the Concomitant and Nonconcomitant Groups. No stratification will be implemented during randomization.
Analysis Populations	Immunogenicity: Per-protocol population Safety: APaT population
Primary Endpoint(s)	**Immunogenicity:** 1. cLIA anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers. 2. SARS-CoV-2 spike protein-specific binding antibody concentration. **Safety:** 1. Solicited injection-site AEs Day 1 through Day 7 postvaccination. 2. Solicited systemic AEs Day 1 through Day 7 postvaccination. 3. SAEs Day 1 through Day 28 postvaccination. 4. Vaccine-related SAEs observed any time during the study.
Key Secondary Endpoints	**Immunogenicity:** • Seroconversion to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 based on cLIA. • Seroresponse to SARS-CoV-2 based on SARS-CoV-2 ECL assay.
Statistical Methods for Key Immunogenicity Analyses	Evaluation of primary and secondary objectives will be performed separately for each immunogenicity parameter. Analysis of variance modeling will be used. The response variable is the natural logarithm of the relevant antibody titers and an indicator variable representing the concomitant vaccination group will be a fixed effect. Point estimates of the GMTs/GMC and corresponding within-group 95% CIs as well as geometric mean ratio and corresponding 95% CI of the geometric mean ratio will be derived from the estimate of the fixed effect.
Statistical Methods for Key Safety Analyses	By-treatment group summaries of safety endpoints will be provided in terms of treatment group-specific counts and proportions (or percent) of participants who are cases of particular safety endpoints. Confidence intervals of risk difference (difference in percent or proportions), when provided, will be calculated using the M&N method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	No interim analyses are planned for this study.
Multiplicity	No multiplicity adjustment will be required, as there is no formal hypothesis testing.
Sample Size and Power	The expected total sample size is approximately 160 participants. Participants are to be randomly assigned in a 1:1 ratio to the Concomitant Group and Nonconcomitant Group. **Immunogenicity:** This is an estimation study. There are no hypotheses to be evaluated. **Safety:** Section 9.9.2 provides information about the ability of this study to estimate the incidence of AEs within the Concomitant and Nonconcomitant Groups.

9.2 Responsibility for Analyses/In-house Blinding

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

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

The Clinical Biostatistics department will generate the randomized allocation schedule for study treatment assignment. The algorithm for the randomized allocation of subjects will be implemented in an interactive response technology by a study vendor.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. This is an estimation study, and no formal hypothesis testing will be performed.

9.4 Analysis Endpoints

Immunogenicity and safety endpoints that will be evaluated for between-treatment differences are listed below.

9.4.1 Immunogenicity Endpoints

Primary immunogenicity analysis endpoints include:

- GMTs of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 measured by cLIA at 4 weeks Postdose 2 of 9vHPV vaccine.

- GMCs of SARS-CoV-2 spike protein-specific binding antibodies at 4 weeks Postdose 2 of mRNA-1273 vaccine.

Secondary immunogenicity analysis endpoints include:

- Seroconversion to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks Postdose 2 of 9vHPV vaccine. Seroconversion is defined as changing from cLIA anti-HPV seronegative prevaccination with 9vHPV vaccine to seropositive at 4 weeks Postdose 2 of 9vHPV vaccine.

- Seroresponse to SARS-CoV-2 at 4 weeks Postdose 2 of mRNA-1273 vaccine. Seroresponse is defined as ≥4-fold rise in SARS-CoV-2 spike protein-specific binding antibody concentration from baseline to 4 weeks Postdose 2 of mRNA-1273 vaccine. If the baseline SARS-CoV-2 spike protein-specific binding antibody concentration is less than the LLOQ of the SARS-CoV-2 ECL assay, a ≥4-fold rise is defined as SARS-CoV-2 spike protein-specific binding antibody concentration ≥4 × LLOQ of the SARS-CoV-2 ECL assay.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs and body temperature measurements postvaccination.

The safety analysis endpoints that address the primary objective include:

- Solicited injection-site AEs Days 1 through 7 postvaccination
- Solicited systemic AEs Days 1 through 7 postvaccination
- SAEs Days 1 through 28 postvaccination
- Serious vaccine-related AEs observed any time during the study

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Population

The PPI population will serve as the primary population for the analysis of immunogenicity relating to 9vHPV vaccination. The PPI population is HPV type-specific. The PPI population consists of all randomized participants who:

1. Have received all vaccinations planned within the context of the study with the correct dose of the 9vHPV vaccine and each vaccination visit has occurred within day ranges acceptable for statistical analysis (see Table 7 for vaccination visits day ranges acceptable for statistical analysis).
2. Were seronegative by HPV-9 cLIA to the appropriate HPV type pre-9vHPV vaccination (see Table 8 for serum collection day ranges acceptable for statistical analysis).
3. Have evaluable serology results based on serum sample collected within 21 to 49 days Postdose 2 of 9vHPV vaccination.
4. Have no protocol deviations that could interfere with the evaluation of participant's immune response to 9vHPV vaccination.

The mRNA-1273 per-protocol (mRNA-1273-PP) population will serve as the primary population for the analysis of immunogenicity relating to mRNA-1273 vaccination. This population consists of all randomized participants who:

1. Have received all vaccinations planned within the context of the study with the correct dose of mRNA-1273 and each vaccination visit has occurred within day ranges acceptable for statistical analysis (see Table 7 for vaccination visits day ranges acceptable for statistical analysis).

2. Have evaluable serology results based on serum sample collected within 21 to 42 days Postdose 2 of mRNA-1273 vaccine.

3. Have no protocol deviations that could interfere with the evaluation of participant's immune response to mRNA-1273 vaccine.

Table 7 Acceptable Day Ranges for Vaccination Visits

Vaccination Dose	Vaccination Visit Window as Specified in the SoA (Relative to Vaccination Dose 1)	Day Range for Inclusion in Statistical Analysis (Relative to Vaccination Dose 1)
Dose 1		
9vHPV vaccine mRNA-1273	0 0	0 0
Dose 2		
9vHPV vaccine mRNA-1273	6 months ± 4 weeks 28 to 42 days	148 to 218 days 21 to 42 days
HPV=human papillomavirus; RNA=ribonucleic acid; SoA=schedule of activities		

Table 8 Acceptable Day Ranges for Collection of Serum Samples

Study Time	Target Collection Day	Day Range for Inclusion in Statistical Analysis
Predose 1 (target collection days and day ranges are relative to vaccination dose 1)		
9vHPV vaccine mRNA-1273	0 0	–14 to 0 –14 to 0
Postdose 2 (target collection day and day range are relative to vaccination dose 2)		
9vHPV vaccine mRNA-1273	28 days 28 days	21 to 49 days 21 to 42 days
HPV=human papillomavirus; RNA=ribonucleic acid; SoA=schedule of activities		

9.5.2 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 any study vaccine. Participants will be included in the treatment group corresponding to the study vaccine they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who received incorrect vaccination regimen for the entire vaccination period; such participants will be included in the treatment group corresponding to the vaccination regimen actually received.

9.6 Statistical Methods

9.6.1 Immunogenicity Analysis Methods

9.6.1.1 Estimation of Immune Response Relating to HPV

Anti-HPV titers reported as less than the HPV type-specific LLOQ will be replaced by a numeric value equal to half of the HPV type-specific LLOQ in analyses of immunogenicity.

For each of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58, the primary objective relating to response to HPV vaccination at 4 weeks Postdose 2 will be evaluated. Separately for each HPV type, the GMTs with 2-sided within-group 95% CIs and GMT ratio with corresponding 2-sided 95% CI will be calculated using an analysis of variance model with a response of log individual anti-HPV titers and a fixed effect for the vaccination groups (Table 9).

9.6.1.2 Estimation of Immune Response Relating to SARS-CoV-2

The primary objective relating to response to mRNA-1273 vaccination at 4 weeks Postdose 2 will be evaluated. The analysis methods are the same as those that will be used for primary objective 1 (see Section 9.6.1.1).

SARS-CoV-2 spike protein-specific binding antibody concentrations reported as less than the LLOQ of the ECL assay will be replaced by a numeric value equal to half of the LLOQ in analyses of immunogenicity.

9.6.1.3 Estimation of Percent Seroconversion and Percent Seroresponse

The seroconversion percentages with respect to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and seroresponse percentage with respect to SARS-CoV-2, will be evaluated by computing point estimates and corresponding 2-sided 95% CIs. Calculation of the CI will be based on the exact binomial method proposed by Clopper and Pearson [CLOPPER, C. J. and PEARSON, E. S. 1934] (Table 9).

Table 9 Strategy for Analysis of Immunogenicity Endpoints

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Immunogenicity Objectives and Hypotheses				
GMTs of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 measured by cLIA at 4 weeks Postdose 2 of 9vHPV vaccine	P	Point estimate, 95% CI by ANOVA	Per-protocol	Observed data only
GMCs of SARS-CoV-2 spike protein-specific binding antibodies at 4 weeks Postdose 2 of mRNA-1273 vaccine	P	Point estimate, 95% CI by ANOVA	Per-protocol	Observed data only
Secondary Immunogenicity Objectives				
Seroconversion to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks Postdose 2 of 9vHPV vaccine	P	Point estimate, 95% CI value by Clopper and Pearson	Per-protocol	Observed data only
Seroresponse to SARS-CoV-2 at 4 weeks Postdose 2 of mRNA-1273 vaccine	P	Point estimate, 95% CI value by Clopper and Pearson	Per-protocol	Observed data only
ANOVA=analysis of variance; CI=confidence interval; cLIA=competitive Luminex Immunoassay; GMC=geometric mean concentration; GMT=geometric mean titer; HPV=human papillomavirus; P=primary; RNA=ribonucleic acid; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2				

9.6.2 Safety Analysis Methods

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs and postvaccination body temperature measurements.

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed number of participants with an event.

Tier 1 Events

Safety parameters or AEs of special interest identified *a priori* that will be subject to inferential testing for statistical significance constitute "Tier 1" safety endpoints. There are no Tier 1 events for this protocol.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the M&N method [Miettinen, O. and Nurminen, M. 1985]. Membership in Tier 2 requires that at least 4 participants in any vaccination group exhibit the event. The threshold of at least 4 participants was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when vaccination groups of equal size each have less than 4 participants and thus would add little to the interpretation of potentially meaningful differences. The 95% CIs for Tier 2 events will be provided without adjustment for multiplicity, thus the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences with respect to the Tier 2 events.

In addition to individual events that occur in ≥4 participants in any vaccination group, the broad AE categories consisting of the proportion of participants with SAEs during Days 1 through 28 postvaccination, AEs of special interest (see Section 10.3.1), MAAEs, and vaccine-related SAEs reported any time during the study, and elevated temperatures (≥37.8°C or ≥100.0°F) will be considered Tier 2 endpoints. The proportion of participants with solicited injection-site AEs and solicited systemic AEs during Days 1 through 7 postvaccination, and severe injection-site AEs during Days 1 through 28 postvaccination will also be included in Tier 2 endpoints. Detailed endpoints and day ranges are summarized in Table 10.

The day ranges (Days 1 through 7 and Days 1 through 28) associated with some Tier 2 endpoints are consistent with those used in clinical studies of the mRNA-1273 vaccine.

Tier 3 Events

Safety endpoints that are not Tier 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 (ie, with no imputation of missing data).

The day ranges (Days 1 through 5 and Days 1 through 15) associated with some Tier 3 endpoints are consistent with those used in clinical studies of the 9vHPV vaccine. Summaries for these endpoints are planned to be provided for comparability with summaries in previous 9vHPV vaccine clinical studies.

Table 10 Strategy for Analysis of Safety Endpoints

Safety Tier	Safety Endpoint[a]	95% CI for Comparison of Concomitant and Nonconcomitant Groups	Descriptive Statistics
Tier 2	Solicited injection-site AEs, Days 1 through 7 postvaccination	X	X
	Severe injection-site AEs, Days 1 through 28 postvaccination	X	X
	Unsolicited injection-site AEs observed in ≥4 participants in either vaccination group, Days 1 through 28 postvaccination	X	X
	Solicited systemic AEs (headache, fatigue, myalgia, arthralgia, nausea, vomiting, and chills), Days 1 through 7 postvaccination	X	X
	Unsolicited systemic AEs observed in ≥4 participants in either vaccination group, Days 1 through 28 postvaccination	X	X
	Elevated temperatures[a], Days 1 through 7 postvaccination	X	X
	Serious AEs, Days 1 through 28 postvaccination	X	X
	Serious vaccine-related AEs reported any time during the study	X	X
	AEs of special interest reported any time during the study	X	X
	MAAEs reported any time during the study	X	X
Tier 3	Solicited injection-site AEs, Days 1 through 5 postvaccination		X
	Severe injection-site AEs, Days 1 through 15 post vaccination		X
	Unsolicited injection-site AEs observed in ≥4 participants in either vaccination group, Days 1 through 15 postvaccination		X
	Systemic (solicited or unsolicited) AEs observed in ≥4 participants in either vaccination group, Days 1 through 15 postvaccination		X
	Elevated temperatures[a], Days 1 through 5 postvaccination		X
	Serious AEs, Days 1 through 15 postvaccination		X
	AEs by SOC		X
	Maximum intensity rating for each category of injection-site AEs		X
	Maximum intensity rating, overall systemic AEs		X
	Maximum temperatures		X

AE=adverse event; CI=confidence interval; MAAE=medically attended adverse event; SOC=system organ class; X=indicating summary statistic will be provided

[a] Defined as maximum (over the follow-up period) temperature ≥37.8°C (≥100°F, oral equivalent).

9.7 Interim Analyses

No interim analyses are planned for this study.

9.8 Multiplicity

No multiplicity adjustment will be required, as there is no formal hypothesis testing.

9.9 Sample Size and Power Calculations

9.9.1 Immunogenicity

This is an estimation study. The study is expected to enroll approximately 160 participants (80 per group). The estimated half-widths of 2-sided 95% CIs for GM Ratios between the Concomitant versus Nonconcomitant Groups for each serotype range between 0.279 to 0.494 (Table 11), corresponding to a sample size of 80 per group. There is no corresponding power since no hypothesis will be tested.

Table 11 Half-widths of 2-sided 95% CIs for Geometric Mean Ratios by Serotype

Serotype	Expected Coefficient of Variation[a]	Expected Number of Participants Enrolled (per group)	Expected Exclusion from Per-Protocol Population[a]	Half-width of 95% CI for GM Ratio[b]
HPV 6	1.11	80	13%	0.300
HPV 11	1.16	80	13%	0.309
HPV 16	1.17	80	9%	0.304
HPV 18	1.35	80	9%	0.334
HPV 31	1.21	80	10%	0.313
HPV 33	1.20	80	9%	0.309
HPV 45	1.38	80	9%	0.338
HPV 52	1.03	80	9%	0.279
HPV 58	1.10	80	10%	0.293
SARS-CoV-2	2.91[c]	80	10%	0.494

CI=confidence interval; GM=geometric mean; HPV=human papillomavirus; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
[a] The HPV-specific expected values are based on data from study NCT01984697 (EudraCT: 2013-001314-15).
[b] The half-width of 95% CI for GM ratio is calculated at 1-sided Type I error α=0.025 under the assumption that the ratio of geometric means in the Concomitant and Nonconcomitant Groups is 1.0.
[c] The standard deviation of the SARS-CoV-2 spike protein-specific binding antibody concentrations in natural-logarithm scale was estimated as 1.5. The corresponding coefficient of variation of concentrations in the untransformed scale was calculated as square-root(exp[1.5*1.5] – 1).

9.9.2 Sample Size for Safety Analysis

The probability of observing at least 1 vaccine-related SAE depends on the number of participants vaccinated and the underlying incidence rate in the study population. In this study with 80 participants in each vaccination group, there is ≥0.90 probability of observing at least 1 vaccine-related SAE in a vaccination group if the incidence of a SAE is ≥2.84% (Table 12).

Table 12 Probability of Observing At Least 1 Vaccine-related Serious Adverse Event in a Group With 80 Participants

Incidence Rate	Probability of ≥1 Participant Out of 80 With Vaccine-related SAE
2.84% (1 of every 35 participants)	0.90
3.68% (1 of every 27 participants)	0.95
8.27% (1 of every 12 participants)	0.99
SAE=serious adverse event	

If no vaccine-related SAE is observed among the approximately 80 participants in a vaccination group, this study will provide 97.5% confidence that the underlying incidence rate of vaccine-related SAE in that vaccination group is ≤4.51% (10 of every 222 individuals).

9.10 Subgroup Analyses

There is no subgroup analysis planned to be conducted.

9.11 Compliance (Medication Adherence)

Compliance in this study is defined as receipt of 2 doses of 9vHPV vaccine and mRNA-1273 vaccine in the context of the study. To summarize compliance, the numbers of participants who receive each vaccination will be tabulated. For each vaccination dose, histograms of the time 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 study participants administered the 9vHPV vaccine and mRNA-1273 vaccine.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional 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 prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary,

authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

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

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

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, 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 his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

Not applicable.

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 trials 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.

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. 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

All female participants will have a serum or urine pregnancy test (sensitive to at least 25 mIU/mL β-hCG) performed at each vaccination visit.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the individual's participation in the study.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- Note: For purposes of AE definition, study intervention 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 8.4.6 for protocol-specific exceptions.

Definition of Solicited and Unsolicited AE

- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant in their VRC.

- An unsolicited AE is an AE that was not solicited using a VRC and that is communicated by a participant who has provided documented informed consent/assent. Unsolicited AEs include serious and nonserious AEs.

Definition of MAAE

- AEs in which medical attention is received during an unscheduled, nonroutine outpatient visit, such as an emergency room visit, office visit, or an urgent care visit with any medical personnel for any reason. Routine visits are not considered MAAEs. Examples of routine visits include physical examination, wellness visits, or vaccinations.

- Note: Determination of MAAEs is the responsibility of the investigator or a qualified designee. Once identified, MAAEs should be reported to the Sponsor per the timeline for NSAE/SAEs reporting.

Definition of AEs of Special Interest

- AEs of special interest (serious and nonserious AEs) for this study are scientific and medical concerns specific to the mRNA-1273 vaccine per regulatory requirements. The list of AEs of special interest is provided below.

Medical Concept	Additional Notes
Anosmia, ageusia	New onset COVID-associated or idiopathic events without other etiology excluding congenital etiologies or trauma.
Subacute thyroiditis	Including but not limited to events of atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis, and thyroiditis.
Acute pancreatitis	• Including but not limited to events of autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis. • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures).
Appendicitis	Include any event of appendicitis.
Rhabdomyolysis	New onset rhabdomyolysis without known etiology such as excessive exercise or trauma.
Acute respiratory distress syndrome	Including but not limited to new events of acute respiratory distress syndrome and respiratory failure.
Coagulation disorders	Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis.
Acute cardiovascular injury	Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction. In addition, investigators will be asked to report as a related AE of special interest if within 7 days of any mRNA-1273 vaccination, clinical signs/symptoms consistent with the CDC case definition of myocarditis and/or pericarditis (https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm#T1_down) [Gargano, J. W., et al 2021]. Participants who meet criteria for both myocarditis and pericarditis may be described under myopericarditis. **Myocarditis Case Definition** Presence of ≥1 new or worsening of the following clinical symptoms: • Chest pain/pressure/discomfort • Dyspnea/shortness of breath/pain with breathing • Palpitations • Syncope OR Presence of ≥2 of the following: • Irritability • Vomiting • Poor feeding • Tachypnea • Lethargy AND For PROBABLE CASE: ≥1 new finding of: • Troponin level above upper limit of normal (any type of troponin) • Abnormal electrocardiogram ECG or EKG or rhythm monitoring findings consistent with myocarditis • To meet the ECG or rhythm monitoring criterion, must include at least one of: o ST segment or T-wave abnormalities o Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias o AV nodal conduction delays or intraventricular conduction defects

Medical Concept	Additional Notes
	• Abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI finding consistent with myocarditis [Ferreira, V. M., et al 2018] • For CONFIRMED CASE: • Histopathologic confirmation of myocarditis (using Dallas criteria) [Aretz, H. T. 1987] OR • Troponin level above upper limit of normal (any type of troponin) AND cMRI findings consistent with myocarditis AND • No other identifiable cause of the symptoms and findings **Pericarditis Case Definition** Presence of ≥2 new or worsening of the following clinical features: • Acute chest pain • (Typically described as made worse by lying down, deep inspiration, or cough; and relieved by sitting up or leaning forward, although other types of chest pain may occur) • Pericardial rub on examination • New ST-elevation or PR-depression on EKG, or • New or worsening pericardial effusion on echocardiogram or MRI
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast agents, etc) • Include all cases that meet the following criteria: ○ Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; OR ○ Increase in serum creatinine to ≥1.5 × baseline, known or presumed to have occurred within prior 7 days; OR ○ Urine volume ≤0.5 mL/kg/hour for 6 hours.
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc) • Include all cases that meet the following criteria: ○ >3-fold elevation above the upper normal limit for ALT or AST OR ○ >2-fold elevation above the upper normal limit for total serum bilirubin or gamma glutamyl transferase or alkaline phosphatase.
Dermatologic findings	• Chilblain-like lesions; • Single organ cutaneous vasculitis; • Erythema multiforme; • Bullous rashes; • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia, and systemic symptoms, and fixed drug eruptions.

Medical Concept	Additional Notes
Multisystem inflammatory disorders	• MIS-C • Kawasaki's disease • HLH **MIS-C Case Definition** Investigators will be asked to report, as AE of special interest, clinical signs/symptoms consistent with the CDC case definition of MIS-C (https://emergency.cdc.gov/han/2020/han00432.asp): • An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND • No alternative plausible diagnoses; AND • Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms: o Fever ≥38.0°C/≥100.4ºF for ≥24 hours, or report of subjective fever lasting ≥24 hours o Including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes, and low albumin Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C. Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.
Thrombocytopenia	• Platelet counts <150 ×109 per mm3 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome.
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (eg, gout, osteoarthritis, and trauma).
New onset of or worsening of neurologic disease	• Including but not limited to o Guillain-Barre syndrome o Acute disseminated encephalomyelitis o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (hemorrhagic and nonhemorrhagic) o Narcolepsy

Medical Concept	Additional Notes
Anaphylaxis	Anaphylaxis is an acute hypersensitivity reaction with multiorgan system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Anaphylaxis is a clinical syndrome characterized by the following: • Sudden onset AND • Rapid progression of signs and symptoms AND • Involves 2 or more organ systems, as follows: ○ Skin/mucosal: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, and red and itchy eyes. ○ Cardiovascular: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, and evidence of reduced peripheral circulation. ○ Respiratory: bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, and rhinorrhea. ○ Gastrointestinal: diarrhea, abdominal pain, nausea, and vomiting.
Other syndromes	• Fibromyalgia • Postural orthostatic tachycardia syndrome • Chronic fatigue syndrome (includes myalgic encephalomyelitis and postviral fatigue syndrome) • Myasthenia gravis
AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AV=atrioventricular; CDC=Centers for Disease Control and Prevention; cMRI=cardiac magnetic resonance imaging; COVID-19=Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2; ECG/EKG=electrocardiogram; HELLP=hemolysis, elevated liver enzymes, and low platelets; MIS-C=multisystem inflammatory syndrome in children; MRI=magnetic resonance imaging; RT-PCR=reverse transcription polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2	

10.3.2 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a 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.

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer.

- Is associated with an overdose.

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

The investigator will assess the overall intensity of each AE and SAE (and other reportable event) reported during the study. An overall intensity grade will be assigned to injection-site AEs, specific systemic AEs, other systemic AEs, and vital sign (temperature) AEs as shown in the following tables. The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

Injection-site AE Overall Intensity Grading Scale

Injection-site Reaction to Study Vaccine[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Injection-site AEs occurring Days 1 through 7 following receipt of study vaccine				
Pain/Tenderness	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ED visit or hospitalization
Erythema/Redness	Size measured as ≤5 cm	Size measured as 5.1 to 10 cm	Size measured as >10 cm	Necrosis or exfoliative dermatitis or results in ED visit or hospitalization
Swelling	Size measured as ≤5 cm	Size measured as 5.1 to 10 cm	Size measured as >10 cm	Necrosis or ED visit or hospitalization
Lymphadenopathy[b]	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Any injection-site reaction that begins ≥8 days after receipt of study vaccine				
Pain/Tenderness Erythema/Redness Swelling/ Lymphadenopathy[b]	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ED visit or hospitalization

AE=adverse event; ED=emergency department; eVRC=electronic Vaccine Report Card

The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

a Based upon information provided by the participant on the eVRC and verbally during eVRC review. For the injection-site redness and swelling: >0 to 5 cm (0 to 2 inches) will be categorized as mild, >5 cm to 10 cm (>2 inches to 4 inches) will be categorized as moderate, and >10 cm (>4 inches) will be categorized as severe. If the participant has an ER visit or is hospitalized for any injection-site AE, that AE is to be assigned an overall intensity of Grade 4, regardless of the size measured.

b Axillary lymphadenopathy ipsilateral to the side of mRNA-1273 vaccine injection

Specific Systemic AE Overall Intensity Grading Scale

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ED visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ED visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ED visit or hospitalization
Arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ED visit or hospitalization
Nausea	No interference with activity or 1 to 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ED visit or hospitalization for hypotensive shock
Vomiting	No interference with activity or 1 to 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ED visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires ED visit or hospitalization

ED=emergency department
The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

Other Systemic AE Overall Intensity Grading Scale

Systemic Illness[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)b
Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and required medical intervention	ED visit or hospitalization

AE=adverse event; ED=emergency department; eVRC=electronic Vaccine Report Card; SAE=serious adverse event
The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

a Based on information provided by the participant on the eVRC and verbally during the eVRC review during the primary safety follow-up period. For SAEs reported beyond the primary safety follow-up period, grading will be based on the initial report and/or follow-up of the event.

b AEs resulting in death will be assessed as Grade 4.

Vital Sign (Temperature) Overall Intensity Grading Scale

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Fever (°C)b	38.0 to 38.4	38.5 to 38.9	39.0 to 40.0	>40.0
(°F)b	100.4 to 101.1	101.2 to 102.0	102.1 to 104.0	>104.0

The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

a Participant should be at rest for all vital sign requirements.

b Oral temperature; no recent hot or cold beverages or smoking.

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 his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a 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.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure 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: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

The recording and follow-up procedures described in this protocol apply to all medical devices as described below. For purposes of this section, medical devices in scope for device information collection include devices intended to be used by a study participant according to the study protocol that are manufactured by the Sponsor or for the Sponsor by a third party, licensed by the Sponsor for human use and/or drug-device combination products as listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

10.4.1 Definitions

Combination Product – A product comprised of 2 or more regulated components (ie, a drug and a device; a biologic and device; a biologic and a drug; or a drug, a device, and a biologic). Combination products can be single entity, copackaged, or colabeled.

Complaint – Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. This would include PQC, AE, and customer feedback.

A complaint does not necessarily need to involve a user or any other person.

Constituent Part – A drug, device, or biological product that is part of a combination product.

Customer Feedback – A report that does not allege a PQC or defect and has no relevant safety information/untoward event associated with it (eg, goodwill or courtesy replacement, consumer preference or suggestion, remark that may suggest an improvement in the functionality or quality of a medical device, or device like features of a drug delivery system).

Malfunction – The failure of a device to meet its performance specifications or otherwise perform as intended.

Medical Device – Any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, including the software necessary for its proper application intended by the MANUFACTURER to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap,
- investigation, replacement, or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.

PQC – Any communication that describes a potential defect related to the identity, strength, quality, purity, or performance of a product identified by external customers. This includes potential device or device component malfunctions. Note: A report of Lack or Limited Efficacy is considered an AE rather than a PQC.

Serious Injury – An injury or illness that:

1. Is life-threatening,

2. Results in permanent impairment of a body function or permanent damage to a body structure, or

3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

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

Recording

When a complaint including 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.

Events occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines. Medical device/device constituent part of drug-device combination product information will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor.

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 such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration should be considered and investigated.

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 as participants enrolled are boys and girls 9 to 11 years of age who have not yet had coitarche and do not plan on becoming sexually active during the vaccination period.

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 8.9 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.

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
APaT	All-Participants-as-Treated
β-hCG	β-human chorionic gonadotropin
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cLIA	competitive Luminex Immunoassay
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CRF	Case Report Form
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
ECL	electrochemiluminescence
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EMA	European Medicines Agency
EUA	Emergency Use Authorization
eVRC	electronic Vaccination Report Card
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSR	First Site Ready
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer

Abbreviation	Expanded Term
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HPV	human papillomavirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
IRT	interactive response technology
IVRS	interactive voice response system
IWRS	integrated web response system
LLOQ	lower limit of quantitation
MAAE	medically attended adverse event
MIS-C	Multisystem Inflammatory Syndrome in Children
mIU	milli international units
mL	milliliter
M&N	Miettinen and Nurminen
NSAE	nonserious AE
PP	per-protocol
PPI	per-protocol immunogenicity
PQC	product quality complaint
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOC	system organ class
sSAP	supplemental Statistical Analysis Plan

Abbreviation	Expanded Term
SUSAR	suspected unexpected serious adverse reaction
US	United States
VLP	vaccine-like particle
VSD	Vaccines Sciences Department
WHO	World Health Organization

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