Official Protocol Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Concomitant Administration of Either 23-Valent Pneumococcal Polysaccharide Vaccine or 15-Valent Pneumococcal Conjugate Vaccine with a Booster Dose of SARS-CoV-2 mRNA Vaccine in Healthy Adults 50 Years of Age or Older.
NCT number:	NCT05158140
Document Date:	12-Dec-2022

TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Concomitant Administration of Either 23-Valent Pneumococcal Polysaccharide Vaccine or 15-Valent Pneumococcal Conjugate Vaccine with a Booster Dose of SARS-CoV-2 mRNA Vaccine in Healthy Adults 50 Years of Age or Older.

Protocol Number: 911-03

Compound Number: V110

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	NCT05158140
EU CT	Not applicable
EudraCT	2021-003414-39
JAPIC-CT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	00618
IND	14977

Approval Date: 12 December 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	12-DEC-2022	CCI [redacted]
Amendment 2	10-JUN-2022	
Amendment 1	19-NOV-2021	
Original Protocol	11-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-driven study to a descriptive study design due to early closure of enrollment brought on by the rescinding of the monovalent booster EUA.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.2 Schema Section 2 Introduction Section 3 Hypotheses, Objective, and Endpoints Section 4.1 Overall Design Section 9 Statistical Analysis Plan Section 9.1 Statistical Analysis Plan Summary Section 9.3 Hypotheses/Estimation Section 9.6.1 Statistical Methods for Immunogenicity Analyses Section 9.6.2 Statistical Methods for Safety Analyses Section 9.8 Multiplicity Section 9.9 Sample Size and Power Calculations	• Changed the study design from comparative, hypothesis-driven to descriptive. • Changed the planned enrollment from approximately 1300 to the approximately 850 participants currently enrolled and dosed (with or without a single booster of the mRNA-1273 SARS-CoV-2) in the study. • Changed study duration from approximately 18 months to approximately 14 months.	The EUA for the monovalent booster (mRNA-1273) was rescinded on 31-AUG-2022 and is no longer available for use as a booster dose.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added NCT and EudraCT numbers.	Include additional study identifiers.
Section 1.1 Synopsis Section 6.1 Study Intervention(s) Administered	• Additional intervention information from Table 1 included in Synopsis. • Dose Formation: "Sterile Solution" and "Sterile Suspension" changed to "Solution" and "Suspension", respectively. • Use: "Experimental" changed to "Test Product"	CCI
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.
Throughout Document	Minor administrative, formatting, editorial, grammatical, and/or typographical changes were made throughout the document. This document has been migrated into a new content development platform to allow for contemporaneous alignment with current industry templates, regulations, and guidelines and to support emerging technology. No content has been updated or otherwise altered relative to the immediately preceding version.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Concomitant Administration of Either 23-Valent Pneumococcal Polysaccharide Vaccine or 15-Valent Pneumococcal Conjugate Vaccine with a Booster Dose of SARS-CoV-2 mRNA Vaccine in Healthy Adults 50 Years of Age or Older.

Short Title: Coadministration of V110 or V114 With mRNA-1273 in Healthy Adults

Acronym: None

Hypotheses, Objectives, and Endpoints:

Objectives and endpoints described below will be evaluated in adults 50 years of age and older who previously completed a 2-dose primary series of the mRNA-1273 SARS-CoV-2 vaccine with or without a single booster dose of the mRNA-1273 SARS-CoV-2 vaccine:

Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of V110 and mRNA-1273 when administered concomitantly or nonconcomitantly with respect to the proportion of participants with adverse events (AEs) within each vaccination group, separately	• Solicited injection-site AEs • Solicited systemic AEs • Vaccine-related serious adverse events (SAEs)
• To evaluate the safety and tolerability of V114 and mRNA-1273 when administered concomitantly or nonconcomitantly with respect to the proportion of participants with AEs within each vaccination group, separately	• Solicited injection-site AEs • Solicited systemic AEs • Vaccine-related SAEs
• To evaluate the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V110 when administered concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses

• To evaluate the serotype-specific OPA GMTs at 30 days postvaccination with V114 when administered concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses
• To evaluate the SARS-CoV-2-specific binding antibody (bAb) GMTs at 30 days postvaccination when administered concomitantly or nonconcomitantly with V110 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses
• To evaluate the SARS-CoV-2-specific bAb GMTs at 30 days postvaccination when administered concomitantly or nonconcomitantly with V114 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses
Secondary Objectives	**Secondary Endpoints**
• To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V110) to 30 days postvaccination with V110 for OPA responses for participants administered V110 concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses
• To evaluate the serotype-specific GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for OPA responses for participants administered V114 concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotypes-specific OPA responses

• To evaluate the GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with mRNA-1273) to 30 days postvaccination with mRNA-1273 for SARS-CoV-2-specific bAb responses for participants administered mRNA-1273 concomitantly or nonconcomitantly with V110 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses
• To evaluate the GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with mRNA-1273) to 30 days postvaccination with mRNA-1273 for SARS-CoV-2-specific bAb responses for participants administered mRNA-1273 concomitantly or nonconcomitantly with V114 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal infection
Population	Adults 50 years of age and older who previously completed a 2-dose primary series of the mRNA-1273 SARS-CoV-2 vaccine with or without a single booster dose of the mRNA-1273 SARS-CoV-2 vaccine
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects Investigator Sponsor

Estimated Duration of Study	The Sponsor estimates that the study will require [redacted] from the time the first participant (or their legally acceptable representative) provides documented informed consent 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 850 participants will be enrolled as described in Section 9.9.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
V110 Concomitant Group	V110	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product
V110 Concomitant Group	mRNA-1273	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product
V110 Concomitant Group	Placebo (Sterile Saline)	N/A	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Placebo
V110 Nonconcomitant Group	Placebo (Sterile Saline)	N/A	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Placebo
V110 Nonconcomitant Group	mRNA-1273	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product
V110 Nonconcomitant Group	V110	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Test Product
V114 Concomitant Group	V114	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product
V114 Concomitant Group	mRNA-1273	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product
V114 Concomitant Group	Placebo (Sterile saline)	N/A	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Test Product
V114 Nonconcomitant Group	Placebo (Sterile saline)	N/A	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Placebo
V114 Nonconcomitant Group	mRNA-1273	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product
V114 Nonconcomitant Group	V114	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Test Product

Total Number of Intervention Groups/Arms	4
Duration of Participation	Each participant will participate in the study for approximately 6 months from the time the participant provides documented informed consent 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.

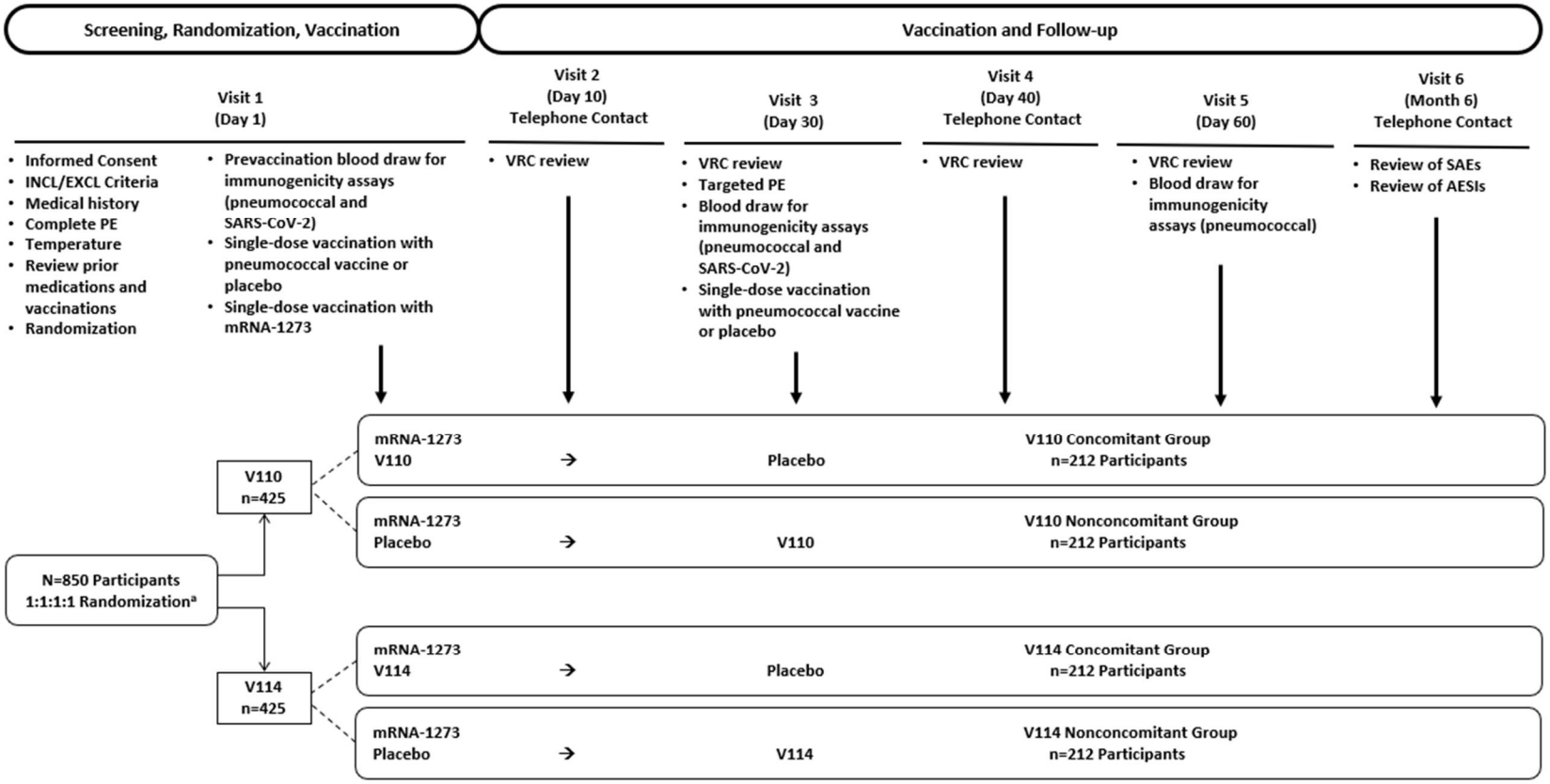
Study Accepts Healthy Participants: Yes

A list of abbreviations is in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



AESI=adverse events of special interest; INCL/EXCL=inclusion/exclusion; PE=physical examination; V110=PNEUMOVAX™23; SAE=serious adverse event; SARS-CoV=Severe Acute Respiratory Syndrome coronavirus; V114=VAXNEUVANCE™; VRC=Vaccination Report Card;
a. Randomization will be stratified by age (50 to 64, 65 to 74, and ≥75 years of age), history of prior pneumococcal vaccination (Yes or No), receipt of prior mRNA-1273 booster dose (Yes or No), and History of prior SARS-CoV-2 infection (Yes or No).

1.3 Schedule of Activities

Study Period	Intervention					Follow-up	Notes
Visit Type:	**Visit (Vaccination 1)**	**TC**	**Visit (Vaccination 2)**	**TC**	**Visit**	**TC**	
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	
Scheduled Time:	**Day 1**	**Day 10**	**Day 30**	**Day 40**	**Day 60**	**Month 6**	
Visit Window:		Day 10 to Day 14 after Visit 1	Day 30 to Day 44 after Visit 1	Day 10 to Day 14 after Visit 3	Day 30 to Day 44 after Visit 3	Day 166 to Day 194 after Visit 1	For calculating the visit windows, the day of vaccination is considered Day 1.
Administrative and General Procedures							
Screening Procedures							
Informed Consent	X						Documented consent must be obtained before any study procedures.
Informed Consent for FBR	X						Participation in FBR is optional and documented consent must be obtained before the blood sample (DNA sample) is collected.
Assignment of Screening Number	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Postrandomization Procedures							
Assignment of Randomization Number	X						
Participant Identification Card	X						
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	X	X		
Pneumococcal Vaccine (V110 or V114) or Placebo Administration (Blinded)-Left Arm	X		X				
SARS-CoV-2 Vaccine (mRNA-1273) Administration (Open label)-Right Arm	X						
Provide or Configure Electronic Device for eVRC Data Collection	X						
Review eVRC Data With Participant		X	X	X	X		
Collect Electronic Device From Participant					X		For participants who received an electronic device.
Complete Telephone Contact Questionnaire						X	

Study Period	Intervention					Follow-up	Notes
Visit Type:	**Visit (Vaccination 1)**	**TC**	**Visit (Vaccination 2)**	**TC**	**Visit**	**TC**	
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	
Scheduled Time:	**Day 1**	**Day 10**	**Day 30**	**Day 40**	**Day 60**	**Month 6**	
Visit Window:		Day 10 to Day 14 after Visit 1	Day 30 to Day 44 after Visit 1	Day 10 to Day 14 after Visit 3	Day 30 to Day 44 after Visit 3	Day 166 to Day 194 after Visit 1	For calculating the visit windows, the day of vaccination is considered Day 1.
Safety Procedures							
Complete Physical Examination	X						Performed by the investigator or medically qualified designee at screening and before vaccination.
Targeted Physical Examination			X				Performed by the investigator or medically qualified designee before vaccination.
Pregnancy Test (If Applicable)	X		X				Urine or serum pregnancy test consistent with local requirements (sensitive to ≤25 IU hCG) must be performed and negative results available before vaccination of females of reproductive potential.
Body Temperature Measurement Before Vaccination	X		X				Measured before vaccination. Participants with febrile illness within 72 hours before vaccination must be rescheduled.
Postvaccination Observation Period	X		X				Observed by blinded study-site personnel for ≥30 minutes postvaccination.
AE Monitoring	X	X	X	X	X	X	Nonserious AEs reported Day 1 through Day 28 after each vaccination. AESIs, SAEs, and deaths reported Day 1 through the duration of study participation.
Immunogenicity Procedures							
Serum for Pneumococcal Immunogenicity Assay (Including Retention Serum)	X		X		X		Samples at Visit 1 and Visit 3 collected before vaccination.
Serum for SARS-CoV-2 Immunogenicity Assays (Including Retention Serum)	X		X				Samples collected before vaccination.
Future Biomedical Research							
Blood (DNA) for FBR	X						Samples obtained before vaccination at Visit 1 for participants who provided FBR consent, or at a later date as soon as the FBR consent is obtained.

AE=adverse event; AESI=adverse event of special interest; DNA=deoxyribonucleic acid; eVRC=electronic Vaccination Report Card; FBR=future biomedical research; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

2 INTRODUCTION

PNEUMOVAX™23 (V110) is a 23-valent pneumococcal polysaccharide vaccine indicated for the prevention of pneumococcal disease caused by the 23 serotypes contained in the vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) in persons 50 years of age and older and in persons 2 years of age and older who are at risk for pneumococcal disease.

VAXNEUVANCE™ (V114) is a 15-valent PCV indicated for the prevention of invasive pneumococcal disease caused by the 15 serotypes contained in the vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) in persons 18 years of age and older.

mRNA-1273 (Moderna Inc., Cambridge, MA) is a nucleoside-modified mRNA vaccine indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in persons 18 years of age and older. mRNA-1273 was authorized for use in the US 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. As of 31-AUG-2022, mRNA-1273 is no longer authorized for use as a booster.

The purpose of this study is to evaluate the concomitant and nonconcomitant use of mRNA-1273 with V110 and V114.

2.1 Study Rationale

The initial EUA (December 2020) of a 2-dose regimen of mRNA-1273 for persons 18 years of age and older was based on a clinical study (mRNA-1273-P301; NCT04470427) that showed an acceptable safety profile and clinical efficacy of the vaccine in preventing symptomatic, laboratory-confirmed SARS-CoV-2 infection [Baden, L. R., et al 2021]. The majority of adults 50 years of age and older in the US have been vaccinated with a COVID-19 vaccine; however, given the emergence of new variants and waning immunity, booster vaccination is also recommended. Various studies have demonstrated the effectiveness of the mRNA-1273 booster doses [Andrews, N., et al 2022] [Regev-Yochay, G., et al 2022].

Pneumococcal pneumonia is a serious complication of COVID-19 that can result in death. Although most individuals experience fever, mild or moderate coughing, and shortness of breath, some individuals develop severe pneumonia. Pneumococcal vaccines are immunogenic and effective with a favorable safety profile [Dinleyici, EC and Yargic, ZA 2008] [Bonten, M. J., et al 2015] [Tomczyk, S., et al 2014] and can be used to decrease respiratory disease burden and health care utilization.

Previous studies have shown the additive benefit of concomitant administration of pneumococcal vaccines and influenza vaccine in elderly populations. The concomitant administration of PCVs with influenza vaccine is supported by the results of clinical studies with both V114 (NCT03615482) and other PCVs [Frenck, R. W. Jr., et al 2012] [Schwarz, T. F., et al 2011] [Schwarz, T. F. 2013] [Song, J. Y., et al 2017], while the concomitant use of V110 and influenza vaccine is effective in preventing pneumonia, death, and hospitalization

during influenza season [Yin, M., et al 2018] [Dominguez, A., et al 2013]. While reduced immune responses to pneumococcal vaccines have been observed when administered concomitantly with influenza vaccine, the clinical significance of this trend is unknown [Frenck, R. W. Jr., et al 2012] [Schwarz, T. F., et al 2011] [Schwarz, T. F. 2013] [Song, J. Y., et al 2017].

There are currently limited data available for SARS-CoV-2 mRNA vaccines coadministered with other vaccines [Lazarus, R., et al 2021] [Andrews, N., et al 2022]; however, in May 2021, the ACIP recommended that SARS-CoV-2 vaccines may be coadministered with other vaccines. CCI [redacted] CCI [redacted]

This study is designed to evaluate the safety, tolerability, and immunogenicity of a single dose of a pneumococcal vaccine (V110 or V114) when administered concomitantly and nonconcomitantly with a booster dose of mRNA-1273 in healthy adults 50 years of age and older who previously completed a 2-dose primary series of the mRNA-1273 SARS-CoV-2 vaccine with or without a single booster dose of the mRNA-1273 SARS-CoV-2 vaccine.

2.2 Background

Refer to the approved labeling for detailed background information on V110.

Refer to the IB/approved labeling for detailed background information on V114.

Refer to the approved labeling for detailed background information on mRNA-1273.

2.2.1 Pharmaceutical and Therapeutic Background

V110 is a pneumococcal polysaccharide vaccine comprised of the polysaccharides from 23 pneumococcal serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). The formulation is not adjuvanted and no carrier protein is used. In the US, V110 is indicated for active immunization in adults 50 years of age and older for the prevention of pneumococcal disease.

V114 is a PCV that contains 15 distinct pneumococcal capsular polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) individually conjugated to the CRM197 carrier protein originating from Corynebacterium diphtheriae C7. Conjugation of polysaccharides to proteins changes the nature of the immune response to polysaccharide antigens from T-cell independent to T-cell dependent [Pilishvili, T. 2015]. In the US, V114 is indicated for active immunization in adults 18 years of age and older for the prevention of invasive pneumococcal disease.

mRNA-1273 is a SARS-CoV-2 vaccine based on a platform of nucleoside-modified mRNA encoding the prefusion stabilized Spike glycoprotein of SARS-CoV-2 virus. In the US, mRNA-1273 is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in persons 18 years of age and older. mRNA-1273 was also authorized for use in the US under an EUA as a first booster dose in adults 18 years of age and older 5 months after

the completion of a primary series. In addition, adults 50 years of age and older, as well as people aged 18 and older with immunocompromising conditions, were eligible for a second booster dose 4 months after receipt of the first booster dose. As of 31-AUG-2022, the mRNA-1273 is no longer authorized for use as a booster.

2.2.2 Preclinical and Clinical Studies

Refer to the approved labeling for information on clinical study experience with V110.

Refer to the V114 IB for information on completed preclinical studies and completed and ongoing clinical studies conducted with V114.

Refer to the approved labeling for clinical study experience with mRNA-1273. Preliminary data are available from an ongoing clinical study assessing the safety and immunogenicity of a single 50-µg booster dose of mRNA-1273 in 20 participants vaccinated at least 6 months prior with 2 doses of mRNA-1273 [Wu, K., et al 2021]. In this study, a single 50-µg booster dose of mRNA-1273 had an acceptable safety profile and was immunogenic. The most common solicited injection-site AE was injection-site pain (90%); the most common solicited systemic AEs were fatigue (70%), headache (55%), arthralgia (50%), and myalgia (45%); and fever was reported by 15% of participants. The majority of solicited injection-site and systemic AEs were mild or moderate in intensity, and there were no SAEs reported. Two weeks after the booster vaccination, antibody neutralization titers against the wild-type original SARS-CoV-2 strain, in addition to the B.1.351 and P.1 variants, increased to levels similar to or higher than peak titers measured after the primary series vaccination.

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 vaccine.

Both V110 and V114 are approved for use in the population enrolled in this study.

A first booster dose of mRNA-1273 was recommended in adults 18 years of age and older who have completed primary COVID-19 vaccination. A second booster dose of mRNA-1273 was recommended in individuals 50 years of age and older and adults 18 years of age and older with certain immunocompromising conditions.

All participants in this study will receive a booster dose of mRNA-1273 at Visit 1, with approximately 50% of participants receiving mRNA-1273 concomitantly with V110 or concomitantly with V114. Participants who do not receive V110 or V114 concomitantly with mRNA-1273 will receive V110 or V114 30 days later.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Objectives and endpoints described below will be evaluated in adults 50 years of age and older who previously completed a 2-dose primary series of the mRNA-1273 SARS-CoV-2 vaccine with or without a single booster dose of the mRNA-1273 SARS-CoV-2 vaccine:

Primary Objectives	**Primary Endpoints**
• To evaluate the safety and tolerability of V110 and mRNA-1273 when administered concomitantly or nonconcomitantly with respect to the proportion of participants with adverse events (AEs) within each vaccination group, separately	• Solicited injection-site AEs • Solicited systemic AEs • Vaccine-related serious adverse events (SAEs)
• To evaluate the safety and tolerability of V114 and mRNA-1273 when administered concomitantly or nonconcomitantly with respect to the proportion of participants with AEs within each vaccination group, separately	• Solicited injection-site AEs • Solicited systemic AEs • Vaccine-related SAEs
• To evaluate the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V110 when administered concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses
• To evaluate the serotype-specific OPA GMTs at 30 days postvaccination with V114 when administered concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses
• To evaluate the SARS-CoV-2-specific binding antibody (bAb) GMTs at 30 days postvaccination when administered concomitantly or nonconcomitantly with V110 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses

• To evaluate the SARS-CoV-2-specific bAb GMTs at 30 days postvaccination when administered concomitantly or nonconcomitantly with V114 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses
Secondary Objectives	**Secondary Endpoints**
• To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V110) to 30 days postvaccination with V110 for OPA responses for participants administered V110 concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotype-specific OPA responses
• To evaluate the serotype-specific GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for OPA responses for participants administered V114 concomitantly or nonconcomitantly with mRNA-1273 within each vaccination group, separately	• Serotypes-specific OPA responses
• To evaluate the GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with mRNA-1273) to 30 days postvaccination with mRNA-1273 for SARS-CoV-2-specific bAb responses for participants administered mRNA-1273 concomitantly or nonconcomitantly with V110 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses

• To evaluate the GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with mRNA-1273) to 30 days postvaccination with mRNA-1273 for SARS-CoV-2-specific bAb responses for participants administered mRNA-1273 concomitantly or nonconcomitantly with V114 within each vaccination group, separately	• SARS-CoV-2-specific bAb responses
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
• To evaluate SARS-CoV-2 specific neutralizing antibody (nAb) GMTs at 30 days postvaccination with mRNA-1273 for participants administered mRNA-1273 concomitantly or nonconcomitantly with V110 within each vaccination group, separately	• SARS-CoV-2-specific nAb responses
• To evaluate SARS-CoV-2 specific nAb GMTs at 30 days postvaccination with mRNA-1273 for participants administered mRNA-1273 concomitantly or nonconcomitantly with V114 within each vaccination group, separately	• SARS-CoV-2-specific nAb responses

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multisite, double-blind study of a pneumococcal vaccine (V110 or V114) administered concomitantly or nonconcomitantly with a booster dose of SARS-CoV-2 vaccine (mRNA-1273) in adults 50 years of age and older who previously completed a 2-dose primary series of the mRNA-1273 SARS-CoV-2 vaccine ≥5 months (150 days) before receipt of study vaccine at Visit 1. Participants may also have received a first booster dose of mRNA-1273 if given ≥4 months (120 days) before receipt of study vaccine at Visit 1.

Approximately 850 participants will be randomly assigned in a 1:1:1:1 ratio to receive either V110 or V114 with concomitant or nonconcomitant mRNA-1273 (Figure 1). Randomization will be stratified by age (50 to 64, 65 to 74, and ≥75 years of age), history of prior pneumococcal vaccination (Yes or No), receipt of prior mRNA-1273 booster dose (Yes or No), and history of prior SARS-CoV-2 infection (Yes or No).

Participants enrolled in the concomitant groups will receive either V110 or V114 (blinded) in the left arm and mRNA-1273 (open label) in the right arm on Day 1, and then will receive placebo (blinded) in the left arm 30 days later at Visit 3 (Day 30).

Participants enrolled in the nonconcomitant groups will receive placebo (blinded) in the left arm and mRNA-1273 (open label) in the right arm on Day 1, and then will receive V110 or V114 (blinded) in the left arm 30 days later at Visit 3 (Day 30).

An eVRC will be used by all participants to record solicited injection-site AEs, solicited systemic AEs, and daily body temperatures from Day 1 through Day 7 after each vaccination. Unsolicited AEs will also be recorded from Day 1 through Day 28 after each vaccination. All participants will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC.

Information for SAEs and deaths, regardless of whether the events are considered to be vaccine-related by the investigator, will be collected from the time consent is obtained through completion of participation in the study.

Blood samples for immunogenicity assays will be drawn immediately before the first vaccination at Visit 1 (Day 1), before vaccination at Visit 3 (Day 30), and at Visit 5 (Day 60). After completion of immunogenicity testing to evaluate the study objectives, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. For participants who provide optional consent for FBR, leftover sera from the study may be used for other purposes, such as the development and/or validation of pneumococcal assays after completion of all study-related immunogenicity testing.

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 clinical study will evaluate the safety, tolerability, and immunogenicity of a booster dose of mRNA-1273 administered concomitantly and nonconcomitantly with V110 or V114 in healthy adults 50 years of age and older. This population is at elevated risk for pneumococcal disease and COVID-19 and associated morbidity and mortality from both diseases [Drijkoningen, J. J 2014] [Centers for Disease Control and Prevention 2021]. Because the majority of adults 50 years of age and older in the US have been vaccinated with a COVID-19 vaccine and a first and second booster dose are now recommended in this population, this study will include participants who have completed a 2-dose primary series of mRNA-1273 ≥5 months before receipt of study vaccine at Visit 1. This study will also include participants who have not yet received a booster dose or who have previously received a first booster dose of mRNA-1273 ≥4 months prior to receipt of study vaccine at Visit 1.

To show that concomitant administration of pneumococcal vaccines with a booster dose of mRNA-1273 does not adversely affect the antibody response to or safety profile of either vaccine, this study is blinded using a saline placebo to the pneumococcal vaccine administered on Day 1 and Day 30. All 4 intervention groups will receive a booster dose of mRNA-1273 and a dose of pneumococcal vaccine (either V110 or V114) in the study.

In the setting of the ongoing COVID-19 pandemic, all participants will receive mRNA-1273 at Visit 1.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

The immunogenicity endpoints and associated comparative statistical criteria are consistent with previous studies evaluating V110, V114, and mRNA-1273.

4.2.1.1.1 Pneumococcal Immunogenicity Endpoints

Sera from participants will be used to measure vaccine-induced, antipneumococcal polysaccharide serotype-specific OPA GMTs using the validated MOPA.

Several studies have shown a positive correlation between serotype-specific IgG antibody concentrations and OPA titers in children and adults [Centers for Disease Control and Prevention 2010] [Anttila, M., et al 1999] [Romero-Steiner, S., et al 1997]. OPA assesses levels of functional antibodies capable of opsonizing pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing, and, therefore, is considered an important immunologic surrogate for protection against IPD in adults. It is noted that IgG antibody and OPA titer threshold values that correlate with protection in adults have not been defined; however, the OPA functional assay is considered an accepted endpoint in adults.

Immune responses will be measured for serotypes included in the validated MOPA (Section 8.2.1). This includes 14 of 23 serotypes contained in V110 (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C,

19A, 19F, 22F, 23F, and 33F) and all 15 serotypes included in V114 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F).

Details on the immunogenicity endpoints evaluated in this study can be found in Section 9.4.1.

4.2.1.1.2 SARS-CoV-2 Immunogenicity Endpoints

Sera from participants will be used to measure vaccine-induced bAb responses using a validated ligand-binding assay specific to the SARS-CoV-2 Spike protein. Sera from a subset of participants (approximately the first 30% of all participants with sufficient serum volume) will be used to quantitatively measure nAb activity directed against the SARS-CoV-2 Spike envelope protein using a validated assay. These endpoints are consistent with Phase 3 clinical studies evaluating mRNA-1273.

Details on the immunogenicity endpoints evaluated in this study can be found in Section 9.4.1.

4.2.1.2 Safety Endpoints

Safety information will be collected from all participants on an eVRC. The eVRC used to record AEs during the postvaccination periods (Section 8.1.9) is structured as recommended in the final US Food and Drug Administration Patient-reported Outcome Guidance [U.S. Food and Drug Administration 2009].

The safety endpoints (ie, AEs and temperature) evaluated in this study are consistent with previous studies of V110, V114, and mRNA-1273. Detailed information for the safety endpoints evaluated in this study is provided in Section 9.4.2.

Definitions and reporting requirements for AEs are provided in Appendix 3.

4.2.1.3 Future Biomedical Research

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4.2.2 Rationale for the Use of Comparator/Placebo

Placebo (sterile saline for injection) is used in this study to maintain blinding to the concomitant and nonconcomitant group assignments.

4.3 Justification for Dose

The dose of V110 and V114 selected for use in this study are consistent with the approved US dosing and product labeling of PNEUMOVAX™23 and VAXNEUVANCE™, respectively.

The dose of mRNA-1273 selected for use in this study is consistent with the EUA Prescribing Information authorized by the FDA for the mRNA-1273 booster dose.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

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

Type of Participant and Disease Characteristics

1. Is in good health. Any underlying chronic illness must be documented to be in stable condition.
2. *Has received a 2-dose primary series of the Moderna mRNA SARS-CoV-2 vaccine ≥5 months (150 days) before receipt of study vaccine at Visit 1.

   In addition to the 2-dose primary series, a participant may have received either:

   - A first booster dose of the Moderna mRNA SARS-CoV-2 vaccine ≥4 months (120 days) before receipt of study vaccine at Visit 1, or
   - No booster dose of the Moderna mRNA SARS-CoV-2 vaccine.

Demographics

3. Is male or female, ≥50 years of age, at the time of signing the informed consent.

Female Participants

4. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   - Is not a WOCBP

     OR

   - Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 3 months after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

     - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

5. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR; However, the participant may participate in the study without participating in FBR.

Additional Requirement(s)

6. The participant has the ability to complete eVRC data collection without assistance.

For items with an asterisk (*), if the participant does not meet these inclusion criteria, the Day 1 visit may be rescheduled for a time when these criteria are met.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a current SARS-CoV-2 infection or a known history of SARS-CoV-2 infection <3 months (90 days) before receipt of study vaccine at Visit 1.

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

3. Has a known hypersensitivity to any component of pneumococcal polysaccharide vaccine, PCV, any diphtheria toxoid-containing vaccine, or following a previous dose of pneumococcal polysaccharide vaccine or PCV.

4. Has a known hypersensitivity to any component of the mRNA-1273 vaccine or following a previous dose of any COVID-19 vaccine.

5. Has a known or suspected impairment of immunological function including, but not limited to, a history of congenital or acquired immunodeficiency, documented HIV infection, functional or anatomic asplenia, or history of autoimmune disease.

6. Has a coagulation disorder contraindicating intramuscular vaccinations.

7. *Had a recent febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C]; axillary or temporal temperature ≥99.4°F [≥37.4°C]) or received antibiotic therapy for an acute illness occurring <72 hours before receipt of study vaccine at Visit 1.

8. Has a known malignancy that is progressing or has required active treatment <3 years before receipt of study vaccine at Visit 1. **Note:** participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

Prior/Concomitant Therapy

9. Received prior administration of a pneumococcal polysaccharide vaccine <5 years before receipt of study vaccine at Visit 1 or is expected to receive a pneumococcal polysaccharide vaccine during the study outside the protocol.

10. Received prior administration of a PCV <1 year before receipt of study vaccine at Visit 1 or is expected to receive a PCV during the study outside the protocol.

11. Received prior administration of any SARS-CoV-2 vaccine other than the 2-dose primary series of the Moderna mRNA vaccine with or without a first booster dose of the Moderna mRNA vaccine, or is expected to receive any SARS-CoV-2 vaccine during the study outside the protocol.

12. Received prior monoclonal antibody treatment for SARS-CoV-2 infection.

13. Received antiviral treatment for SARS-CoV-2 infection <3 months (90 days) before receipt of study vaccine at Visit 1.

14. Received systemic corticosteroids (≥20 mg/day prednisone equivalent) for ≥14 consecutive days and has not completed intervention ≥30 days before receipt of study vaccine at Visit 1.

15. Received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) ≤14 days before receipt of study vaccine. **Note:** Topical, ophthalmic, intraarticular or soft-tissue (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.

16. Is currently receiving immunosuppressive therapy, including chemotherapeutic agents used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease.

17. *Received any nonlive vaccine ≤14 days before receipt of study vaccine or is scheduled to receive any nonlive vaccine ≤30 days after receipt of study vaccine. **Exception:** Inactivated influenza vaccine allowed if given ≥7 days before or ≥15 days after receipt of study vaccine.

18. *Received any live virus vaccine ≤30 days before receipt of study vaccine or is scheduled to receive any live virus vaccine ≤30 days after receipt of study vaccine.

19. Received a blood transfusion or blood products (including globulin) ≤6 months before receipt of study vaccine or is scheduled to receive a blood transfusion or blood product ≤30 days after receipt of study vaccine. Autologous blood transfusions are not considered an exclusion criterion.

Prior/Concurrent Clinical Study Experience

20. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 2 months of participating in this current study.

Diagnostic Assessments

Not applicable.

Other Exclusions

21. In the opinion of the investigator, has a history of clinically relevant drug or alcohol use that would interfere with participation in protocol-specified activities.

22. Has a history or current evidence of any condition, therapy laboratory abnormality, or other circumstance that might predispose the participant to risk by participating in the study, confound the results of the study, or interfere with the participant's participation for the full duration of the study in the opinion of the investigator.

23. 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 with an asterisk (*), if the participant meets these exclusion criteria, the Day 1 visit may be rescheduled for a time when these criteria are not met.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal

information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who 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 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 intervention(s) 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 Adminis-tration	Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
V110 Concomitant Group	Experimental	V110	Biological/Vaccine	Solution	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product	IMP	Central
V110 Concomitant Group	Experimental	mRNA-1273	Biological/Vaccine	Suspension	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product	IMP	Central and Local
V110 Concomitant Group	Experimental	Placebo (Sterile Saline)	Biological/Vaccine	Solution	N/A	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Placebo	IMP	Central
V110 Nonconcomitant Group	Experimental	Placebo (Sterile Saline)	Biological/Vaccine	Solution	N/A	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Placebo	IMP	Central
V110 Nonconcomitant Group	Experimental	mRNA-1273	Biological/Vaccine	Suspension	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product	IMP	Central and Local
V110 Nonconcomitant Group	Experimental	V110	Biological/Vaccine	Solution	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Test Product	IMP	Central
V114 Concomitant Group	Experimental	V114	Biological/Vaccine	Suspension	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product	IMP	Central
V114 Concomitant Group	Experimental	mRNA-1273	Biological/Vaccine	Suspension	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product	IMP	Central and Local
V114 Concomitant Group	Experimental	Placebo (Sterile saline)	Biological/Vaccine	Solution	N/A	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Test Product	IMP	Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
V114 Nonconcomitant Group	Experimental	Placebo (Sterile saline)	Biological/Vaccine	Solution	N/A	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Placebo	IMP	Central
V114 Nonconcomitant Group	Experimental	mRNA-1273	Biological/Vaccine	Suspension	50 µg	0.25 mL	IM	Single Dose at Visit 1 (Day 1)	Test Product	IMP	Central and Local
V114 Nonconcomitant Group	Experimental	V114	Biological/Vaccine	Suspension	Refer to product labeling	0.5 mL	IM	Single Dose at Visit 3 (Day 30)	Test Product	IMP	Central

Admin=administration; EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; mRNA-1273=Moderna SARS-CoV-2 vaccine; N/A=not applicable; NIMP/AxMP=noninvestigational/auxiliary medicinal product; V110=PNEUMOVAX™23; V114=VAXNEUVANCE™.

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 EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.1.1 Medical Devices

Drug-device combination product(s), which is legally marketed, provided for use in this study are: PNEUMOVAX™23 prefilled syringes and VAXNEUVANCE™ prefilled 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.

Specific procedures that are required for dose preparation are outlined in the Investigator Trial File Binder.

As detailed in Section 6.3.3, study vaccines will be prepared by an unblinded member of the study-site staff.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 4 study intervention arms. Participants will be assigned randomly in a 1:1:1:1 ratio to receive either V110 concomitantly with mRNA-1273, V114 concomitantly with mRNA-1273, V110 nonconcomitantly with mRNA-1273, or V114 nonconcomitantly with mRNA-1273.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

- Participant age at time of randomization (50 to 64, 65 to 74, ≥75 years of age). The categories for age stratification are consistent with prior clinical studies of pneumococcal vaccines in adults.
- History of prior pneumococcal vaccination (Yes, No), where "Yes" includes any prior vaccination with a pneumococcal polysaccharide vaccine and/or PCV, and "No" indicates no prior vaccination with a pneumococcal polysaccharide vaccine or PCV (ie, vaccine-naïve).
- Receipt of prior mRNA-1273 booster dose (Yes, No).
- History of prior SARS-CoV-2 infection (Yes, No).

6.3.3 Blinding

A double-blinding technique will be used. V110, V114, and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Because V110, V114, and placebo have different appearances, a member of the study-site staff will be unblinded for the purposes of receiving, maintaining, preparing and/or dispensing, and administering these study vaccines (Section 8.1.8). Although mRNA-1273 is provided open label in this study, it will also be prepared and/or dispensed and administered by unblinded study-site staff for consistency. Procedures for handling, preparing, and administering the unblinded vaccines are in the Investigator Trial File Binder.

To avoid bias, the unblinded study personnel will have no further contact with study participants for any study-related procedures/assessments after administration of study vaccines, which includes all safety follow-up procedures. Blinded site personnel will not be present in the examination room when study vaccines are administered. Contact between participants and unblinded study personnel after vaccination administration is strictly prohibited. Blinded site personnel will be responsible for all safety and immunogenicity follow-up procedures after vaccine administration.

An unblinded Clinical Research Associate will monitor vaccine accountability at the study site. All other Sponsor personnel or delegate(s) and MSD Research Laboratories employees directly involved with the conduct of this study will remain blinded to the participant-level intervention assignment.

See Section 8.1.13 for a description of the method of unblinding a participant during the study should such action be warranted.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified vaccination plan (see Section 1.2) 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.

It is important to record the use of any analgesic or antipyretic medication that occurs on the day of vaccination on the eVRC and appropriate eCRF.

Listed below are specific restrictions for concomitant therapy or vaccination:

- Any administration of a nonstudy pneumococcal vaccine or SARS-CoV-2 vaccine is prohibited during the study.
- Administration of monoclonal antibody treatment for SARS-CoV-2 infection is prohibited during the study.

- Nonstudy vaccines may only be administered before or after the receipt of study vaccines according to the time frames specified in the Exclusion Criteria (Section 5.2). If the participant is scheduled to receive any nonstudy vaccine, the investigator should discuss this with the Sponsor Clinical Director as soon as possible. **Exception:** Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of study vaccine or at least 15 days after receipt of study vaccine.

- Participants should not receive systemic corticosteroids (≥20 mg/day prednisone equivalent) for ≥14 consecutive days starting from 30 days before each vaccination through 30 days after each vaccination.

- Participants should not receive systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) starting from 14 days before any vaccination. **Note:** Topical, ophthalmic, intraarticular or soft-tissue (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.

Any deviation from the above requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Use of prior and concomitant medications/vaccinations should be recorded as described in Section 8.1.5.

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

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.13). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.13 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified vaccination regimen will 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 8.1.12 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 requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.12. The procedures to be performed should a participant repeatedly fail to return

for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for 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 procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- CCI [redacted] CCI [redacted] In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant at each visit will not exceed 30 mL, and total amount of blood collected over the duration of the study will not exceed 70 mL (Table 2).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

CCI [redacted]

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The participant's relevant medical history for the 5 years before Visit 1, including any known history of SARS-CoV-2 infection, will be obtained to ensure that the participant satisfies the inclusion and exclusion criteria of the study. History of tobacco use will be collected for all participants.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior vaccinations and medication taken by the participant within 30 days before the study vaccination at Visit 1.

The following must be documented before vaccination at Visit 1 and recorded on the appropriate eCRF:

- Any analgesic or antipyretic medication taken on the day of vaccination before vaccination
- SARS-CoV-2 vaccination history
- Any history of vaccination with a pneumococcal polysaccharide vaccine or PCV

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record vaccinations and medications, if any, taken by the participant during the study.

Any analgesic or antipyretic medication taken must be recorded on the eVRC and appropriate eCRF.

The participant will use their eVRC (Section 8.1.9) to record new and/or concomitant medications taken and nonstudy vaccines received from the day of each vaccination through 28 days postvaccination.

8.1.6 Assignment of Screening Number

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

8.1.7 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 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.

8.1.8 Study Intervention Administration

Unblinded study personnel not otherwise involved in the conduct of the study will prepare and administer all study vaccines (Section 6.3.3). 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. Unblinded study personnel should follow the procedures for handling, preparing, and administering V110 and V114 as specified in the product label and mRNA-1273 as specified in the EUA Prescribing Information; these documents are provided in the Investigator Trial File Binder.

The time of vaccination should be documented in the participant's medical record.

Study vaccine will be administered according to the schedule specified in Section 1.3. V110, V114, or placebo should be administered as a single IM injection in the deltoid region of the participant's left arm, while mRNA-1273 should be administered as a single IM injection in the deltoid region of the participant's right arm. mRNA-1273 will be administered open label. Adequate treatment provision, including epinephrine and equipment for maintaining an airway, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

Unblinded study personnel should not have contact with participants for any study-related procedures/assessments after administration of study vaccine, which includes all safety follow-up procedures. All safety and immunogenicity assessments will be conducted by blinded personnel, and the participant will be blinded to the study vaccine received. Vaccination information, such as time of vaccination, must be recorded on the appropriate eCRF as per the data entry guidelines.

8.1.8.1 Timing of Dose Administration

Study vaccines will be administered as indicated in Section 1.3. Vaccinations may be administered at any time of day and without regard to timing of meals.

All participants will be observed for at least 30 minutes after vaccination for any immediate reactions (Section 8.3.4). This observation must be performed by blinded site personnel for all study vaccines (Section 6.3.3).

Participants must be afebrile for at least 72 hours before vaccination (Section 1.3 and Section 8.3.3).

The collection of blood samples and administration of pregnancy tests (if applicable) must be performed before vaccine administration.

8.1.9 Electronic Vaccination Report Card

The eVRC is structured as recommended in the final Food and Drug Administration Patient-reported Outcome Guidance [U.S. Food and Drug Administration 2009].

The participant will use the eVRC to record body temperature (Section 8.3.3), solicited injection-site AEs, and solicited systemic AEs (Section 8.4.9.1). Unsolicited AEs (Section 8.4.9.2), concomitant medications (including use of any analgesic or antipyretic medication), and nonstudy vaccinations (Section 8.1.5.2) will also be reported. 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 review the data captured on the eVRC with the participant as indicated in Section 1.3.

8.1.10 Telephone Contact on Day 10 Postvaccination

Site personnel will contact the participant on Day 10 after each vaccination to review eVRC data. Any differences between eVRC data and AEs entered into the clinical database must be clearly explained in the participant's source documentation.

8.1.11 Telephone Contact Questionnaire

Site personnel will contact the participant approximately 6 months after Visit 1 to collect additional information based on a Telephone Contact Questionnaire provided by the Sponsor. Data to be reported from this discussion will include AESIs, SAEs, and/or any updates to previously reported safety information.

8.1.12 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 withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit 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.

8.1.12.1 Withdrawal From Future Biomedical Research

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

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

8.1.13 Participant Blinding/Unblinding

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

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

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

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

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

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

8.1.14 Calibration of Equipment

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

8.2 Immunogenicity Assessments

Sera from participants will be used to measure pneumococcal vaccine-induced OPA responses and mRNA-1273-induced bAb and nAb responses. These endpoints will be tested for all immunogenicity blood draws specified in Section 1.3. The total amount of blood to be drawn over the course of the study, including approximate blood volumes drawn by visit and by sample type per participant, can be found in Section 8. Blood collection, storage, and shipment instructions for serum samples will be provided in the operations/laboratory manual.

The MOPA will be used for measuring OPA responses. Opsonization of pneumococci for phagocytosis is an important mechanism by which antibodies to polysaccharides protect against disease in vivo. The OPA assay is a useful tool for assessing the protective function of serotype-specific antibodies and, therefore, the immunogenicity of pneumococcal vaccine formulations.

The SARS-CoV-2 ECL assay will be used to measure the concentration of bAbs to the SARS-CoV-2 Spike protein, nucleocapsid, and receptor binding domain.

The SARS-CoV-2 nAb assay will be used to measure nAb activity directed against the SARS-CoV-2 Spike envelope protein.

8.2.1 Multiplex Opsonophagocytic Assay

The MOPA is an antibody-mediated killing assay that measures the ability of human serum to kill S. pneumoniae serotypes with the help of complement and phagocytic effector cells

[Burton, Robert L. and Nahm, Moon H. 2006]. The ability of the assay to simultaneously assess 4 serotypes at a time reduces the amount of serum needed for testing. CCI

CCI

8.2.2 SARS-CoV-2 Electrochemiluminescence Assay

PPD Vaccines Sciences Department 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. CCI

CCI

8.2.3 SARS-CoV-2 Neutralizing Antibody Assay

The PhenoSense® Anti-SARS-CoV-2 Neutralizing Antibody Assay (CoV nAb Assay) has been developed to enable quantitative measurements of nAb activity directed against the SARS-CoV-2 (and SARS-CoV) Spike envelope protein.

CCI

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard before vaccination at Visit 1. A targeted physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard before vaccination at Visit 3. A targeted physical examination includes obtaining vital signs (heart rate, respiratory rate, blood pressure, body temperature) and a physical examination focused on complaints based on medical history. The targeted physical examination should focus on examining systems related to any ongoing conditions and/or follow up on previously reported AEs.

Findings related to the physical examinations should be documented in the source documents. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Pregnancy Testing

A pregnancy test consistent with local requirements (sensitive to at least 25 IU hCG) must be performed before vaccination at Visit 1 and Visit 3 in WOCBP as described in Section 1.3. Urine or serum tests can be used and results must be negative before vaccination can occur. A detailed definition of WOCBP is provided in Appendix 5.

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - 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 subject's participation in the study.

8.3.3 Body Temperature Measurement

Each participant’s body temperature must be taken by study-site staff before each vaccination as described in Section 1.3. Participants who have febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C]; axillary or temporal temperature ≥99.4°F [≥37.4°C]) <72 hours before vaccination must be rescheduled.

Participants will also record oral body temperature measurements using the eVRC (Section 8.1.9) from Day 1 to Day 7 after each vaccination.

8.3.4 Postvaccination Observation Period

All participants will be observed for at least 30 minutes after each vaccination for any immediate reactions. If any immediate AEs 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.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- 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 or within 30 to 44 days after the last dose of study intervention, 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.

8.4 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, but before randomization, must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a

protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

All nonserious AEs and other reportable safety events (excluding pregnancy and lactation exposure) must be reported by the investigator from the day of randomization through 28 days after the first vaccination and from the time of each subsequent vaccination through 28 days postvaccination.

All SAEs and AESIs must be reported by the investigator throughout the duration of the individual's participation in the study, regardless of whether related to the study intervention.

- In this study, myocarditis and pericarditis are always considered to be SAEs. The investigator should ensure that all applicable serious criteria outlined in Appendix 3 are recorded in the study database. Definitions of myocarditis and pericarditis are provided in Appendix 3.
- The list of AESIs for this study is provided in Appendix 3.

All pregnancies and lactation exposure during breastfeeding must be reported by the investigator from the day of randomization through 3 months postvaccination.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

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

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

Type of Event	**Reporting Period: Consent 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
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

DILI=drug-induced liver injury; 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

Not applicable for 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 a VRC 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 4.

Table 4 Solicited Adverse Events

Type of Solicited Adverse Event	Predefined Solicited Adverse Events (Preferred Term)	Solicited Time Period
Injection site	• Injection-site redness (erythema) • Injection-site swelling • Injection-site pain/tenderness • Underarm gland swelling or tenderness (lymphadenopathy)	Day 1 to Day 7 postvaccination
Systemic	• Headache • Tiredness (fatigue) • Muscle aches all over body (myalgia) • Joint pain (arthralgia) • Nausea • Vomiting • Chills	Day 1 to Day 7 postvaccination

8.4.9.2 Unsolicited Adverse Events

Unsolicited AEs for this study are events that are 1) not predefined in Table 4 or 2) predefined in Table 4 but reported at any time outside the solicited time period.

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than 1 dose of any individual study vaccine in any 24-hour period.

No specific information is available on the treatment of overdose.

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

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Future Biomedical Research Sample Collection

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

- DNA for future research
- Leftover serum from immunogenicity testing stored for future research

8.10 Health Economics Medical Resource Utilization and Health Economics

Not applicable.

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

Screening procedures will be conducted at Visit 1 as outlined in Section 1.3. Potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

If Visit 1 is rescheduled (see Section 5.1 and Section 5.2), a review of prior medications/vaccinations and medical history, a complete physical examination, and a body temperature measurement must be repeated before vaccination.

8.11.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3.

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

A participant who discontinues from study intervention will continue to participate in protocol-specified activities as outlined in Section 1.3, including blood draws for immunogenicity testing and AE monitoring activities, as long as the participant does not withdraw consent.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary analyses, or the statistical methods related to those analyses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before unblinding/final database lock, will be documented in an sSAP and referenced in the CSR for the study.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Concomitant Administration of Either 23-Valent Pneumococcal Polysaccharide Vaccine or 15-Valent Pneumococcal Conjugate Vaccine with a Booster Dose of SARS-CoV-2 mRNA-1273 Vaccine in Healthy Adults 50 Years of Age or Older.
Treatment Assignment	Approximately 850 participants will be randomly assigned in a 1:1:1:1 ratio to receive either V110 or V114 with concomitant or nonconcomitant mRNA-1273. Randomization will be stratified by age (50 to 64, 65 to 74, and ≥75 years of age), history of prior pneumococcal vaccination (Yes or No), receipt of prior mRNA-1273 booster dose (Yes, No), and history of prior SARS-CoV-2 infection (Yes, No).
Analysis Populations	Safety: APaT population Immunogenicity: PP population
Primary Endpoint(s)	**Safety** • Proportion of participants with solicited injection-site AEs from Day 1 through Day 7 after any vaccination • Proportion of participants with solicited systemic AEs from Day 1 through Day 7 after any vaccination • Proportion of participants with vaccine-related SAEs from Day 1 through Month 6 **Immunogenicity** • Serotype-specific OPA GMTs at 30 days postvaccination with V110 • Serotype-specific OPA GMTs at 30 days postvaccination with V114 • SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273
Statistical Methods for Key Immunogenicity Analyses	Immunogenicity analyses will be conducted separately for 14 of 23 pneumococcal serotypes in V110, each of the 15 serotypes in V114 and SARS-CoV-2 of mRNA-1273. To address the primary immunogenicity objective, evaluation of the OPA GMTs or bAb GMTs at 30 days postvaccination receiving V110 or V114 when administered concomitantly or nonconcomitantly with mRNA-1273 will include descriptive summaries and within-group 95% CIs for each vaccination group.

Statistical Methods for Key Safety Analyses	The analysis of safety will follow a tiered approach. Point estimates with the corresponding within-group 95% CIs based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. 1934] will be provided for the proportion of participants with events.
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	**Immunogenicity:** The planned sample size is approximately 850 participants. Participants are to be randomly assigned in a 1:1:1:1 ratio to receive either V110 or V114 with concomitant or nonconcomitant mRNA-1273. It is assumed that 190 participants in each group will be evaluable for PP immunogenicity analyses (90% evaluability rate). There are no hypotheses to be evaluated, but Section 9.9.1 provides information about the expected variability of the OPA GMTs of V110/V114 and bAb GMTs of mRNA-1273. **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 for V114 and V110.

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 will be conducted as a double-blind study under in-house blinding procedures.

The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

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

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

9.4.1 Immunogenicity Endpoints

A description of the immunogenicity assays is provided in Section 8.2.

For endpoints related to V110 and V114, immune responses will be measured for serotypes included in the validated MOPA. This includes 14 of 23 serotypes contained in V110 (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) and all 15 serotypes included in V114 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F).

The primary immunogenicity endpoints include:

- Serotype-specific OPA GMTs at 30 days postvaccination with V110
- Serotype-specific OPA GMTs at 30 days postvaccination with V114
- SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273

The secondary immunogenicity analysis endpoints include:

- Serotype-specific GMFRs and proportions of participants with a 4-fold rise from baseline (prevaccination with V110) to 30 days postvaccination with V110 for OPA responses
- Serotype-specific GMFRs and proportions of participants with a 4-fold rise from baseline (prevaccination with V114) to 30 days postvaccination with V114 for OPA responses
- GMFRs and proportions of participants with a ≥4-fold rise from baseline (prevaccination with mRNA-1273) to 30 days postvaccination with mRNA-1273 for SARS-CoV-2-specific bAb responses

The exploratory immunogenicity analysis endpoints include:

- SARS-CoV-2-specific nAb GMTs at 30 days postvaccination with mRNA-1273

9.4.2 Safety Endpoints

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

The safety endpoints that address the primary objectives include:

- Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, pain/tenderness, underarm gland swelling or tenderness/lymphadenopathy) from Day 1 through Day 7 after any vaccination
- Proportion of participants with solicited systemic AEs (headache, tiredness/fatigue, muscle aches all over body/myalgia, joint pain/arthralgia, nausea, vomiting, chills) from Day 1 through Day 7 after any vaccination
- Proportion of participants with vaccine-related SAEs from Day 1 through Month 6

Additional safety endpoints include:

- Proportion of participants with the broad AE categories of any AE and any vaccine-related AE from Day 1 through Day 28 after any vaccination
- Proportions of participants with the broad AE categories consisting of any AESI, any SAE, discontinuation of study intervention due to an AE, and death from Day 1 through duration of participation in the study

- Proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 7 after any vaccination

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. Potential deviations that may result in the exclusion of a participant from the PP population for immunogenicity analyses include, but are not limited to:

- Failure to receive any study vaccine at Visit 1 (Day 1)
- Failure to receive correct clinical material as per randomization schedule at Visit 1 (Day 1)
- Receipt of a prohibited medication or prohibited vaccine before study vaccination

Additional potential deviations that may result in the exclusion of a participant from the PP population for specific immunogenicity analyses (depending on the time point or specific immunogenicity endpoint) include, but are not limited to:

- Failure to receive any study vaccine at Visit 3 (Day 30)
- Failure to receive correct clinical material as per randomization schedule at Visit 3 (Day 30)
- Receipt of a prohibited medication or prohibited vaccine before a blood sample collection
- Collection of a blood sample outside the prespecified window (as described in Section 1.3)
- Participants who develop COVID-19 during the study

The final determination on protocol deviations that impact the immunogenicity analysis, and thereby the composition of the PP population, will be made before the final unblinding of the database. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the PP population.

A supportive analysis using the FAS population will also be performed for the primary immunogenicity endpoints. The FAS population consists of all randomized participants who received at least 1 study vaccination and have at least 1 serology result. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the FAS population.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study vaccination. Participants will be included in the group corresponding to the study vaccination they actually received. Data for participants who receive the same vaccine at both Visit 1 and Visit 3 (ie, they inadvertently receive 2 doses of V110, 2 doses of V114, 2 dose of mRNA-1273, or 2 doses of placebo) will be excluded from the APaT and will be summarized separately.

At least 1 temperature measurement obtained after administration of study intervention is required for inclusion in the analysis of temperature.

9.6 Statistical Methods

9.6.1 Statistical Methods for Immunogenicity Analyses

Primary Endpoints

Immunogenicity analyses will be conducted for each of the 14 of 23 pneumococcal serotypes in V110 and for each of the 15 serotypes in V114 separately. To address the primary immunogenicity objective, evaluation of the OPA GMTs at 30 days postvaccination with V114 or V110 will include descriptive summaries and within-group 95% CIs for each vaccination group. The point estimates will be calculated by exponentiating the estimates of the mean of the natural log values, and the within-group CIs will be derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

Similarly, evaluation of the SARS-CoV-2-specific bAb GMT at 30 days postvaccination with mRNA-1273 will include descriptive summaries and within-group 95% CIs for each vaccination group. The V110 nonconcomitant group and V114 nonconcomitant group will be combined, as they share the same administration for the first visit (mRNA-1273 and placebo).

Secondary/Exploratory Endpoints

Descriptive statistics with point estimates and within-group 95% CIs will be provided for all other immunogenicity endpoints. For the continuous endpoints, a similar statistical approach described in the primary objective will be used. For the dichotomous endpoints, the within-group CIs will be calculated based on the exact method proposed by Clopper and Pearson [Clopper, C. J. 1934].

Reverse Cumulative Distribution Curves for OPA titers at 30 days postvaccination with V110 and V114 will be graphically displayed by serotype. Reverse Cumulative Distribution Curves for SARS-CoV-2-specific bAb titers at 30 days postvaccination with mRNA-1273 will be graphically displayed.

A detailed analysis strategy for key immunogenicity endpoints is listed in Table 5.

Table 5 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Endpoints				
OPA GMTs at 30 days postvaccination with V110	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
OPA GMTs at 30 days postvaccination with V114	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
bAb GMTs at 30 days postvaccination with mRNA-1273	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints				
GMFRs and proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination with V110 for OPA responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
GMFRs and proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination with V114 for OPA responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
GMFRs and proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination with mRNA-1273 for SARS-CoV-2-specific bAb responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

bAb=binding antibody; CI=confidence interval; FAS=full analysis set; GMFR=geometric mean fold rise; GMT=geometric mean titer; OPA=opsonophagocytic activity; P=primary; PP=per-protocol; S=supportive.
[a] The statistical methods for immunogenicity are described in Section 9.6.1.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements. The primary safety analysis will consist of safety summaries for all safety endpoints after any vaccination. Separate summaries will be provided for the V110 concomitant and V110 nonconcomitant groups and for the V114 concomitant and V114 nonconcomitant groups.

The V110 nonconcomitant group and the V114 nonconcomitant group will be combined to summarize the safety results following vaccination 1 as they share the same vaccinations (mRNA-1273 and placebo) at Day 1. The V110 concomitant group and the V114 concomitant group will be combined to summarize the safety results following vaccination 2 as they share the same vaccinations (placebo alone) at Day 30.

The analysis of AEs and temperature measurements will follow a tiered approach (Table 6). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as

well as SOC terms) are either prespecified as Tier 1 events or will be classified as belonging to Tier 2 or Tier 3 based on the number of events observed.

Tier 1 Events

Safety events or AESI that are identified a priori constitute Tier 1 events that will be subject to inferential testing for statistical significance. No Tier 1 events are defined for this study.

Tier 2 Events

Tier 2 events will be assessed via point estimates with the corresponding within-group 95% CIs based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. 1934].

For this study, solicited injection-site AEs, solicited systemic AEs, and body temperature measurements collected from Day 1 though Day 7 postvaccination are considered Tier 2 events. In addition, the broad AE categories consisting of the proportion of participants with any AE, any vaccine-related AE, any AESI, any SAE, any vaccine-related SAE, discontinuation of study intervention due to an AE, and death will be considered Tier 2 events. Nonserious AEs will be followed for 28 days after each vaccination and AESIs and SAEs will be followed through the duration of participation in the study.

Tier 3 Events

Events not defined above are considered Tier 3 events. Only point estimates by treatment group will be provided for Tier 3 events.

Table 6 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoints	Within Group[a] 95% CI	Descriptive Statistics
Tier 2	Solicited injection-site AE (redness/erythema, swelling, pain/tenderness, underarm gland swelling or tenderness/lymphadenopathy from Days 1 through Day 7 after any vaccination)	X	X
	Solicited systemic AE (headache, tiredness/fatigue, muscle aches all over body/myalgia, joint pain/arthralgia, nausea, vomiting, chills from Days 1 through Day 7 after any vaccination)	X	X
	Any vaccine-related SAE[b,c]	X	X
	Any AE[b]	X	X
	Any vaccine-related AE[b,c]	X	X
	Any AESI[d]	X	X
	Any SAE[b]	X	X
	Discontinuation of study intervention due to an AE[b]	X	X
	Death[b]	X	X
	Maximum temperature measurements (Days 1 to Day 7)	X	X
Tier 3	AEs by SOC and PT[e]	-	X

Safety Tier	Safety Endpoints	Within Groupa 95% CI	Descriptive Statistics
AE=adverse event; AESI=adverse event of special interest; CI=confidence interval; PT=preferred term; SAE=serious adverse event; SOC=system organ class; X=results will be provided. a Within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. 1934]. b These endpoints are broad AE categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least 1 AE. c Determined by the investigator to be vaccine-related. d A list of AESIs pertaining to the safety evaluation of mRNA-1273 is provided in Appendix 3. This list is consistent with the safety evaluation of mRNA-1273 in Phase 3 studies per regulatory guidance. e Includes only those endpoints not prespecified as Tier 2 endpoints.			

In addition to the primary safety analysis following any vaccination, a supportive analysis of select safety endpoints will be provided after each vaccination. Point estimates by vaccination group will be provided for injection-site AEs following V110, V114, mRNA-1273, and placebo separately. That is, the proportion of participants with injection-site AEs after administration of V110 or V114 will include AEs reported from Day 1 through Day 7 after V110 or V114 administration in the limb corresponding to the location of V110 or V114 administration. Similarly, the proportion of participants with injection-site AEs after administration of mRNA-1273 will include AEs reported from Day 1 through Day 7 after mRNA-1273 administration in the limb corresponding to the location of mRNA-1273 administration. The proportion of participants with injection-site AEs after administration of placebo will include both the V110 and V114 nonconcomitant groups for AEs reported from Day 1 through Day 7 after Visit 1 and both the V110 and V114 concomitant groups for AEs reported from Day 1 to Day 7 after Visit 3.

Additionally, descriptive summaries of systemic AEs reported from Day 1 through Day 7 will be summarized following administration of:

- V110 and mRNA-1273 in the concomitant group at Visit 1 (Day 1)
- V114 and mRNA-1273 in the concomitant group at Visit 1 (Day 1)
- mRNA-1273 with placebo in both the V110 nonconcomitant group and V114 nonconcomitant group at Visit 1 (Day 1)
- V110 alone in the nonconcomitant group at Visit 3 (Day 30)
- V114 alone in the nonconcomitant group at Visit 3 (Day 30)
- Placebo alone in both the V110 concomitant group and V114 concomitant group at Visit 3 (Day 30)

Safety analyses will be based on the observed data (ie, with no imputation of missing data).

9.6.3 Demographic and Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed by the use of summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, and gender), baseline characteristics, and prior and concomitant vaccinations and therapies will be summarized by vaccination group either by descriptive statistics or categorical tables.

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 Analyses

This is a descriptive study. This study will randomize 212 participants into each V110 and V114 concomitant group and 212 participants into each V110 and V114 nonconcomitant group. It is assumed that approximately 190 in each group will be evaluable for PP immunogenicity analyses (based on a 90% evaluability rate).

The width of the within-group 95% CIs for the serotype-specific OPA GMTs and SARS-CoV-2-specific bAb GMTs depend on the sample size, variability of the natural log concentrations, and the magnitude of the OPA or bAb GMTs. In Table 7, 95% CIs for various hypothetical OPA and bAb GMTs and various hypothetical standard deviation estimates for the natural log titers are displayed.

Table 7 Within-group 95% CIs for Varying OPA/bAb GMTs and Standard Deviations

SD of Natural log Titers	Serotype-specific OPA GMT or SARS-CoV-2-specific bAb GMT					
	500		1000		5000	
	V110/V114	mRNA-1273	V110/V114	mRNA-1273	V110/V114	mRNA-1273
1.0	(433, 577)	-	(867, 1154)	-	(4333, 5768)	-
1.5	(403, 620)	(403, 620)	(807, 1239)	(807, 1239)	(4034, 6197)	(4034, 6197)
2.0	(376, 666)	-	(751, 1331)	-	(3756, 6657)	-

bAb=binding antibody; CI=confidence interval; GMT=geometric mean tier; OPA=opsonophagocytic activity; SD=standard deviation.
Based on 190 evaluable participants in each of the group.
The estimates of the standard deviation and OPA GMTs are representative of those observed in V114-019 and V110-029, which is between 1 to 2. The estimates of the standard deviation of SARS-CoV-2 specific bAb is representative of those observed in mRNA-1273 studies, which is around 1.5.

9.9.2 Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying incidence of participants with a SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 212 participants in each of the concomitant/nonconcomitant groups if the underlying incidence of a SAE is 0.76% (1 of every 132 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 212 participants in each of the concomitant/nonconcomitant groups if the underlying incidence of a SAE is 0.33% (1 of every 303 participants receiving the vaccine). If no SAEs are observed among 212 participants in each of the concomitant/nonconcomitant groups, this study will provide 97.5% confidence that the underlying percentage of participants with a SAE is <1.73% (1 in every 58 participants).

9.10 Subgroup Analyses

Subgroup analyses will be performed for the primary immunogenicity endpoints and selected safety endpoints (summary of AEs and summary of solicited AEs). Subgroup classification variables include age (50 to 64 years, 65 to 74 years, and ≥75 years), sex, race, ethnicity, prior pneumococcal vaccination (Yes or No), receipt of prior mRNA-1273 booster dose (Yes or No) and history of prior SARS-CoV-2 infection (Yes or No). The 95% CI will only be calculated if there are more than 10 participants in each vaccination group for each subgroup.

9.11 Compliance (Medication Adherence)

Compliance will not be calculated as participants will receive a single dose of V110 or V114 and a single dose of mRNA-1273. The number and proportion of randomized participants receiving each vaccination will be summarized (Section 9.12).

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V110, the number and proportion of randomized participants administered V114, and the number and proportion of randomized participants administered mRNA-1273.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

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

enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript.

All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, 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 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.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical 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.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, 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.

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study

completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)
Other Screening Tests	• FSH (as needed in WONCBP only)
FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.	

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent 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.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a VRC and that is communicated by a participant/participant's legally authorized representative who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.

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

Definition of AESI

- AESIs for this study are consistent with regulatory guidance for the safety evaluation of COVID-19 vaccines, including mRNA-1273. The list of AESIs for this study is provided below.
- Events falling into the descriptions below should be reported as AESIs even when they occur during/following SARS-CoV-2 infection.

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

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.

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/Placebo[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/placebo				
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	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
Other	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
Any injection-site reaction that begins ≥8 days after receipt of study vaccine/placebo				
Pain/Tenderness Erythema/Redness Swelling Lymphadenopathy Other	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 on information provided by the participant on the eVRC and verbally during VRC review. Erythema/Redness and Swelling are specific injection-site AEs with size designations of letters A (<2.5 cm), B (2.5 to 5 cm), C (5.1 to 7.4 cm), D (7.5 to 10 cm), or E (>10 cm), based on a graphic in the eVRC. If the participant has an ED 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.

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	ED visit or hospitalization

AE=adverse event; ED=emergency department; IV=intravenous.

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 their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

10.3.5 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

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

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

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c] • IUS[d] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. • Male and female condom should not be used together (due to risk of failure with friction).

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
ACE2	Angiotensin-converting enzyme 2
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ARDS	adult respiratory distress syndrome
AST	aspartate aminotransferase
bAb	binding antibody
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	confidence interval
cLDA	constrained longitudinal data analysis
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
CTFG	Clinical Trials Facilitation Group
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	events of clinical interest
ECL	electrochemiluminescence
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Authorization
eVRC	electronic Vaccination Report Card
FAS	Full Analysis Set
FBR	future biomedical research

Abbreviation	Expanded Term
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
hCG	human chorionic gonadotropin
HEK293	Human embryonic kidney 293
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular
IPD	invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
MOPA	multiplexed opsonophagocytic assay
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
PK	pharmacokinetic
PP	Per-protocol
PQC	product quality complaint
RNA	ribonucleic acid
SAE	serious adverse event

Abbreviation	Expanded Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SLAB	supplemental laboratory test
SoA	Schedule of Activities
SOC	system organ class
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TMPRSS2	Transmembrane serine protease 2
US	United States
V110	PNEUMOVAX™23 (Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F)
V114	VAXNEUVANCE™ (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F)
VRC	vaccination report card
WOCBP	woman (or women) of childbearing potential
WONCBP	woman (or women) of nonchildbearing potential

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