Official Protocol Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Children and Adolescents With Increased Risk of Pneumococcal Disease
NCT number:	NCT06177912
Document Date:	20-Feb-2024

TITLE PAGE

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Children and Adolescents With Increased Risk of Pneumococcal Disease

Protocol Number: 013-01

Compound Number: V116

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	Pending
EU CT	2023-506236-32
EudraCT	Not applicable
jRCT	Pending
WHO	Not applicable
UTN	U1111-1293-4944
IND	19316

Approval Date: 20 February 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 1	20-FEB-2024	The reason for this amendment is to address health authority feedback.
Original Protocol	18-SEP-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendment:

The reason for this amendment is to address health authority feedback.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 10.7.2, EEA-specific Requirements	Added new section providing EEA-specific requirements for: • Exclusion Criteria 17 and 18, • maximum blood volumes, and • contraceptive requirements.	This change was made to address health authority feedback to align the protocol with requirements for EEA countries.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 10.2, Appendix 2: Clinical Laboratory Tests	Added a footnote to Table 8 to specify that maximum blood volumes should follow local guidelines/recommendations, if specified.	Refer to Section 10.7.2 rationale.
	Added a reference to Appendix 7 for EEA-specific requirements.	Refer to Section 10.7.2 rationale.
Section 10.5.2, Contraceptive Requirements	Added a reference to Appendix 7 for EEA-specific requirements.	Refer to Section 10.7.2 rationale.

TABLE OF CONTENTS

DOCUMENT HISTORY **3**
PROTOCOL AMENDMENT SUMMARY OF CHANGES **3**
1 PROTOCOL SUMMARY **11**
1.1 Synopsis **11**
1.2 Schema **15**
1.3 Schedule of Activities **16**
2 INTRODUCTION **18**
2.1 Study Rationale **18**
2.2 Background **19**
2.2.1 Pharmaceutical and Therapeutic Background 20
2.2.2 Information on Other Study-related Therapy 20
2.2.2.1 PPSV23 20
2.2.2.2 Pneumococcal Vaccination Guidelines 21
2.3 Benefit/Risk Assessment **22**
3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS **23**
4 STUDY DESIGN **25**
4.1 Overall Design **25**
4.2 Scientific Rationale for Study Design **26**
4.2.1 Rationale for Endpoints 27
4.2.1.1 Safety Endpoints 27
4.2.1.2 Immunogenicity Endpoints 27
4.2.1.3 Future Biomedical Research 28
4.2.2 Rationale for the Use of Comparator 28
4.3 Justification for Dose **28**
4.4 Beginning and End-of-Study Definition **29**
4.4.1 Clinical Criteria for Early Study Termination 29
5 STUDY POPULATION **30**
5.1 Inclusion Criteria **30**
5.2 Exclusion Criteria **32**
5.3 Lifestyle Considerations **34**
5.4 Screen Failures **34**
5.5 Participant Replacement Strategy **34**
6 STUDY INTERVENTION **35**
6.1 Study Intervention(s) Administered **35**
6.1.1 Drug-Device Combination Products/Combination Medicinal Products 37
6.2 Preparation/Handling/Storage/Accountability **37**
6.2.1 Dose Preparation 37

6.2.2 Handling, Storage, and Accountability 37
6.3 Measures to Minimize Bias: Randomization and Blinding 38
6.3.1 Intervention Assignment 38
6.3.2 Stratification 38
6.3.3 Blinding 39
6.4 Study Intervention Compliance 39
6.5 Concomitant Therapy 39
6.5.1 Rescue Medications and Supportive Care 40
6.6 Dose Modification 40
6.6.1 Stopping Rules 40
6.7 Intervention After the End of the Study 40
6.8 Clinical Supplies Disclosure 40
6.9 Standard Policies 41
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL 42
7.1 Discontinuation of Study Intervention 42
7.2 Participant Withdrawal From the Study 42
7.3 Lost to Follow-up 42
8 STUDY ASSESSMENTS AND PROCEDURES 43
8.1 Administrative and General Procedures 43
8.1.1 Informed Consent 43
8.1.1.1 General Informed Consent 43
8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 44
8.1.2 Inclusion/Exclusion Criteria 44
8.1.3 Participant Identification Card 44
8.1.4 Medical History 45
8.1.5 Prior and Concomitant Medications Review 45
8.1.5.1 Prior Medications 45
8.1.5.2 Concomitant Medications 45
8.1.6 Assignment of Screening Number 45
8.1.7 Assignment of Randomization Number 46
8.1.8 Study Intervention Administration 46
8.1.8.1 Timing of Dose Administration 46
8.1.9 Telephone Contact Questionnaire 47
8.1.10 Electronic Vaccination Report Card 47
8.1.11 Discontinuation and Withdrawal 47
8.1.11.1 Withdrawal From Future Biomedical Research 47
8.1.12 Participant Blinding/Unblinding 48

8.1.13 Calibration of Equipment....49
8.2 Immunogenicity Assessments....49
8.2.1 Multiplex Opsonophagocytic Assay....49
8.2.2 Pneumococcal Electrochemiluminescence Assay....50
8.3 Safety Assessments....50
8.3.1 Physical Examinations....50
8.3.2 Clinical Safety Laboratory Assessments....51
8.3.3 Pregnancy Testing....51
8.3.4 Body Temperature Measurement....51
8.3.5 Postvaccination Observation Period....52
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events....52
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information....52
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events....54
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information....55
8.4.4 Regulatory Reporting Requirements for SAE....55
8.4.5 Pregnancy and Exposure During Breastfeeding....55
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs....56
8.4.7 Events of Clinical Interest....56
8.4.8 Drug-device Combination Products/Combination Medicinal Products – Complaints, PQCs, and Malfunctions....56
8.4.9 Adverse Events on the VRC....56
8.4.9.1 Solicited Adverse Event....56
8.4.9.2 Unsolicited Adverse Events....57
8.5 Treatment of Overdose....57
8.6 Pharmacokinetics....57
8.7 Pharmacodynamics....57
8.8 Biomarkers....57
8.9 Future Biomedical Research Sample Collection....57
8.10 Medical Resource Utilization and Health Economics....58
8.11 Visit Requirements....58
8.11.1 Screening....58
8.11.2 Treatment Period/Vaccination Visit....58
9 KEY STATISTICAL CONSIDERATIONS....59
9.1 Responsibility for Analyses/In-house Blinding....59
9.2 Hypotheses/Estimation....59
9.3 Analysis Endpoints....59

9.3.1 Immunogenicity Endpoints 59
9.3.2 Safety Endpoints 60
9.4 Analysis Populations 60
9.4.1 Immunogenicity Analysis Populations 60
9.4.2 Safety Analysis Populations 61
9.5 Statistical Methods 61
9.5.1 Statistical Methods for Immunogenicity Analyses 61
9.5.2 Statistical Methods for Safety Analyses 64
9.5.2.1 Overall Safety Assessment 64
9.6 Interim Analyses 65
9.7 Multiplicity 66
9.8 Sample Size and Power Calculations 66
9.8.1 Sample Size and Power for Immunogenicity Analyses 66
9.8.2 Sample Size and Power for Safety Analyses 67
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 69
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 69
10.1.1 Code of Conduct for Interventional Clinical Trials 69
10.1.2 Financial Disclosure 72
10.1.3 Data Protection 73
10.1.3.1 Confidentiality of Data 73
10.1.3.2 Confidentiality of Participant Records 73
10.1.3.3 Confidentiality of IRB/IEC Information 74
10.1.4 Committees Structure 74
10.1.4.1 Executive Oversight Committee 74
10.1.4.2 External Data Monitoring Committee 74
10.1.4.3 Scientific Advisory Committee (SAC) 74
10.1.5 Publication Policy 75
10.1.6 Compliance with Study Registration and Results Posting Requirements 75
10.1.7 Compliance with Law, Audit, and Debarment 75
10.1.8 Data Quality Assurance 76
10.1.9 Source Documents 77
10.1.10 Study and Site Closure 77
10.2 Appendix 2: Clinical Laboratory Tests 78
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 79
10.3.1 Definitions of Medication Error, Misuse, and Abuse 79
10.3.2 Definition of AE 79
10.3.3 Definition of SAE 80

10.3.4 Additional Events Reported 81
10.3.5 Recording AE and SAE 81
10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor 86
10.4 Appendix 4: Drug-Device Combination Products/ Combination Medicinal Products: Complaints, Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up 88
10.4.1 Definitions 88
10.4.2 Recording, Assessing Causality, and Follow-up of PQCs/Malfunctions 89
10.5 Appendix 5: Contraceptive Guidance 91
10.5.1 Definitions 91
10.5.2 Contraceptive Requirements 92
10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research 93
10.7 Appendix 7: Country-specific Requirements 97
10.7.1 Country-specific Requirements for Japan 97
10.7.2 EEA-specific Requirements 98
10.8 Appendix 8: Abbreviations 100
11 REFERENCES 103

LIST OF TABLES

Table 1 Study Interventions 36
Table 2 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events 53
Table 3 Solicited Adverse Events for V116-013 57
Table 4 Analysis Strategy for Immunogenicity Variables 63
Table 5 Analysis Strategy for Safety Parameters 65
Table 6 Differences in Incidence of Adverse Event Rates Between the 2 Vaccination Groups That Can be Detected With an Approximately 80% Probability 68
Table 7 Protocol-required Safety Laboratory Assessments 78
Table 8 Blood Volumes Collected by Visit for Immunogenicity Assessments 78
Table 9 Injection-site AE Overall Intensity Grading Scale 82
Table 10 Specific Systemic AE Overall Intensity Grading Scale 83
Table 11 Other Systemic AE Overall Intensity Grading Scale 84
Table 12 Vital Sign (Temperature) Overall Intensity Grading Scale 84

LIST OF FIGURES

Figure 1 Schema 15

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Children and Adolescents With Increased Risk of Pneumococcal Disease

Short Title: Safety and Immunogenicity of V116 in Children and Adolescents With Increased Risk for Pneumococcal Disease

Acronym: STRIDE-13

Hypotheses, Objectives, and Endpoints:

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

Primary Objective	Primary Endpoint
To evaluate the safety and tolerability of V116 with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs Day 1 through Day 5 postvaccination • Solicited systemic AEs Day 1 through Day 5 postvaccination • Vaccine-related serious AEs (SAEs) Day 1 through the duration of participation in the study
To compare the serotype-specific opsonophagocytic (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V116 versus PPSV23. **Hypothesis (H1):** V116 is noninferior to PPSV23 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 12 common serotypes in V116 and PPSV23. (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval [CI] of the OPA GMT ratio [V116/PPSV23] to be >0.5.) **Hypothesis (H2):** V116 is superior to PPSV23 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 9 unique serotypes in V116. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V116/PPSV23] to be >2.0.)	Serotype-specific OPA responses

Secondary Objectives	**Secondary Endpoints**
To evaluate the serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days postvaccination with V116 compared with PPSV23.	Serotype-specific IgG responses
To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise in serotype-specific OPA responses and IgG responses from baseline to 30 days postvaccination within each vaccination group.	Serotype-specific OPA and IgG responses

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal infection
Population	Children and adolescents ≥2 to <18 years of age with increased risk for pneumococcal disease.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active Control Without Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects Care Provider Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 13 months 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 820 participants will be randomized, with approximately 492 participants in the V116 intervention group and 328 participants in the PPSV23 intervention group.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
V116	Pneumococcal 21-valent conjugate vaccine	4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product
PPSV23	Pneumococcal Vaccine, Polyvalent (23-valent)	25 µg of each PnPs antigen (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F)	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Comparator

EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PnPs=pneumococcal polysaccharide; PPSV23=pneumococcal vaccine, polyvalent (23-valent) (PNEUMOVAX™23); V116=pneumococcal 21-valent conjugate vaccine.

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.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: V116: polyvalent pneumococcal conjugate vaccine (pPCV).

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study for at least 6 months from the time the participant or participant's legally acceptable representative provides documented informed consent/assent through the final contact or discontinuation from the study.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

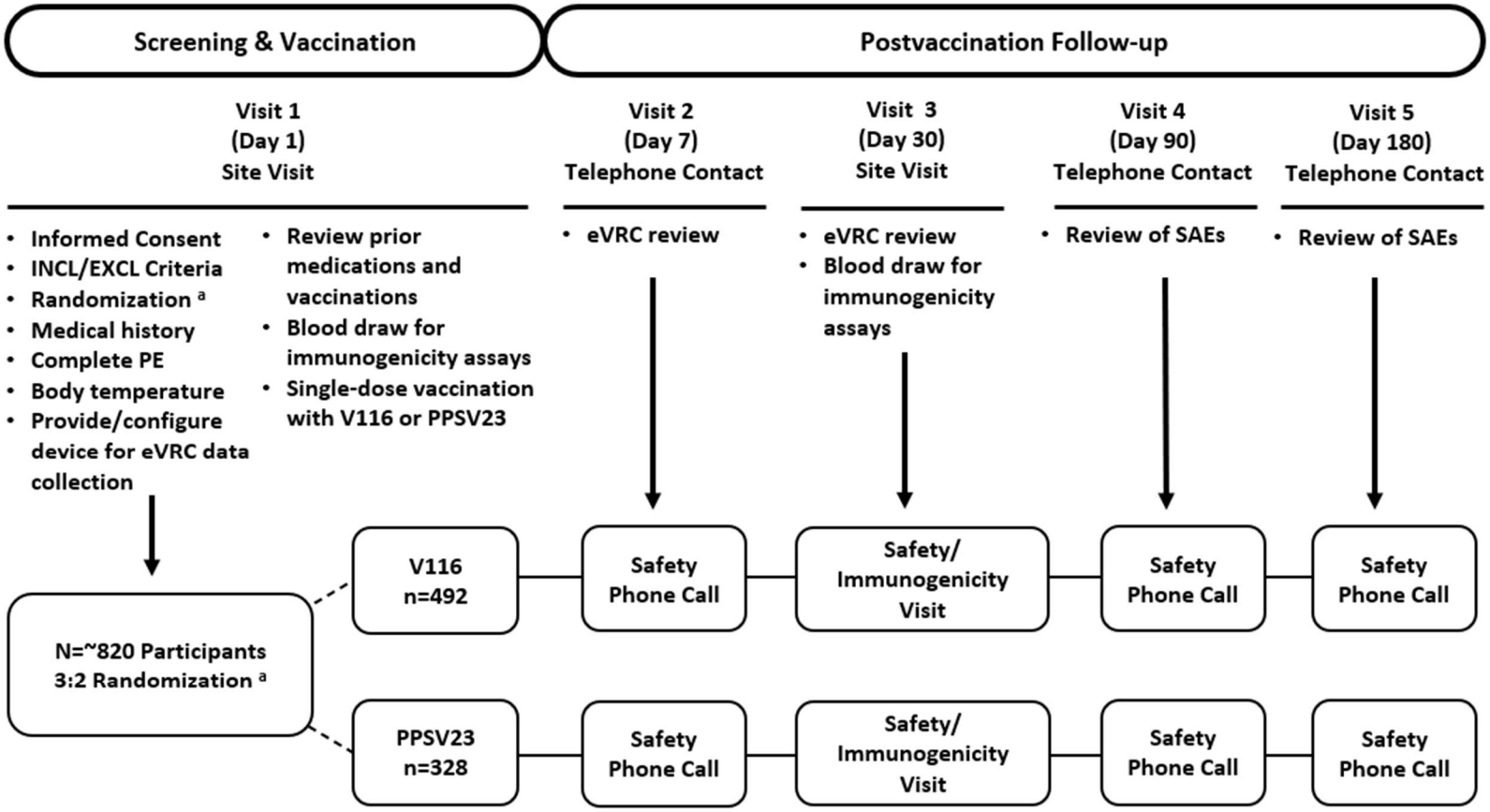
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Schema



eVRC = electronic Vaccination Report Card; INCL/EXCL = inclusion/exclusion; PE = physical examination; SAE = serious adverse event

[a] Randomization will be stratified by number of increased-risk conditions for pneumococcal disease and by prior pneumococcal vaccination and age.

1.3 Schedule of Activities

Study Period:	**Intervention and Follow-up**					**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	
Visit Type:	**Visit**	**TC**	**Visit**	**TC**	**TC**	
Study Day:	**Day 1**	**Day 7**	**Day 30**	**Day 90**	**Day 180**	
Visit Window:	-	Day 7 to Day 10	Day 30 to Day 44	Day 76 to Day 104	Day 166 to Day 194	
Administrative Procedures						
Screening Procedures						
Informed Consent/Assent	X					Must be obtained before any study procedures are conducted.
Informed Consent/Assent for Optional FBR	X					Must be obtained before FBR sample collection.
Assignment of Screening Number	X					
Participant Identification Card	X					
Inclusion/Exclusion Criteria	X					
Medical History	X					
Postrandomization Procedures						
Assignment of Randomization Number	X					
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	X	X	
V116/PPSV23 Administration (blinded)	X					
Provide Electronic Device (if needed) or Configure Device (Personal or Provisioned) for eVRC Data Collection	X					Instructions for using the eVRC will be reviewed with the participant or participant's legally acceptable representative.
Review eVRC Data With Participant or Participant's LAR		X	X			
Collect Electronic Device From Participant or Participant's Legally Acceptable Representatives Who Received an Electronic Device or Deactivate Personal Devices			X			
Complete Telephone Contact Questionnaire				X	X	
Safety Procedures						
Complete Physical Examination	X					Performed by investigator or medically qualified designee before vaccination.
Pregnancy Test (if applicable)	X					Participants of childbearing potential must have a negative urine or serum test (consistent with local requirements and sensitive to ≤25 IU hCG) result before vaccination.

Study Period:	**Intervention and Follow-up**					**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	
Visit Type:	**Visit**	**TC**	**Visit**	**TC**	**TC**	
Study Day:	**Day 1**	**Day 7**	**Day 30**	**Day 90**	**Day 180**	
Visit Window:	-	Day 7 to Day 10	Day 30 to Day 44	Day 76 to Day 104	Day 166 to Day 194	
Body Temperature Measurement	X					Measured before vaccination. Participants with febrile illness (temperature ≥100.4°F [≥38.0°C]) within 72 hours before vaccination must be rescheduled.
Postvaccination Observation Period	X					Observed by blinded study-site personnel for at least 30 minutes postvaccination.
AE Monitoring	X	X	X	X	X	Nonserious AEs collected through Day 30 postvaccination; all SAEs and deaths collected through Day 180.
Immunogenicity Assessments						
Serum for Immunogenicity Assays	X		X			Visit 1 sample should be collected before vaccination.
Future Biomedical Research						
Collect Buccal Swab for FBR	X					Buccal swab DNA samples for analysis should be obtained prior to the vaccination on Visit 1, on randomized and FBR consented/assented participants only, or at a later date as soon as the informed consent/assent is obtained.

AE=adverse event; DNA=deoxyribonucleic acid; eVRC=electronic vaccination report card; FBR=future biomedical research; hCG=human chorionic gonadotropin; IU=international units; LAR=legally acceptable representative; PPSV23=pneumococcal vaccine, polyvalent (23-valent) (PNEUMOVAX™23); SAE=serious adverse event; TC=telephone contact; V116=pneumococcal 21-valent conjugate vaccine.

2 INTRODUCTION

The Sponsor is developing an investigational polyvalent pneumococcal 21-valent conjugate vaccine (V116) for the prevention of pneumococcal disease caused by the serotypes in the vaccine.

2.1 Study Rationale

Streptococcus pneumoniae is a major cause of vaccine-preventable disease worldwide. It is associated with considerable morbidity and mortality, with the highest burden in children <5 years and adults ≥70 years of age [Troeger, C., et al 2018]. Vaccines directed against *S pneumoniae* have reduced the incidence of disease caused by vaccine serotypes in the age groups being vaccinated (primarily children <5 years of age in most countries) and have reduced vaccine type disease in other age groups (indirect effect).

Both adults and children with certain underlying medical conditions are at higher risk for pneumococcal disease compared to their healthy counterparts, even with widespread use of PCVs (Section 2.2.1). Populations at higher risk for pneumococcal disease can be further classified as immunocompetent at increased risk (individuals with chronic comorbid conditions such as chronic heart disease, chronic lung disease, and diabetes mellitus); and high-risk (individuals with immunocompromising conditions such as nephrotic syndrome or on immunosuppressive therapy) [Pelton, S. I., et al 2015]. Patients with chronic kidney failure, cerebrospinal fluid leaks, or cochlear transplants are often classified as high-risk. A retrospective cohort analysis of children <18 years of age during 2007–2010 found that the incidence rate ratios for IPD of at-increased-risk children and high-risk children compared to children without risk factors were 1.8 to 3.3 (<5 years of age) and 11.2 to 40.1 (5 to 17 years of age), respectively [Pelton, S. I., et al 2014].

Children with chronic comorbid conditions remain at increased risk due to non-vaccine serotypes and/or limited vaccine efficacy. During the post-PCV13 era, IPD cases among children with comorbidities (mainly immunosuppression due to primary immunodeficiency, immunosuppressive, or radiation therapies and chronic respiratory diseases, including asthma) caused by non-PCV13 serotypes accounted for the majority of cases. PPSV23-only serotypes were responsible for 50% of cases, and non-vaccine serotypes were responsible for the remaining 50%, with serotypes 11A and 15B (PPSV23 serotypes) and 6C, 23A, and 35B (non-vaccine serotypes) predominating [Lagousi, T., et al 2021].

Children and adolescents at increased risk for pneumococcal disease may benefit from receiving V116, as V116 has the potential to provide broader protection against pneumococcal disease compared with currently licensed pneumococcal vaccines, and complement the protection afforded by primary pneumococcal vaccination regimens (Section 2.2.2.2). V116 offers additional advantages due to being a conjugate vaccine, which includes improved immune and memory response, longer lasting protection, potential for herd immunity, and improved immunogenicity in children [World Health Organization 2021] [Goldblatt, D. 2000].

This clinical study is designed to evaluate the safety, tolerability, and immunogenicity of a single dose of V116 in children and adolescents at increased risk for pneumococcal disease. This study will be conducted in children and adolescents ≥2 to <18 years of age who have completed a primary pneumococcal vaccination regimen and who are at increased risk of pneumococcal disease due to chronic medical conditions, including: chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and chronic kidney disease. These chronic medical conditions were selected for inclusion based on their overall prevalence in a significant proportion of the overall pediatric population in the EU and US compared to other increased-risk or high-risk conditions [Sahota, A. K., et al 2020] [Bell, R. A., et al 2009] [Schwimmer, J. B., et al 2006] [Chen, M. Y., et al 2018] [Temple, J. L., et al 2016] [Zahran, H. S., et al 2018] [Mayer-Davis, E. J., et al 2018] [Lascar, N., et al 2018] [Bloom, C. I., et al 2019] [Viasus, D., et al 2011]. Vaccination recommendations for individuals with these conditions are generally aligned in the guidelines in the US, EU, and many other countries globally. While guidelines typically also include children with cerebrospinal fluid leaks and cochlear implants as being immunocompetent but with increased risk, these conditions are not included in this study due to their low prevalence in the population.

Additionally, individuals considered to be immunocompromised will not be included in this study. Data generated from V116 in the increased-risk children without immunocompromising conditions are anticipated to be applicable to the immunocompromised risk groups of children. Based on prior experience with PCVs and current pneumococcal vaccination guidelines for at-risk children, which recommend vaccination of some risk groups based on data from studies of other risk conditions, it is expected that V116 data may be generalizable to other at-risk populations, including immunocompromised children. Both PCV7 and PCV13 were evaluated in children with HIV and nephrotic syndrome, and were found to be generally safe and well tolerated [Liakou, C. D., et al 2011] [Nunes, M. C. 2012]. Randomized, controlled studies evaluated the immunogenicity and safety of PCV15 compared with PCV13 in persons aged 5–17 years with sickle cell disease [Quinn, C. T., et al 2023], and persons aged 6–17 years living with HIV infection [Wilck, M., et al 2023] and was found to be safe and immunogenic in both populations. PCV20 was recently approved in all children including at-risk and immunocompromised children based on data from healthy children and prior experience from PCV13 [Kobayashi, M. 2023].

2.2 Background

To date, the following studies have been completed with V116 in adults:

- Phase 1/2 study (V116-001)
- Phase 1 study in Japan (V116-002)
- 4 Phase 3 studies (V116-003, V116-004, V116-005, V116-006)

Results from Phase 1, 2, and 3 studies showed that V116 is immunogenic and has acceptable safety and tolerability in adults. Refer to the IB for detailed background information on V116.

2.2.1 Pharmaceutical and Therapeutic Background

Pneumococcal disease (disease caused by *S pneumoniae*) continues to be a major cause of vaccine-preventable disease worldwide, resulting in considerable morbidity and mortality in both children and adults. Humans are the sole reservoir of *S pneumoniae* and the bacteria reside in the nasopharynx. It is estimated that in the year 2000, there were 14.5 million cases of pneumococcal disease worldwide and approximately 800,000 children <5 years of age died of the disease [O'Brien, K., et al 2009]. In particular, older adults (≥65 years of age), infants (<1 year of age) and individuals, including children, with certain medical conditions (eg, chronic lung disease, chronic liver disease, chronic heart disease, diabetes mellitus, chronic kidney disease), and immunocompromised individuals (eg, HIV, hematopoietic stem cell transplantation patients) are at increased risk of developing pneumococcal disease [Pelton, S. I., et al 2014] [Viasus, D., et al 2011].

The introduction of infant vaccination with PCV7, PCV10, and PCV13 has significantly reduced the overall incidence of IPD in adults through indirect protection. However, despite reductions in IPD, there is still a burden of residual pneumococcal disease in older adults in countries which have broadly implemented pneumococcal vaccination in the pediatric population which is largely accounted for by non-vaccine serotypes[Lynch, J. P., III and Zhanel, G. G. 2010] [European Centre for Disease Prevention and Control 2020]. *S pneumoniae* serotypes were selected for inclusion in V116 based, in part, on available global epidemiology data with a primary focus on older adults (≥65 years of age) in the US and EU countries with an established pediatric vaccination program. V116 includes select serotypes from PPSV23, PCV13, PCV15, and PCV20, as well as unique serotypes not included in any licensed pneumococcal vaccine, thereby addressing the unmet medical need of preventing residual pneumococcal disease. V116 is being developed to prevent invasive disease and pneumonia caused by *S pneumoniae* serotypes 3, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in children aged ≥2 to <18 years with underlying conditions and adults ≥18 years of age.

Note that in the formulation of V116, serotype 15C is represented by deOAc15B as the molecular structures for deOAc15B and 15C are similar. V116 and PPSV23 contain 12 common serotypes. Advances in serotyping methods led to reclassification of serotype 20 as serotype 20A [Calix, J. J., et al 2012]. The serotype is represented as 20 in PPSV23 product labeling, and as 20A in V116; immune responses to serotype 20A are assessed in this study.

2.2.2 Information on Other Study-related Therapy

2.2.2.1 PPSV23

Refer to the approved labeling for detailed background information on PPSV23.

PPSV23 is comprised of the polysaccharides from 23 of the serotypes causing disease in adults (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.

PPSV23 was first approved in the US in 1983 and is now licensed in >90 countries worldwide. PPSV23 is indicated for the prevention of pneumococcal disease in adults ≥50 years of age and in individuals ≥2 years of age at increased risk for pneumococcal disease.

2.2.2.2 Pneumococcal Vaccination Guidelines

PCV7 was introduced in 2000 in the US and 2001 in the EU and widely adopted in NIPs for children worldwide. PCV10 and PCV13 were licensed in 2009-2010, replacing PCV7 in NIPs [Pilishvili, Tamara, et al 2010]. In June 2022 and April 2023, respectively, PCV15 and PCV20 were licensed for use in children in the US with worldwide licensing expected [European Medicines Agency 2023] [Fink, D. L. 2022] [European Medicines Agency 2023a] [Toerner, J. G. 2023].

PCVs are commonly used in a 3-dose schedule or 4-dose schedule, where 2 or 3 doses are administered starting as early as 2 months of age, and the last dose administered at 12 to 15 months of age [World Health Organization 2019] [U.S. Prescribing Information 2023] [U.S. Prescribing Information 2023a]. The choice of vaccine and schedule is based on several factors, including baseline incidence of disease, prior use of PCV7, and programmatic factors such as timeliness of vaccination and expected coverage. In addition to routine childhood immunization with PCV, there are recommendations to vaccinate children ≥2 years at increased risk for pneumococcal disease due to underlying disease, occupation, or institutionalization as individuals with conditions at increased risk for IPD might have infections caused by a broader range of serotypes than healthy children.

- In the US, ACIP recommendations were recently updated to include PCV20 [Centers for Disease Control and Prevention 2023]. For children aged 2–18 years with any risk condition who have received all recommended doses of PCV before age 6 years, a dose of PCV20 or PPSV23 administered at least 8 weeks after the most recent dose of PCV is recommended if PCV13 or PCV15 were received in the primary schedule. An additional dose of PPSV23 5 years after the first dose is recommended in children with altered immunocompetence. If PCV20 was received in the primary schedule, no additional doses of any pneumococcal vaccine are indicated.

- European national guidelines vary by country in recommendations for at-risk children as well as by age, risk condition, vaccine type and revaccination. In the EU, vaccination guidelines recommend mostly PCV13 (or PCV15 in countries that have updated their recommendations [ie, Greece]) and PPSV23 or PPSV23 only in at-risk children after completing a primary PCV regimen [European Centre for Disease Prevention and Control 2023]. Fewer countries recommend the sequential vaccination regimen of PCV13 (or PCV15) followed by PPSV23 regardless of whether the primary PCV regimen was completed or not [Castiglia P. 2014]. A single dose of PPSV23 (with or without revaccination, ≥5 years after the first dose) is the most widely recommended regimen in children ≥2 years of age with increased risk of pneumococcal disease in most EU countries, as well as in Australia, New Zealand, and several South American countries.

2.3 Benefit/Risk Assessment

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

V116 includes the most prevalent serotypes that cause IPD in adults ≥65 years. With the broadest potential for protection against pneumococcal disease compared to any other adult licensed pneumococcal vaccine, V116 has been primarily developed to address the unmet medical need in adults. However, in most high income countries and several middle income countries with pneumococcal vaccination guidelines, children ≥2 to <18 years of age with an increased risk of pneumococcal disease are currently recommended to receive an additional pneumococcal vaccination(s) to broaden the serotype coverage afforded by their routine primary vaccination course. Therefore, V116 has the potential to also provide this broader protection against pneumococcal disease in children and complement the protection afforded by primary vaccination regimens.

The benefit-risk profile for V116 supports continued evaluation.

In this study, approximately 40% of participants will receive PPSV23, a vaccine indicated in the majority of guidelines globally in pediatric at-risk population. PPSV23 is currently registered and approved in >90 countries worldwide. V116 is expected to provide comparable immune responses to PPSV23 for the common serotypes while providing additional coverage for the serotypes unique to V116. It is unknown if the investigational V116 will have the same clinical benefit as PPSV23.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Primary Objectives	**Primary Endpoints**
To evaluate the safety and tolerability of V116 with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs Day 1 through Day 5 postvaccination • Solicited systemic AEs Day 1 through Day 5 postvaccination • Vaccine-related serious AEs (SAEs) Day 1 through the duration of participation in the study
To compare the serotype-specific opsonophagocytic (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V116 versus PPSV23. **Hypothesis (H1):** V116 is noninferior to PPSV23 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 12 common serotypes in V116 and PPSV23. (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval [CI] of the OPA GMT ratio [V116/PPSV23] to be >0.5.) **Hypothesis (H2):** V116 is superior to PPSV23 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 9 unique serotypes in V116. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio [V116/PPSV23] to be >2.0.)	Serotype-specific OPA responses

Secondary Objectives	**Secondary Endpoints**
To evaluate the serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days postvaccination with V116 compared with PPSV23.	Serotype-specific IgG responses
To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise in serotype-specific OPA responses and IgG responses from baseline to 30 days postvaccination within each vaccination group.	Serotype-specific OPA and IgG responses
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination.	Serotype-specific OPA and IgG responses

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, double-blind, active comparator-controlled clinical study to evaluate the safety, tolerability, and immunogenicity of V116 in children and adolescents aged ≥2 to <18 years who have completed a primary pneumococcal vaccination regimen and who are at increased risk of pneumococcal disease (ie, chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, or chronic kidney disease).

Approximately 820 participants will be randomized in a 3:2 ratio to receive a single dose of either V116 or PPSV23 on Day 1. Randomization will be stratified by the number of increased-risk conditions for pneumococcal disease (1 increased-risk condition, or ≥2 increased-risk conditions) and by prior pneumococcal vaccination and age:

- Prior PCV7 alone
- Prior PCV7 and one prior PPSV23 dose
- Prior PCV10 alone and ≥2 to <6 years old
- Prior PCV10 alone and ≥6 to <18 years old
- Prior PCV10 and one prior PPSV23 dose
- Prior PCV13 alone and ≥2 to <6 years old
- Prior PCV13 alone and ≥6 to <18 years old
- Prior PCV13 and one prior PPSV23 dose

Note: Participants who previously received a combination of PCV7, PCV10, and/or PCV13 or any doses of PCV15 or PCV20 will be excluded from this study.

Participants are to have ≥1 increased-risk condition listed in Inclusion Criteria #1 (Section 5.1). It is expected that ≥25 participants per risk condition will be enrolled. In participants with ≥2 increased-risk conditions, each condition will count towards the total per condition.

Participants risk condition(s) must be considered stable for ≥3 months with no anticipated major change in treatment expected for the duration of the study and with ≤1 hospitalization directly related to the risk condition within 3 months before study vaccination.

An eVRC will be used by the participant/participant's legally authorized representative to record solicited injection-site AEs, solicited systemic AEs, and daily body temperatures from Day 1 through Day 5 after vaccination. Unsolicited AEs will also be recorded from Day 1 through Day 30 after vaccination. The participant/participant's legally authorized representative will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC.

Blood samples for immunogenicity assays will be drawn on Day 1 (Visit 1) and Day 30 (Visit 3).

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

An external DMC will conduct a periodic review of safety and tolerability data for the V116 Phase 3 program. A description of the structure and function of the DMC, along with the timing and content of the safety reviews, will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1.

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

4.2 Scientific Rationale for Study Design

This study will evaluate the safety, tolerability, and immunogenicity of V116 in children and adolescents ≥2 to <18 years of age who have completed a primary pneumococcal vaccination regimen and who are at increased risk for pneumococcal disease.

Children and adolescents with one or more stable chronic medical conditions, including chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and chronic kidney disease will be included in this study. The population of children and adolescents with these chronic medical conditions are at increased risk for IPD and were selected for inclusion based on their overall prevalence in the pediatric population (Section 2.1).

The randomization ratio of 3:2 was chosen to increase the number of participants exposed to V116 to expand the V116 safety and immunogenicity data in a population at increased risk for pneumococcal disease.

Participants will be stratified by prior PCV regimen received in infancy and prior PPSV23 vaccination, as prior pneumococcal vaccination may impact immune responses to V116 and PPSV23 for the shared serotypes. Participants will also be stratified by the number of risk conditions (1 increased-risk condition only or ≥2 increased-risk conditions) as it is expected that the number of participants enrolled with 1 or more conditions will vary and to ensure balance between the intervention groups. Participants will also be stratified by age (≥2 to <6 and ≥6 to <18 years of age) for those who received PCV10 and PCV13 alone to ensure balance between the intervention groups.

Individuals with severe heart, liver, lung, or kidney disease, and those with uncontrolled diabetes will be excluded from this study to allow them to prioritize their medical care over participation in this study and to avoid associating the effects of medical treatment with the safety and immunogenicity of the vaccine.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

Safety information will be collected from all participants (or participant's legally acceptable representative) on an eVRC. The eVRC used to record AEs during the postvaccination period(s) (Section 8.1.10) is structured as recommended in the final US FDA 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 V116 and published data from marketed PCVs. Detailed information for the safety endpoints evaluated in this study can be found in Section 9.3.2.

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

4.2.1.2 Immunogenicity Endpoints

The immunogenicity endpoints are consistent with previous studies evaluating PCVs.

According to the CHMP and WHO guidance documents, immunogenicity studies can be conducted to support the licensing of new pneumococcal vaccines [European Medicines Agency 2006] [World Health Organization 2016] [World Health Organization 2013]. The OPA GMT, IgG GMC, GMFR, and proportion of participants with a 4-fold rise in OPA and IgG responses are acceptable assessments used to evaluate novel PCVs. Several studies have shown a positive correlation between serotype-specific OPA titers and IgG antibody concentrations in children and adults [Centers for Disease Control and Prevention 2010] [Anttila, M., et al 1999] [Romero-Steiner, S., et al 1997].

Thresholds of protection have been established in children <2 years of age, where serotype-specific IgG of ≥0.35 µg/mL measured by ELISA one month after primary immunization was used for the licensing of PCV based on analyses of pooled immunogenicity and efficacy data from randomized controlled studies of the initial 7-valent and investigational 9-valent PCVs [World Health Organization 2013]. However, this threshold is not as relevant for older children, especially those who have already completed a primary pneumococcal vaccination regimen. OPA titers provide an assessment of functional immune responses as a surrogate marker for vaccine efficacy against pneumococcal disease and have been shown to correlate with vaccine-induced protection. Based on this, OPA titers will be used as the primary immunogenicity endpoint in this study. It is noted that OPA titer threshold values that correlate with protection in any age group have not been defined.

Sera from participants will be used to assess vaccine-induced, anti-PnPs, serotype-specific OPA and IgG responses using the validated MOPA and Pn ECL assay, respectively. Immunogenicity endpoints will be evaluated for all serotypes included in V116 and for cross-reactive serotypes within a serogroup.

Details on the immunogenicity endpoints evaluated in this study can be found in Section 9.3.1.

4.2.1.3 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator

Placebo-controlled clinical studies for new PCVs are no longer practical given the proven clinical efficacy and widespread use of licensed pneumococcal vaccines worldwide.

PPSV23 is chosen as the comparator as it is the vaccine included in the majority of guidelines globally in this pediatric increased-risk population. Of the currently licensed pneumococcal vaccines, PPSV23 affords the broadest serotype protection and has the most serotypes in common with V116 (12 serotypes). PPSV23 is indicated for use in persons ≥2 years of age for whom there is an increased risk of morbidity and mortality from pneumococcal disease due to aging and/or underlying medical conditions. As children with conditions at increased risk for IPD might have infections caused by a broader range of serotypes than healthy children, an additional dose of PPSV23 is recommended in children with altered immunocompetence as described in (Section 2.2.2).

Additionally, there is evidence to support effectiveness of PPSV23 against IPD in the pediatric population at increased risk of pneumococcal disease [Lagousi, T., et al 2021] [Fiore, A. E, et al 1999].

The use of PPSV23 in this study is consistent with the product labeling.

4.3 Justification for Dose

The single dose of V116 in the proposed pediatric study is the same regimen, formulation, and dose of V116 used in the adult Phase 3 studies. The V116 dose of 4 µg/each PnPs was selected based on review of safety and immunogenicity data from the Phase 1 and Phase 2 studies in adults. In Phase 1, 2 doses of V116 were evaluated: a single dose containing 2 µg/each PnPs and a single dose of 4 µg/each PnPs. Based on the data from Phase 1, the V116 dose of 4 µg/each PnPs was selected for further evaluation in Phase 2. Results from Phase 2 showed that the V116 dose of 4 µg/each PnPs is well tolerated and generates serotype-specific immune responses. These data supported the selection of the V116 dose of 4 µg/each PnPs for further development in Phase 3.

The overall V116 Phase 3 program includes over 8,000 adults aged ≥18 years, of whom over 5,000 received V116. The safety profile of V116 in pediatric participants is expected to be

consistent with the safety profile established in the Phase 3 adult populations and based on prior experience with PCVs. Refer to the IB for detailed background information on V116.

The dose of PPSV23 selected for use in this study is the approved dose for both adults and children that is consistent with the approved US and EU dosing and product labeling of PNEUMOVAX™23.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects 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 as described in Appendix 1.10.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Documented diagnosis of ≥1 of the following risk conditions for pneumococcal disease as determined by the investigator, according to local clinical standards, which includes history and physical examination in combination with diagnostic tests and procedures and managed per local guidelines:

    - Diabetes mellitus receiving treatment with antidiabetic medication
    - Chronic compensated liver disease
    - Chronic lung disease, including but not limited to asthma (a diagnosis of asthma requires current medical therapy)
    - Chronic heart disease due to heart failure, congenital heart disease, cardiomyopathy, and/or valvular heart disease
    - Chronic kidney disease, with chronic kidney insufficiency/impairment

2. Receiving stable medical management for the risk conditions listed in Inclusion Criterion #1 for ≥3 months with no anticipated major change in treatment expected for the duration of the study and with ≤1 hospitalization directly related to the risk condition within 3 months before study vaccination.

3. At least 8 weeks prior to enrollment, completed primary PCV regimen with PCV7, PCV10, or PCV13 with either a 2+1 or 3+1 regimen according to local recommendations; all doses of the primary regimen must be of the same vaccine.

    a. 2+1: 2 priming doses followed by 1 booster dose administered prior to 2 years of age

    or

    b. 3+1: 3 priming doses followed by 1 booster dose administered prior to 2 years of age

4. Is PPSV23 vaccine-naïve (participant who has never received PPSV23), or PPSV23 vaccine-experienced (participant who has received not more than 1 dose of PPSV23) ≥5 years before study vaccination.

Demographics

5. Is an individual of any sex/gender, from ≥2 years to <18 years of age, at the time of providing the informed consent/assent.

Assigned Female Sex at Birth

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

- Is not a POCBP
  OR
- Is a POCBP and:
  - Uses an acceptable contraceptive method, or is abstinent from penile-vaginal 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 6 weeks 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. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) 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 8.3.3.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant (or participant's legally acceptable representative) may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

5.2 Exclusion Criteria

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

Medical Conditions

1. Had a curative procedure/surgery for chronic heart disease and does not require medication, follow-up, additional interventions, or further management per local guidelines.

2. Has a history of active hepatitis within 3 months before study vaccination (Day 1).

3. Has a history of diabetic ketoacidosis or 2 or more episodes of severe, symptomatic hypoglycemia within 3 months before study vaccination (Day 1).

4. Has a history of severely decreased kidney function (outlined in the Investigator Trial File Binder for this study), dialysis, autoimmune related chronic kidney disease, nephrotic syndrome of any cause, or an acute/reversible cause of kidney disease.

5. Has a history of severe pulmonary hypertension or history of Eisenmenger syndrome.

6. Has a history of IPD (positive blood culture, positive cerebrospinal fluid culture, or positive culture at another sterile site) or known history of other culture-positive pneumococcal disease within 3 years before study vaccination (Day 1).

7. Has a known hypersensitivity to any component of PPSV23 or V116 (including diphtheria toxoid).

8. Has a known or suspected impairment of immunological function including, but not limited to, congenital or acquired immunodeficiency, documented HIV infection, functional or anatomic asplenia, or autoimmune disease (including, but not limited to, the autoimmune conditions outlined in the Investigator Trial File Binder for this study).

9. Has a coagulation disorder contraindicating intramuscular vaccination.

10. *Had a recent febrile illness (defined as temperature ≥100.4°F [≥38.0°C]) or received antibiotic therapy for any illness occurring within 72 hours before receipt of study vaccine.

11. Has a known malignancy that is progressing or has required active treatment <3 years before randomization. **Note:** Participants with basal cell and/or squamous cell carcinoma of the skin, or carcinoma in situ that have undergone potentially curative therapy, are not excluded.

12. Planned organ transplantation (heart, liver, lung, kidney, or pancreas) or other planned major surgical procedure during the duration of this study.

13. Expected survival for <1 year according to the investigator's judgment.

Prior/Concomitant Therapy

14. Received ≥1 dose of PCV15 or PCV20.

15. Is expected to receive any pneumococcal vaccine during the study outside of the protocol.

16. *Received or is scheduled to receive systemic corticosteroids (total daily dose prednisone equivalent of ≥2 mg/kg or ≥20 mg/day for children >10 kg) for ≥14 consecutive days and has not completed intervention ≥14 days before receipt of study vaccine (Day 1) and through 30 days following vaccination. **Note:** Physiologic replacement doses (prednisone equivalent of approximately 5 mg/day), topical, ophthalmic, intraarticular or soft-tissue (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.

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

18. *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 and SARS-CoV-2 mRNA or SARS-CoV-2 protein subunit vaccine may be administered but must be given ≥7 days before or ≥15 days after receipt of study vaccine.

19. *Received any live virus vaccine (including SARS-CoV-2 live virus vaccines) ≤30 days before receipt of study vaccine or is scheduled to receive any live virus vaccine ≤30 days after receipt of study vaccine.

20. Received a blood transfusion or blood products, including immunoglobulin ≤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.

21. Receiving chronic home oxygen therapy.

Prior/Concurrent Clinical Study Experience

22. 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

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

24. Has history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might expose 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.

25. Has a parent/legal guardian/legally acceptable representative who is unlikely to adhere to study procedures, keep appointments, or is planning to relocate during the study.

26. 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 Exclusion Criteria with an asterisk (*), if the participant meets these exclusion criteria, Visit 1 may be rescheduled for a time when these criteria are not met.

Country-specific criteria are included in Appendix 7.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants with documented consent/assent 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 (V116 and PPSV23) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1.

Country-specific requirements are noted in Appendix 7.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP / AxMP	Sourcing
V116	Experimental	Pneumococcal 21-valent conjugate vaccine	Biological/Vaccine	Injection, Solution	4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Test Product	IMP	Central
PPSV23	Active Comparator	Pneumococcal Vaccine, Polyvalent (23-valent)	Biological/Vaccine	Injection, Solution	25 µg of each PnPs antigen (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F)	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Comparator	IMP	Central or local

EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PnPs=pneumococcal polysaccharide; PPSV23=pneumococcal vaccine, polyvalent (23-valent) (PNEUMOVAX™23); V116=pneumococcal 21-valent conjugate vaccine.
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 where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.1.1 Drug-Device Combination Products/Combination Medicinal Products

The drug-device product(s)/combination medicinal product(s), which are marketed and provided for use in this study is PNEUMOVAX™23 (PPSV23). Refer to Section 8.4.8 and Appendix 4 for reporting events associated with these devices.

The investigational drug-device combination product(s)/investigational combination medicinal product(s) provided for use in this study are V116 pre-filled 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 pharmacist or qualified study-site personnel.

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 2 study intervention arms. Participants will be assigned randomly in a 3:2 ratio to receive either V116 or PPSV23, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

- Prior pneumococcal vaccination and age:
  - Prior PCV7 alone
  - Prior PCV7 and one prior PPSV23 dose
  - Prior PCV10 alone and ≥2 to <6 years old
  - Prior PCV10 alone and ≥6 to <18 years old
  - Prior PCV10 and one prior PPSV23 dose
  - Prior PCV13 alone and ≥2 to <6 years old
  - Prior PCV13 alone and ≥6 to <18 years old
  - Prior PCV13 and one prior PPSV23 dose

- Number of increased-risk conditions for pneumococcal disease (including chronic heart disease or chronic lung disease or diabetes mellitus or chronic liver disease, and/or chronic kidney disease):
  - 1 increased-risk condition
  - ≥2 increased-risk conditions*

    *Note: The participant must meet the inclusion/exclusion criteria for each of the increased-risk conditions in order to be included in this stratum.

It is expected that ≥25 participants per risk condition listed in Inclusion Criteria #1 (Section 5.1) will be enrolled. In participants with ≥2 increased-risk conditions, each condition will count towards the 25 total per condition.

6.3.3 Blinding

A double-blinding technique will be used. Study intervention will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, participant's legally acceptable representative, 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 V116 and PPSV23 have a different appearance, the unblinded pharmacist (or qualified study-site personnel) will be responsible for receiving, maintaining, preparing and/or dispensing, and administering these study vaccines (Section 8.1.8).

To avoid bias, contact between the unblinded study-site personnel and study participants and their legally acceptable representatives is strictly prohibited for any study-related procedures/assessments other than administration of study vaccines. Blinded site personnel will be responsible for all other study procedures/assessments specified in Section 1.3.

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

See Section 8.1.12 for the description of unblinding if a medical emergency occurs during the study.

6.4 Study Intervention Compliance

Given that a single dose of V116 or PPSV23 will be administered in this study, intervention compliance will not be assessed.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (Section 5.2).

If there is a clinical indication for any medications or vaccinations specifically prohibited, 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/participant's legally acceptable representative.

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:

- Administration of a nonstudy pneumococcal vaccine is prohibited during the study.
- Nonstudy vaccines may only be administered before or after the receipt of study vaccine according to the time frames specified in the Exclusion Criteria (Section 5.2).
- Receipt of systemic corticosteroids (total daily dose prednisone equivalent of ≥2 mg/kg or ≥20 mg/day for children >10 kg) for ≥14 consecutive days is prohibited from 14 days before vaccination through 30 days following vaccination. **Note:** Physiologic replacement doses (prednisone equivalent of approximately 5 mg/day), 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.

6.6.1 Stopping Rules

There are no prespecified stopping rules for 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 8.1.12). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention 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 8.1.12 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

In clinical studies with a single intervention, discontinuation of study intervention can only occur before the intervention and generally represents withdrawal from the study.

Participants who receive a single-dose intervention cannot discontinue 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/assent from the study.

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.11. 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/participant's legally acceptable representative 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/participant's legally acceptable representative, the following procedures are to be performed:

- The site must attempt to contact the participant/participant's legally acceptable representative and reschedule the missed visit. If contacted, the participant/participant's legally acceptable representative 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/participant's legally acceptable representative 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.

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 providing documented informed consent/assent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent/assent be obtained from the participant (or participant's legally acceptable representative). In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in Appendix 2.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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

8.1.1.1 General Informed Consent

Informed consent/assent given by the participant or their legally acceptable representative must be documented on an ICF. The form must include the study protocol number, study

protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent/assent discussion.

A copy of the signed and dated ICF 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 or their legally acceptable representative 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 willingness of the participant or their legally acceptable representative to continue participation in the study. The communication of this information will be provided and documented via a revised ICF or addendum to the original ICF 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 ICF.

Informed consent/assent 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/assent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent/assent before performing any procedure related to FBR. A copy of the informed consent/assent will be given to the participant (or participant's legally acceptable representative) 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 (or participant's legally acceptable representative) 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 (or participant's legally acceptable representative) with a participant identification card immediately after documented informed consent/assent is provided. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID 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 will be obtained to ensure that the participant satisfies the inclusion and exclusion criteria of the study.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The following must be documented by the investigator or qualified designee before vaccination at Visit 1 and recorded on the appropriate eCRF:

- Prior vaccinations and medication taken by the participant within 30 days before study vaccination at Visit 1.
- Any prior pneumococcal vaccination regardless of timing prior to Visit 1.
- Any analgesic or antipyretic medication taken on the day of vaccination before vaccination.

8.1.5.2 Concomitant Medications

The participant/participant's legally acceptable representative will use the eVRC (Section 8.1.10) to record concomitant medications (including the use of any analgesic or antipyretic medication) and nonstudy vaccinations received from the day of vaccination through 30 days postvaccination.

The investigator or qualified designee must record concomitant medications and nonstudy vaccinations on the appropriate eCRF through Day 30 after vaccination. Outside this period, report only concomitant medications related to an SAE.

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.

Any participant who is screened multiple times will retain the original screening number assigned at the Screening Visit. Specific details on the Screening Visit requirements are in Section 8.11.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Randomization Number

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

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

8.1.8 Study Intervention Administration

Unblinded study personnel will prepare and administer all study vaccines (Section 6.3.3). The unblinded study personnel who administer study vaccines should not have contact with participants/participant's legally acceptable representative for any other study-related procedures/assessments.

Blinded site personnel will not be present in the examination room when study vaccines are administered.

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.

Procedures for handling, preparing, and administering the unblinded vaccines are provided in the Investigator Trial File Binder.

Study vaccine will be administered as a single IM injection, preferably in the deltoid region of the participant's arm, according to the schedule specified in Section 1.3. 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].

8.1.8.1 Timing of Dose Administration

Study intervention 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 8.3.5). This observation must be performed by blinded site personnel (Section 6.3.3).

Participants must not have a fever reported within 72 hours before each vaccination (Section 1.3 and Section 8.3.4).

Administration of pregnancy tests (if applicable) must be performed before vaccine administration.

The collection of blood samples should be performed before vaccine administration.

8.1.9 Telephone Contact Questionnaire

Site personnel will contact the participant (or the participant's legally acceptable representative, as applicable) as indicated in Section 1.3 to collect additional information based on a Telephone Contact Questionnaire provided by the Sponsor. Data to be reported from this discussion will include SAEs and/or any updates to previously reported safety information.

8.1.10 Electronic Vaccination Report Card

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

The participant/participant's legally acceptable representative will use the eVRC to record body temperature (Section 8.3.4), solicited injection-site AEs, and solicited systemic AEs (Section 8.4.9.1). Unsolicited AEs (Section 8.4.9.2), concomitant medications, and nonstudy vaccinations (Section 8.1.5.2) will also be reported. The participant/participant's legally acceptable representative will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC. If the participant receives assistance completing the eVRC, all data reported on the eVRC must be entered as reported by the participant.

The investigator or qualified delegate will review the data captured on the eVRC with the participant/participant's legally acceptable representative as indicated in Section 1.3. Any changes to the data reported by the participant on the eVRC must be clearly explained in the participant's source documents.

8.1.11 Discontinuation and Withdrawal

Participants who receive a single-dose intervention cannot discontinue study intervention (see Section 7.1).

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.

8.1.11.1 Withdrawal From Future Biomedical Research

Participants or participant's legally acceptable representative may withdraw their consent/assent for FBR. Participants/Participant's legally acceptable representative may withdraw consent or assent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent or assent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the

investigator to inform the participant or participant's legally acceptable representative 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.

8.1.12 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.

8.1.13 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 vaccine-induced OPA and IgG responses. These endpoints will be tested for all immunogenicity blood draws specified in Section 1.3.

Blood collection, storage, and shipment instructions for serum samples will be provided in the operations/laboratory manual.

After completion of immunogenicity testing to evaluate the study objectives and hypotheses, serum samples will be stored to conduct any additional study-related testing as requested by regulatory agencies or the Sponsor. 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. These samples may be stored and further analysis may be performed, if required.

8.2.1 Multiplex Opsonophagocytic Assay

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 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 test 4 serotypes at a time reduces the amount of serum needed for testing. The assay readout is the opsonization index, which is the reciprocal of the highest dilution that gives ≥50% bacterial killing, as determined by comparison to assay background controls. The Sponsor has developed and optimized the MOPA in a high throughput microcolony platform, which not only covers all 21 serotypes in V116, but also includes serotypes 6C and 15B so that antibodies induced by vaccine serotypes 6A and 15C but cross-reactive to serotypes 6C and 15B, respectively, can be measured. The assay has been validated for various performance parameters of the assay including precision, ruggedness, relative accuracy/dilutional linearity, and the limit of detection of the assay.

8.2.2 Pneumococcal Electrochemiluminescence Assay

Serotype-specific IgG will be measured using the Pn ECL assay to assess the concentration of binding antibodies to capsular polysaccharide of *S pneumoniae*.

The Sponsor has developed, optimized, and validated a multiplex, ECL-based detection method for the quantitation of IgG serotype-specific antibodies. This multiplexed ECL assay not only detects all 21 serotypes contained in V116 but also detects serotypes 6C and 15B so that antibodies induced by vaccine serotypes 6A and 15C but cross-reactive to serotypes 6C and 15B, respectively, can be measured. The ECL assay is based on the Meso-Scale Discovery technology, which employs disposable multispot microtiter plates. Briefly, PnPs are bound to the surface of 96-well 10 plex carbon microplates, and serum containing purported anti-PnPs antibodies is added. The anti-PnPs antibodies bind to the coated plates and form an antibody-antigen complex. The bound antibody-antigen complex can be detected using a ruthenium labeled anti-human IgG. Plates are read by measure of the chemiluminescent signal emitted from the ruthenium tag upon electrochemical stimulation initiated at the electrode surfaces of the microplates. To improve the specificity to the pneumococcal serotypes in the vaccine, capsular polysaccharide, PnPs 25, and PnPs 72 are used for preadsorption of samples, standard, and controls. Assay validation studies showed excellent performance operating characteristics for precision (intraassay and interassay), dilutability, ruggedness (to different plate lots and analysts), relative accuracy, and specificity.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard before vaccination at Visit 1. The directed 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 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.

8.3.3 Pregnancy Testing

A pregnancy test consistent with local requirements (sensitive to at least 25 IU hCG) must be performed before study vaccination at Visit 1 (Day 1) in POCBP as described in Section 1.3.

Urine or serum tests can be used, and results must be negative before study vaccination can occur. A detailed definition of POCBP 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 participant's participation in the study.

8.3.4 Body Temperature Measurement

Each participant's body temperature must be taken by study-site staff before vaccination as described in Section 1.3. The prevaccination temperature should be documented in the participant's source documents. Participants who have febrile illness (defined as ≥100.4°F [≥38.0°C]) <72 hours before vaccination must be rescheduled.

The participant/participant's legally acceptable representative will record oral (preferred in participants ≥3 years of age) or axillary (underarm) body temperature measurements on the eVRC (Section 8.1.10) from Day 1 to Day 5 after vaccination. Elevated temperatures

(≥100.4°F [≥38.0°C]) reported by the participant/participant's legally acceptable representative Day 1 through Day 5 postvaccination will be reported as a solicited systemic event of pyrexia.

8.3.5 Postvaccination Observation Period

All participants will be observed for at least 30 minutes after 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.

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

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. 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 (or their legally acceptable representative) provides documented informed consent/assent, 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 30 days postvaccination.

All pregnancies and lactation exposure during breastfeeding must be reported by the investigator from the day of randomization through 6 weeks postvaccination.

All SAEs must be reported by the investigator through 6 months postvaccination, regardless of whether related to the study intervention.

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 2.

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

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

Type of Event	**Reporting Period: Consent/Assent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
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

Type of Event	**Reporting Period: Consent/Assent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
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 (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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 (or participant's legally acceptable representative) 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 (spontaneously reported to the investigator or their designee) that occurs in a participant 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 Drug-device Combination Products/Combination Medicinal Products – Complaints, PQCs, and Malfunctions

The method of documenting and reporting complaints, PQCs, and malfunctions will occur as below and in Appendix 4. Refer to Appendix 7 for country-specific information and definitions.

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 drug-device combination products/combination medicinal 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/participant's legally acceptable representative will use an eVRC to report solicited and unsolicited AEs.

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

8.4.9.1 Solicited Adverse Event

Solicited AEs for this study are summarized in Table 3.

Table 3 Solicited Adverse Events for V116-013

Type of Solicited Adverse Event	Predefined Solicited Adverse Events (Preferred Term)	Solicited Period
Injection-site Adverse Event	• Injection-site pain or tenderness (injection-site pain) • Injection-site redness (injection-site erythema) • Injection-site swelling (injection-site swelling)	Day 1 to Day 5 postvaccination
Systemic Adverse Event	• Muscle aches all over body (myalgia) • Headache (headache) • Tiredness (fatigue) • Hives or Welts (urticaria) • Irritability (irritability) • Joint pain (arthralgia) • Drowsiness (somnolence) • Feeling sick (malaise)	Day 1 to Day 5 postvaccination
Note: Daily temperatures will be solicited Day 1 through Day 5 postvaccination. Elevated temperatures of ≥100.4°F (≥38.0°C) from Day 1 through Day 5 postvaccination will be categorized as solicited events of pyrexia.		

8.4.9.2 Unsolicited Adverse Events

Unsolicited AEs for this study are events that are 1) not predefined in Table 3 or 2) predefined in Table 3 but reported at any time outside the solicited period.

8.5 Treatment of Overdose

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

No specific information is available on the treatment of overdose.

8.6 Pharmacokinetics

Pharmacokinetic 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

All sample collections for study-specific assessments shown in the SoA are described within the main Informed Consent.

If the participant or participant's legally acceptable representative has provided documented informed consent/assent for FBR, leftover samples will be used for FBR. The following specimens will be included for FBR:

- Buccal swab DNA for future research

8.10 Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening

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 5.2), a pregnancy test (if applicable); a body temperature measurement; and a review of inclusion/exclusion criteria, prior medications/vaccinations, and medical history must be repeated before vaccination.

8.11.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3. Participants are to be followed for at least 6 months after vaccination or until discontinuation from the study.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study; further details will be provided in the SAP. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to any unblinding/final database lock, will be documented in the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Responsibility for Analyses/In-house Blinding

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

The 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 of the Sponsor will generate the randomized allocation schedule(s) for study intervention assignment. Randomization will be implemented in an IRT system.

Blinding issues related to the planned IAs are described in Section 9.6.

9.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3 of the protocol.

9.3 Analysis Endpoints

Immunogenicity and safety endpoints will be evaluated for within- and/or between-intervention.

9.3.1 Immunogenicity Endpoints

Immune responses will be measured for all 21 serotypes contained in V116: 12 serotypes common to V116 and PPSV23 (3, 7F, 8, 9N, 10A, 11A, 12F, 17F, 19A, 20A, 22F, and 33F) and 9 serotypes unique to V116 (6A, 15A, 15C, 16F, 23A, 23B, 24F, 31, and 35B), and 2 cross-reactive serotypes (6C and 15B).

The primary immunogenicity endpoint includes:

- Serotype-specific OPA GMTs at 30 days postvaccination

The secondary immunogenicity endpoints include:

- Serotype-specific IgG GMCs at 30 days postvaccination
- Serotype-specific GMFR and proportion of participants with a ≥4-fold rise from baseline (Day 1) to 30 days postvaccination for both OPA and IgG responses

The exploratory immunogenicity endpoints include the summaries of the cross-reactive immune responses to serotypes within a serogroup using serotype-specific OPA and IgG responses at 30 days postvaccination.

9.3.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs and vital signs.

The safety endpoints for overall safety assessment that address the primary objectives include:

- Proportion of participants with solicited injection-site AEs [redness (erythema), swelling (swelling), and pain or tenderness (pain)] from Day 1 through Day 5 postvaccination
- Proportion of participants with solicited systemic AEs [(muscle aches all over body (myalgia), headache (headache), tiredness (fatigue), hives or welts (urticaria), irritability (irritability), join pain (arthralgia), drowsiness (somnolence), feeling sick (malaise), fever (pyrexia)] from Day 1 through Day 5 postvaccination. Note: Daily temperatures will be solicited Day 1 through Day 5 postvaccination. Elevated temperatures of ≥100.4°F (≥38.0°C) will be categorized as solicited events of pyrexia.
- Proportion of participants with vaccine-related SAEs from Day 1 through the duration of participation in the study

Additional safety endpoints for overall safety assessment include:

- Proportion of participants with the broad AE categories consisting of any AE, any unsolicited AEs, and any vaccine-related AE from Day 1 through Day 30 postvaccination
- Proportion of participants with the broad AE categories consisting of any SAE, any vaccine-related SAEs, and death from Day 1 through the duration of participation in the study. As this is a single-dose study, the broad AE category of discontinuation of study intervention due to an AE is not applicable
- Proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 5 postvaccination

9.4 Analysis Populations

9.4.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the immunogenicity endpoint(s). The PP population excludes participants due to important deviations from the protocol that

may substantially affect the results of the primary immunogenicity endpoint(s). Potential deviations that may result in the exclusion of a participant from the PP population include:

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

- Receipt of a prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of a blood sample outside the prespecified window

The final determination on important protocol deviations, and thereby the composition of the PP population, will be made prior to the final unblinding of the database and will be documented in a separate memo.

A supportive analysis using the FAS population will also be performed for the primary immunogenicity endpoint. 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 the immunogenicity data using the FAS population.

9.4.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received one dose of study intervention. Participants will be included in the vaccination group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. This will be the group to which they are randomized except for participants who take incorrect study vaccination; such participants will be included in the group corresponding to the study vaccination actually received.

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

9.5 Statistical Methods

9.5.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the primary and secondary immunogenicity objectives.

Immunogenicity analyses will be conducted for each serotype separately.

Primary Endpoints/Hypotheses (H1 and H2)

The first primary objective (to compare the serotype-specific OPA GMTs at 30 days postvaccination with V116 versus PPSV23) will be assessed via the 2 hypotheses.

For the 12 common serotypes, the primary noninferiority hypothesis (H1) regarding OPA GMT levels between recipients of V116 and PPSV23 is:

H0: GMT1/GMT2 ≤0.50 versus

H1: GMT1/GMT2 >0.50

where GMT1 is the serotype-specific OPA GMT for the V116 group and GMT2 is the serotype-specific OPA GMT for the PPSV23 group. A ratio of 0.50 corresponds to an OPA GMT that is 2.0-fold lower in the V116 group compared with the PPSV23 group. Rejecting the null hypothesis (H0) at the 1-sided α=0.025 level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (V116/PPSV23) being >0.50 and would lead to the conclusion that the OPA response to V116 for the common serotype is noninferior to that of PPSV23.

For the 9 serotypes that are unique to V116, the primary superiority hypothesis (H2) regarding OPA GMT levels between recipients of V116 and PPSV23 is:

H0: GMT1/GMT2 ≤2.0 versus

H1: GMT1/GMT2 >2.0

where GMT1 is the serotype-specific OPA GMT for the V116 group, and GMT2 is the serotype-specific OPA GMT for the PPSV23 group. A ratio of 2.0 corresponds to an OPA GMT that is 2.0-fold higher in the V116 group compared with the PPSV23 group. Rejecting the null hypothesis (H0) at the 1-sided α=0.025 level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (V116/PPSV23) being >2.0 and would lead to the conclusion that the OPA response to V116 for the unique serotype is superior to that of PPSV23.

To address the first primary immunogenicity objective, the serotype-specific OPA GMTs at 30 days postvaccination will be compared between vaccination groups. The GMT ratio estimation, 95% CI, and the hypothesis test (ie, 1-sided p-value) will be calculated using a cLDA method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000] using data from both vaccination groups. In this model, the response vector consists of the log-transformed antibody titers at baseline and 30 days postvaccination. This model allows the inclusion of participants who are missing either the baseline or postbaseline measurements, thereby increasing efficiency.

Secondary Endpoints

A similar statistical model as used for the first primary objective will be used to address the secondary objective that compares the serotype-specific IgG GMCs at 30 days postvaccination with V116 compared with PPSV23.

Descriptive statistics with point estimates and within-group 95% CIs will be provided for all other immunogenicity endpoints. For the continuous endpoints, 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 bounds of the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group CIs will be calculated based on the exact method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Reverse Cumulative Distribution Curves for both OPA titers and IgG concentrations at 30 days postvaccination will be graphically displayed by serotype.

A detailed analysis strategy for immunogenicity endpoints is listed in Table 4.

Table 4 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
OPA GMTs at 30 days postvaccination for the 12 common serotypes in V116 and PPSV23	P	cLDA (estimate, 95% CI, p-values)	PP	Model-based
	S		FAS	
OPA GMTs at 30 days postvaccination for the 9 unique serotypes in V116	P	cLDA (estimate, 95% CI, p-values)	PP	Model-based
	S		FAS	
Secondary Endpoints				
IgG GMCs at 30 days post vaccination for the 1) 12 common serotypes between V116 and PPSV23 2) 9 unique serotypes in V116	P	cLDA (estimate, 95% CI)	PP	Model-based
GMFRs and proportions of participants with a ≥4-fold rise from baseline to 30 days postvaccination for 1) serotype-specific OPA responses and 2) serotype-specific IgG responses within each vaccination group	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

CI=confidence interval; cLDA=constrained longitudinal data analysis; FAS=full analysis set; GMC=geometric mean concentration; GMFR=geometric mean fold rise; GMT=geometric mean titer; IgG=immunoglobulin G; OPA=opsonophagocytic activity; PP=per-protocol.

[a] P=Primary approach; S=Supportive approach.

9.5.2 Statistical Methods for Safety Analyses

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

9.5.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by vaccination group (V116 group and PPSV23 group) of the number and percentage of participants with any AEs, any unsolicited AEs, any vaccine-related AEs, any SAEs, any vaccine-related SAEs, and any AEs resulting in death after vaccination. Point estimates and 95% CIs for the between-group differences (V116 compared with PPSV23) in the percentages of participants with the event will be provided for these events.

The number and percentage of participants with specific AEs will also be provided. Point estimates and 95% CIs for the differences between vaccination groups in the percentages of participants with specific AEs will be provided for solicited AEs and AEs that occur in ≥2% of participants in the V116 group or PPSV23 group.

The number and percentage of participants with maximum temperature measurements meeting the Brighton Collaboration cut points [Marcy, S. M., et al 2004] will be provided along with point estimates and 95% CIs of between-group differences.

CIs for between-group differences will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985]. Rainfall plots with point estimates and 95% CIs will be displayed for AEs that occur in ≥5% of participants in the V116 group or PPSV23 group.

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

Table 5 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	Between-group 95% CI	Graphical Display
Overall Safety Assessment	Solicited injection-site AE (Day 1 through Day 5 postvaccination)[a]	X	X	
	Solicited systemic AE (Day 1 through Day 5 postvaccination)[a]	X	X	
	Any AE[b]	X	X	
	Any unsolicited AE[b]	X	X	
	Any vaccine-related AE[b]	X	X	
	Any SAE[b]	X	X	
	Any vaccine-related SAE[b]	X	X	
	Death[b]	X	X	
	Specific AEs by SOC and PT[c]	X	X	X
	Maximum temperatures (Day 1 through Day 5 postvaccination)[d]	X	X	

AE=adverse event; CI=confidence interval; PT=preferred term; SAE=serious adverse event; SOC=system organ class.

[a] Solicited injection-site AEs include redness (erythema), swelling (swelling), and pain and tenderness (pain); solicited systemic AEs include muscle aches all over body (myalgia), headache (headache), tiredness (fatigue), hives or welts (urticaria), irritability (irritability), join pain (arthralgia), drowsiness (somnolence), feeling sick (malaise), fever (pyrexia). Note: Daily temperatures will be solicited Day 1 through Day 5 postvaccination. Elevated temperatures of ≥100.4°F (≥38.0°C) will be categorized as solicited events of pyrexia.

[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] Descriptive statistics, 95% Between-group CI, and Graphical Display will be provided for specific AEs with an incidence >0%, ≥ 2%, and ≥5% of participants, respectively, in each vaccination group.

[d] Maximum temperature measurements are categorized by Brighton Collaboration cut points.

9.6 Interim Analyses

A periodic review of safety and tolerability data across the V116 pediatric study will be conducted by an independent, unblinded, external DMC. A description of the structure and function of the DMC, along with the timing and content of the safety review, will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1. Unblinded immunogenicity data will be made available to the DMC upon request to enable a benefit-risk assessment.

The DMC will serve as the primary reviewer of the results of the ongoing safety reviews and will make recommendations for discontinuation of the study or protocol modifications to an EOC of the Sponsor (see Appendix 1 for details on the Committees Structure for this study). If the DMC recommends modifications to the design of the protocol or discontinuation of the

study, the EOC of the Sponsor (and potentially other limited Sponsor personnel) may be unblinded to results at the intervention level to act on these recommendations. The extent to which individuals are unblinded with respect to ongoing safety reviews will be documented. Additional logistical details will be provided in the DMC charter.

Study enrollment may be ongoing at the time of external DMC review. Blinding to intervention assignment will be maintained at all investigational sites. Participant-level unblinding will be restricted to an external unblinded statistician performing ongoing safety reviews. Intervention-level ongoing safety reviews will be provided by the external unblinded statistician to the DMC. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the safety reviews.

9.7 Multiplicity

The study will have met its primary immunogenicity objectives if noninferiority is demonstrated with respect to the OPA GMTs for the 12 common serotypes (via H1), and superiority is demonstrated with respect to OPA GMTs for the 9 unique serotypes (via H2). All hypotheses will be tested individually for each serotype at a 1-sided 0.025 alpha-level. This approach controls the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment will be required.

9.8 Sample Size and Power Calculations

9.8.1 Sample Size and Power for Immunogenicity Analyses

The study will randomize approximately 820 participants, allocated in a 3:2 ratio to receive either V116 or PPSV23 (492 participants in the V116 group and 328 participants in the PPSV23 group).

Primary Immunogenicity Endpoints/Hypotheses (H1 and H2)

For the primary hypotheses, this study has >90% power to declare noninferiority of V116 to PPSV23 for the 12 common serotypes (H1) and superiority of V116 to PPSV23 for the 9 unique serotypes (H2) at an overall 1-sided 2.5% alpha-level.

The sample size and power calculations are based on the following assumptions:

- For the 12 common serotypes, the underlying serotype-specific OPA GMT ratios (V116/PPSV23) and the standard deviation of natural log-transformed OPA results are assumed to be the same as that observed in the V116-004 Phase 3 study. The OPA GMT ratios range from 0.84 to 1.74. The standard deviations range from 0.93 to 1.43 for V116 and range from 0.96 to 1.43 for PPSV23.
- For the 9 unique serotypes, the underlying serotype-specific OPA GMT ratios (V116/PPSV23) and the standard deviation of natural log-transformed OPA results are assumed to be the same as that observed in the V116-004 Phase 3 study. The OPA GMT

ratios range from 2.90 to 23.72. The standard deviations range from 1.03 to 1.52 for V116 and range from 1.05 to 2.54 for PPSV23.

- 90% evaluability (443 participants in the V116 group and 295 participants in the PPSV23 group).

Based on the assumptions above, the power for the primary hypotheses is calculated using a simulation-based approach. This approach uses the cLDA model for comparing OPA GMTs between the 2 vaccination groups. The power is estimated as the number of successful iterations out of the total iterations in the simulation. The success within each iteration is defined as meeting both primary hypotheses for each serotype (ie, noninferiority for the 12 common serotypes [H1] and superiority for the 9 unique serotypes [H2]).

9.8.2 Sample Size and Power for 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 an SAE in the study population. The sample size was selected to achieve a reasonably sized safety database exposed to V116. Calculations below assume that 100% of randomized participants will be evaluable for safety analyses.

There is 80% probability of observing at least 1 SAE among 492 participants in the V116 group if the true incidence rate is 0.33% (1 of every 306 participants receiving the vaccine). There is a 50% probability of observing at least 1 SAE among 492 participants in the V116 group if the true incidence rate is 0.14% (1 of every 710 participants receiving the vaccine). If no SAEs were observed among 492 participants, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.75% (1 out of every 133 participants) in the V116 group.

The percentage point differences between the 2 vaccination groups that could be detected with 80% probability are summarized in Table 6 for a variety of hypothetical underlying incidences of an AE.

Table 6 Differences in Incidence of Adverse Event Rates Between the 2 Vaccination Groups That Can be Detected With an Approximately 80% Probability

Incidence of an Adverse Event		**Risk Difference**
V116 (%) N=492	PPSV23 (%) N=328	Percentage Points
2.4	0.1	2.3
6.0	2.0	4.0
10.4	5.0	5.4
16.9	10.0	6.9
22.9	15.0	7.9
28.6	20.0	8.6
39.5	30.0	9.5
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. The incidences assume a 2-sided 5% alpha-level with 492 participants in the V116 group and 328 participants in the PPSV23 group. No multiplicity adjustments were made. Based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. and Manning, G. 1990]		

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, 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 MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and 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. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. 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. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in 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 and ICH Guidelines. 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. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

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.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.6) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.3 Scientific Advisory Committee (SAC)

This study was developed in collaboration with an SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, 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, https://euclinicaltrials.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 Regulation 536/2014 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 Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 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 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for POCBP)
hCG=human chorionic gonadotropin; POCBP=participant/participants of childbearing potential	

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

Blood volumes collected from each participant over the duration of the study are detailed in Table 8.

Country-specific criteria are included in Appendix 7.

Table 8 Blood Volumes Collected by Visit for Immunogenicity Assessments

	Visit 1	Visit 3	Total
Parameter	**Approximate Blood Volume**		
Immunogenicity assessment	10 mL	10 mL	20 mL
Note: The maximum blood volume to be collected for each visit in this population should follow local guidelines/recommendations, if specified.			

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

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

Events NOT meeting the AE definition

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

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.

10.3.3 Definition of SAE

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

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

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

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

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

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

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

Table 9 Injection-site AE Overall Intensity Grading Scale

Injection-site Reaction to Study Vaccine/Placebo	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Injection-site AEs occurring Day 1 through Day 5 following receipt of study vaccine				
Pain/Tenderness	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ED visit or hospitalization
Erythema/Redness	Size measured as ≤5 cm	Size measured as 5.1 to 10 cm	Size measured as >10 cm	Necrosis or exfoliative dermatitis or results in ED visit or hospitalization
Swelling	Size measured as ≤5 cm	Size measured as 5.1 to 10 cm	Size measured as >10 cm	Necrosis or ED visit or hospitalization
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

Injection-site Reaction to Study Vaccine/Placebo	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Any injection-site reaction that begins ≥6 days after receipt of study vaccine				
Pain/Tenderness Erythema/Redness Swelling 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
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].

Table 10 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
Urticaria	No interference with activity	Some interference with activity	Significant; prevents daily activity	ED visit or hospitalization
Somnolence	No interference with activity	Some interference with activity	Significant; prevents daily activity	ED visit or hospitalization
Irritability	No interference with activity	Some interference with activity	Significant; prevents daily activity	ED visit or hospitalization
Malaise	No interference with activity	Some interference with activity	Significant; prevents daily activity	ED visit or hospitalization

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

Table 11 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 vaccination 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.

Table 12 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/Pyrexia				
(°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 Body 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.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 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: Drug-Device Combination Products/ Combination Medicinal Products: Complaints, Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

The recording and follow-up procedures described in this protocol apply to drug-device combination products/combination medicinal products. For purposes of this section, devices in scope for device information collection include drug-device combination products/combination medicinal 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 composed of any combination of a drug, a device, and a biological product. Each drug, device, and biological product included in a combination product is referred to as a "constituent part" of the combination product.

Complaint – Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution.

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.

Malfunction – The failure of a device including the device component of a combination product to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the medical device/device constituent part. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Medical Device – Any instrument, apparatus, appliance, implement, machine, contrivance, implant, in-vitro reagent or other similar or related article, including a component part, or accessory which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

PQC – Any communication (written or oral) 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.

Serious deterioration of Health/Serious Injury/Serious Illness- This includes:

1. Life-threatening illness, even if temporary in nature ,
2. Results in permanent impairment of a body function or permanent damage to a body structure,
3. A condition necessitating medical or surgical intervention, including hospitalization or prolonged hospitalization to preclude permanent impairment of a body function or permanent damage to a body structure,
4. Cases that are considered medically significant,
5. Fetal distress, fetal death or any congenital abnormality or birth defects.

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

Japan specific definitions and documenting/reporting requirements can be found in Section 10.7.

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

Recording

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

Adverse Events occurring during the study will be recorded in the participant's medical records (or equivalent), in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines (or equivalent). Device constituent part of drug-device combination product/combination medicinal product information (regardless of participant or associated person) 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

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant 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.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal 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
  - 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 participants assigned female sex at birth who are 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.
  - Participants assigned female sex at birth who are 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:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[b,c] • IUS[b,d] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b,c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b,c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, 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 • Penile/external or vaginal/internal condom with or without spermicide[e] • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] Penile/external condoms must be used in addition to the POCBP's hormonal contraception [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [d] IUS is a progestin releasing IUD [e] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)[e]

Country-specific criteria are included in Appendix 7.

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.

13. References

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Requirements for Japan

Section 5.2 Exclusion Criteria

For study sites in Japan, to comply with current Japan national guidance, the following criterion replaces Exclusion Criterion 18 in Section 5.2:

18. *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 may be administered but must be given ≥7 days before or ≥15 days after receipt of study vaccine. SARS-CoV-2 mRNA or protein subunit vaccines may be administered but must be given ≥14 days before or ≥15 days after receipt of study vaccine. SARS-CoV-2 vaccines other than mRNA and protein subunit vaccines are not eligible for this exception and are subject to requirements of exclusion criteria 18 and 19.

Section 6.1.1 Drug-Device Combination Products/Combination Medicinal Products

The investigational drug-device combination product(s)/investigational combination medicinal product(s) provided for use in this study are V116 pre-filled syringes and PNEUMOVAX™23 (PPSV23) pre-filled syringes. Refer to Section 8.4.8 and Appendix 4 for reporting events associated with these devices.

Section 10.4 Appendix 4: Drug-Device Combination Products/Combination Medicinal Products: Complaints, Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

10.4.1 Definitions

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

Combination Medicinal Product - The products to be manufactured and marketed as a single drug, medical device, or regenerative medical product by combining 2 or more different type of drugs, medical devices or processed cells that are presumed to fall under the category of drugs, medical devices, or regenerative medical products if it is distributed alone.

Malfunction - The condition of the device constituent of product specified as combination product/medical device in this protocol is not good in terms of wide range of quality, safety, or performance, such as damage or failure in operation. Regardless of whether it occurs at any stage of design, delivery, storage, or use.

Serious Adverse Event due to Malfunction - Any SAE occurred in participant and/or the associated person in clinical trial, which caused by or suspected effects of the use of the device constituent of product specified as combination product/medical device in this protocol or the device recognized to have the same structure and principle as the device.

Malfunction Which may Lead to Serious Adverse Events - Any malfunction of a device constituent of product specified as combination product in this protocol which might have led to the death of a participant and/or the associated person or to a serious deterioration in their state of health. "Which might have led to" means that there is the possibility that death or a serious deterioration might have occurred in a participant and/or the associated person, although these cases have not actually occurred.

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

Malfunction which may lead to SAEs will be reported to the Sponsor within 5 calendar days of the information via a paper reporting form.

10.7.2 EEA-specific Requirements

Section 5.2 Exclusion Criteria

For study sites in EEA countries, Exclusion Criteria 17 and 18 are as follows:

17. Received immunosuppressive therapy within 6 months before vaccination, including chemotherapeutic agents or other immunotherapies/immunomodulators used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease.

18. *Received any nonlive vaccine ≤15 days before receipt of study vaccine or is scheduled to receive any nonlive vaccine ≤30 days after receipt of any study vaccine. **Exception**: inactivated influenza vaccine and SARS-CoV-2 mRNA or protein subunit vaccine may be administered but must be given ≥15 days before or after receipt of study vaccine.

Section 10.2 Clinical Laboratory Tests

For study sites in EEA countries, the following note applies to Table 8 (Blood Volumes Collected by Visit for Immunogenicity Assessments):

***NOTE**: This table specifies the maximum blood volume to be collected for each visit. The blood draw limit should not exceed the EMA recommendation of 0.9 mL/kg body weight, which corresponds to 1% of total blood volume at a single time point. Additionally, during a period of 4 weeks, the blood draw limit should not exceed 2.4 mL/kg body weight, which is equivalent to 3% of the total blood volume.*

Section 10.5.2 Contraceptive Requirements

For study sites in EEA countries, the contraceptive methods allowed during the study include only those methods considered to be highly effective, as specified below:

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[b,c] • IUS[b,d] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b,c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b,c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, 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.
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] Penile/external condoms must be used in addition to the POCBP's hormonal contraception [c] If locally required, in accordance with CTFG guidelines, acceptable 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 • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
APaT	All-Participants-as-Treated
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
deOAc	De-O-acetylated
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
ECL	Electrochemiluminescence
eCRF	Electronic case report form
EDC	Electronic data collection
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EU	European Union
eVRC	Electronic vaccination report card
FAS	Full Analysis Set
FBR	Future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation	Expanded Term
FSH	Follicle-stimulating hormone
FSR	First site ready
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HRT	Hormone-replacement therapy
IA	Interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent/Assent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular(ly)
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IPD	Invasive pneumococcal disease
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LAM	Lactational amenorrhea method
M&N	Miettinen and Nurminen
MOPA	Multiplexed Opsonophagocytic Assay
mRNA	Messenger RNA
NIP	National immunization program

Abbreviation	Expanded Term
OPA	Opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
Pn ECL	Pneumococcal electrochemiluminescence
PnPs	Pneumococcal polysaccharide
POCBP	Participant/participants of childbearing potential
PP	Per-protocol
PPSV23	Pneumococcal vaccine, polyvalent (23-valent) (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)
PQC	Product quality complaint
RNA	Ribonucleic acid
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SLAB	Supplemental laboratory test(s)
SoA	Schedule of activities
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
US	United States
V116	Pneumococcal 21-valent conjugate vaccine
VRC	Vaccination report card
WHO	World Health Organization

11 REFERENCES

[Anttila, M., et al 1999]	Anttila M, Voutilainen M, Jäntti V, Eskola J, Käyhty H. Contribution of serotype-specific IgG concentration, IgG subclasses and relative antibody avidity to opsonophagocytic activity against Streptococcus pneumoniae. Clin Exp Immunol 1999;118(3):402-7.	[03QY70]
[Bell, R. A., et al 2009]	Bell RA, Mayer-Davis EJ, Beyer JW, D'Agostino RB Jr, Lawrence JM, Linder B, et al. Diabetes in non-Hispanic white youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;32(Suppl 2):S102-S111.	[03R2G9]
[Bloom, C. I., et al 2019]	Bloom CI, Saglani S, Feary J, Jarvis D, Quint JK. Changing prevalence of current asthma and inhaled corticosteroid treatment in the UK: population-based cohort 2006-2016. Eur Respir J. 2019;53:1802130.	[05R7BX]
[Burton, Robert L. and Nahm, Moon H. 2006]	Burton RL, Nahm MH. Development and validation of a fourfold multiplexed opsonization assay (MOPA4) for pneumococcal antibodies. Clin Vaccine Immunol 2006;13(9):1004-9.	[03QT2R]
[Calix, J. J., et al 2012]	Calix JJ, Porambo RJ, Brady AM, Larson TR, Yother J, Abeygunwardana C, et al. Biochemical, genetic, and serological characterization of two capsule subtypes among Streptococcus pneumoniae serotype 20 strains: discovery of a new pneumococcal serotype. J Biol Chem. 2012 Aug 10;287(33):27885-94.	[08B5C0]
[Castiglia P. 2014]	Castiglia P. Recommendations for pneumococcal immunization outside routine childhood immunization programs in Western Europe. Adv Ther. 2014Oct;31(10):1011-44.	[04P7LW]

[Centers for Disease Control and Prevention 2010]	Centers for Disease Control and Prevention. Prevention of Pneumococcal Disease Among Infants and Children - Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine; Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59(RR-11):1-19.	[03RSB6]
[Centers for Disease Control and Prevention 2015]	Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. 13th ed. Hamborsky J, Kroger A, Wolfe S, editors. Washington (DC): Department of Health and Human Services (HHS); c2015. Chapter 6, Vaccine administration; p. 79-106.	[0508PV]
[Centers for Disease Control and Prevention 2023]	Centers for Disease Control and Prevention [Internet]. Washington (DC): Department of Health and Human Services (HHS). ACIP recommendations; [cited 2023 Aug 1]; [about 4 screens]. Available from: https://www.cdc.gov/vaccines/acip/recommendations.html.	[08CSMK]
[Chen, M. Y., et al 2018]	Chen MY, Riehle-Colarusso T, Yeung LF, Smith C, Farr SL. Children with heart conditions and their special health care needs - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018 Sep 28;67(38):1045-9.	[05R66D]
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ and Pearson ES. The use of confidence of fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03RRVC]
[European Centre for Disease Prevention and Control 2020]	European Centre for Disease Prevention and Control. Invasive pneumococcal disease: annual epidemiological report for 2018. Stockholm (Sweden): European Centre for Disease Prevention and Control (ECDC); 2020 Sep. 11 p.	[07XGL2]

[European Centre for Disease Prevention and Control 2023]	European Centre for Disease Prevention and Control [Internet]. Stockholm (Sweden): European Centre for Disease Prevention and Control (ECDC). Pneumococcal disease: recommended vaccinations; [cited 2023 Aug 1]; [about 4 screens]. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=25&SelectedCountryIdByDisease=-1.	[08CSMQ]
[European Medicines Agency 2006]	European Medicines Agency. Committee for medicinal products for human use CHMP. London (England): European Medicines Agency (EMA); 2006. 19 p. EMEA/CHMP/VWP/164653/2005.	[07XGL4]
[European Medicines Agency 2023]	European Medicines Agency [Internet]. Amsterdam (Netherlands): European Medicines Agency (EMA); c1995-2023. Vaxneuvance: pneumococcal polysaccharide conjugate vaccine (adsorbed); [cited 2023 May 26]; [about 13 screens]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vaxneuvance.	[08B8RL]
[European Medicines Agency 2023a]	European Medicines Agency [Internet]. Amsterdam (Netherlands): European Medicines Agency (EMA); c1995-2023. Apexxnar: pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed); [cited 2023 May 26]; [about 12 screens]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/apexxnar.	[08B8Q4]
[Farrington, C. P. and Manning, G. 1990]	Farrington CP and Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990;9:1447-54.	[04FS6L]
[Fink, D. L. 2022]	Fink DL (Acting Deputy Director, Food and Drug Administration, Silver Spring, MD). Letter to: J. Yi (Merck Sharp and Dohme Corp, North Wales, PA). 2022 Jun 17. 4 p. June 17, 2022 approval letter – VAXNEUVANCE.	[08B8SD]

[Fiore, A. E, et al 1999]	Fiore AE, Levine OS, Elliott JA, Facklam RR, Butler JC. Effectiveness of pneumococcal polysaccharide vaccine for preschool-age children with chronic disease. Emerg Infect Dis 1999;5(6):828-31.	[03NXDX]
[Food and Drug Administration 2007]	Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD. Sep 2007.	[05B4S4]
[Goldblatt, D. 2000]	Goldblatt D. Conjugate vaccines [editorial]. Clin Exp Immunol. 2000;119:1-3.	[06CSCY]
[Kobayashi, M. 2023]	Kobayashi M. Evidence to recommendations framework and policy options: use of 20 valent pneumococcal conjugate vaccine in U.S. children. Slides presented at: Advisory Committee on Immunization Practices (ACIP) Meeting; 2023 Jun 21-23; Atlanta, GA.	[08CJKF]
[Lagousi, T., et al 2021]	Lagousi T, Papadatou I, Strempas P, Chatzikalil E, Spoulou V. Pneumococcal immunization strategies for high-risk pediatric populations worldwide: one size does not fit all. Vaccines. 2021 Nov 24;9:1390.	[07YC86]
[Lascar, N., et al 2018]	Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. Lancet Diabetes Endocrinol. 2018 Jan;6:69-80.	[05R7BY]
[Liakou, C. D., et al 2011]	Liakou CD, Askiti V, Mitsioni A, Stefanidis CJ, Theodoridou MC, Spoulou VI. Safety, immunogenicity and kinetics of immune response to 7-valent pneumococcal conjugate vaccine in children with idiopathic nephrotic syndrome. Vaccine. 2011;29:6834-7.	[07XGL9]
[Liang, K-Y and Zeger, S. L. 2000]	Liang K-Y, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankyha: The Indian Journal of Statistics 2000;62(Series B, Part 1):134-48.	[00V5V6]

[Lynch, J. P., III and Zhanel, G. G. 2010]	Lynch JP, III, Zhanel GG. Streptococcus pneumoniae: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. Curr Opin Pulm Med 2010;16:217-25.	[03RMXB]
[Marcy, S. M., et al 2004]	Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Connell Jones M, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;22:551-6.	[03PVW0]
[Mayer-Davis, E. J., et al 2018]	Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, et al. ISPAD Clinical Practice Consensus Guidelines 2018: definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes. 2018 Oct;19(suppl 27):7-19.	[05R797]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[Nunes, M. C. 2012]	Nunes MC, Madhi SA. Safety, immunogenicity and efficacy of pneumococcal conjugate vaccine in HIV-infected individuals. Hum Vaccin Immunother. 2012 Feb;8(2):161-73.	[07XGLD]
[O'Brien, K., et al 2009]	O'Brien K, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009;374:893-902.	[03QZM3]
[Pelton, S. I., et al 2014]	Pelton SI, Weycker D, Farkouh RA, Strutton DR, Shea KM, Edelsberg J. Risk of pneumococcal disease in children with chronic medical conditions in the era of pneumococcal conjugate vaccine. Clin Infect Dis. 2014 Sep 1;59(5):615-23.	[05R6YJ]
[Pelton, S. I., et al 2015]	Pelton SI, Shea KM, Weycker D, Farkouh RA, Strutton DR, Edelsberg J. Rethinking risk for pneumococcal disease in adults: the role of risk stacking. Open Forum Infect Dis. 2015;2(1):ofv020.	[050XJ0]

[Pilishvili, Tamara, et al 2010]	Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010;201(1):32-41.	[03R5S4]
[Quinn, C. T., et al 2023]	Quinn CT, Wiedmann RT, Jarovsky D, Lopez-Medina E, Rodriguez HM, Papa M, et al. Safety and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, in children with SCD: a V114-023 (PNEU-SICKLE) study. Blood Adv. 2023 Feb 14;7(3):414-21.	[08CJKJ]
[Romero-Steiner, S., et al 1997]	Romero-Steiner S, Libutti D, Pais LB, Dykes J, Anderson P, Whitin JC, et al. Standardization of an opsonophagocytic assay for the measurement of functional antibody activity against streptococcus pneumoniae using differentiated HL-60 cells. Clin Diagn Lab Immunol 1997;4(4):415-22.	[03NWQ5]
[Sahota, A. K., et al 2020]	Sahota AK, Shapiro WL, Newton KP, Kim ST, Chung J, Schwimmer JB. Incidence of nonalcoholic fatty liver disease in children: 2009-2018. Pediatrics. 2020 Dec;146(6):e20200771.	[05R5K7]
[Schwimmer, J. B., et al 2006]	Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics. 2006 Oct;118(4):1388-93.	[05P54C]
[Temple, J. L., et al 2016]	Temple JL, Cordero P, Li J, Nguyen V, Oben JA. A guide to non-alcoholic fatty liver disease in childhood and adolescence. Int J Mol Sci. 2016 Jun 15;17:947.	[05R6W4]
[Toerner, J. G. 2023]	Toerner JG (Acting Deputy Director, Food and Drug Administration, Silver Spring, MD). Letter to: S. Bauer (Wyeth Pharmaceuticals LLC, New york, NY). 2023 Apr 27. 4 p. April 27, 2023 approval letter - PREVNAR 20.	[08B8SB]

[Troeger, C., et al 2018]	Troeger C, Blacker BF, Khalil IA, Rao PC, Cao S, Zimsen SRM, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018 Nov;18:1191-210.	[07XTBZ]
[U.S. Food and Drug Administration 2009]	U.S. Food and Drug Administration (CDER, CBER, CDRH). Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims [Internet]. Washington: U.S. Department of Health and Human Services; 2009. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf	[04MG9J]
[U.S. Prescribing Information 2023]	U.S. Prescribing Information: VAXNEUVANCE (pneumococcal 15-valent conjugate vaccine), suspension for intramuscular injection: Apr 2023.	[08DTX6]
[U.S. Prescribing Information 2023a]	U.S. Prescribing Information: PREVNAR 20 (pneumococcal 20-valent conjugate vaccine), suspension for intramuscular injection: Apr 2023.	[089NG7]
[Viasus, D., et al 2011]	Viasus D, Garcia-Vidal C, Cruzado JM, Adamuz J, Verdaguer R, Manresa F, et al. Epidemiology, clinical features and outcomes of pneumonia in patients with chronic kidney disease. Nephrol Dial Transplant. 2011;26:2899-906.	[08B6SD]
[Wilck, M., et al 2023]	Wilck M, Barnabas S, Chokephaibulkit K, Violari A, Kosalaraksa P, Yesypenko S, et al. A phase 3 study of safety and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, followed 23-valent pneumococcal polysaccharide vaccine, in children with HIV. AIDS. 2023;37(8):1227–37.	[08CJKH]
[World Health Organization 2013]	World Health Organization. Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines. Geneva (Switzerland): World Health Organization (WHO); 2013. 61 p.	[07XGLN]

[World Health Organization 2016]	World Health Organization. Guidelines on clinical evaluation of vaccines: regulatory expectations. Geneva (Switzerland): World Health Organization (WHO); 2016. 91 p.	[07XGLL]
[World Health Organization 2019]	World Health Organization. Vaccins antipneumococciques conjugues chez les nourrissons et les enfants de moins de 5 ans: note de synthese de l'OMS - fevrier 2019 [Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper - February 2019]. Wkly Epidemiol Rec. 2019 Feb 22;94(8):85-104.	[05R5TF]
[World Health Organization 2021]	WHO Vaccine Safety Basics. More about conjugate vaccines: conjugate vaccines target several leading causes of vaccine-preventable deaths. Geneva (Switzerland): World Health Organization (WHO); 2021.	[07XGKR]
[Zahran, H. S., et al 2018]	Zahran HS, Bailey CM, Damon SA, Garbe PL, Breysse PN. Vital signs: asthma in children - United States, 2001-2016. MMWR Morb Mortal Wkly Rep. 2018 Feb 9;67(5):149-55.	[05R6VK]