

<b>Official Protocol Title:</b>	A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults 18 to 64 years of Age With Increased Risk for Pneumococcal Disease
<b>NCT number:</b>	NCT05696080
<b>Document Date:</b>	24-Oct-2022

## TITLE PAGE

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**Protocol Title:** A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults 18 to 64 years of Age With Increased Risk for Pneumococcal Disease

**Protocol Number:** 008-00

**Compound Number:** V116

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

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**Approval Date:** 24 October 2022

### Sponsor Signatory

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Typed Name:

Title:

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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.

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Typed Name:

Title:

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Date

## DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original Protocol	24-OCT-2022	Not applicable

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## 1 PROTOCOL SUMMARY

### 1.1 Synopsis

**Protocol Title:** A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults 18 to 64 years of Age With Increased Risk for Pneumococcal Disease

**Short Title:** Safety and Immunogenicity of V116 in Adults With Increased Risk for Pneumococcal Disease

**Acronym:** STRIDE-8

#### Hypotheses, Objectives, and Endpoints:

There is no hypothesis testing in this study.

Objectives and endpoints described below will be evaluated in pneumococcal vaccine-naïve participants 18 to 64 years of age (inclusive) who are at increased risk for pneumococcal disease due to an underlying medical condition.

Primary Objectives	Primary Endpoints
To evaluate the safety and tolerability of V116 as assessed by the proportion of participants with adverse events (AEs).	<ul style="list-style-type: none"><li>Solicited injection-site AEs from Day 1 through Day 5 postvaccination.</li><li>Solicited systemic AEs from Day 1 through Day 5 postvaccination.</li><li>Vaccine-related Serious Adverse Events (SAEs) from Day 1 through the duration of participation in the study.</li></ul>
To evaluate the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) postvaccination with V116 (30 days postvaccination [Day 30]) and PCV15 + PPSV23 (30 days postvaccination with the final dose in the regimen [Week 12]) within each vaccination group separately.	<p>Serotype-specific OPA responses:</p> <ul style="list-style-type: none"><li>13 serotypes common between V116 and PCV15 + PPSV23.</li><li>8 serotypes unique to V116.</li></ul>

Secondary Objectives	Secondary Endpoints
To evaluate the serotype-specific Immunoglobulin G (IgG) geometric mean concentrations (GMCs) postvaccination with V116 (Day 30) and PCV15 + PPSV23 (Week 12) within each vaccination group separately.	Serotype-specific IgG responses: <ul style="list-style-type: none"> <li>13 serotypes common between V116 and PCV15 + PPSV23.</li> <li>8 serotypes unique to V116.</li> </ul>
To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a $\geq 4$ -fold rise from baseline (Day 1) to postvaccination with V116 (Day 30) and from baseline (Day 1) to postvaccination with PCV15 + PPSV23 (Week 12) for both OPA and IgG responses within each vaccination group separately.	Serotype-specific OPA and IgG responses: <ul style="list-style-type: none"> <li>13 serotypes common between V116 and PCV15 + PPSV23.</li> <li>8 serotypes unique to V116.</li> </ul>

### Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal infection
Population	Pneumococcal vaccine-naïve adults 18 to 64 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 Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 14 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 500 participants will be randomized, with approximately 375 participants in the V116 group and 125 participants in the PCV15 + PPSV23 group.

### Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	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, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 2 (Day 1)	Test Product
V116	Placebo (sterile saline)	N/A	0.5 mL	IM	Single dose at Visit 5 (Week 8)	Placebo
PCV15 + PPSV23	Pneumococcal 15-valent conjugate vaccine	2 µg of each PnPs antigen (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) and 4 µg of PnPs antigen 6B	0.5 mL	IM	Single dose at Visit 2 (Day 1)	Comparator
PCV15 + 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 5 (Week 8)	Comparator

IM=intramuscular; PCV15=pneumococcal 15-valent conjugate vaccine; PnPs=pneumococcal polysaccharide; PPSV23=pneumococcal vaccine, polyvalent (23-valent).

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 approximately 6 months from the time the participant provides documented informed consent through the final contact.

**Study Governance Committees:**

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

Study governance considerations are outlined in Appendix 1.

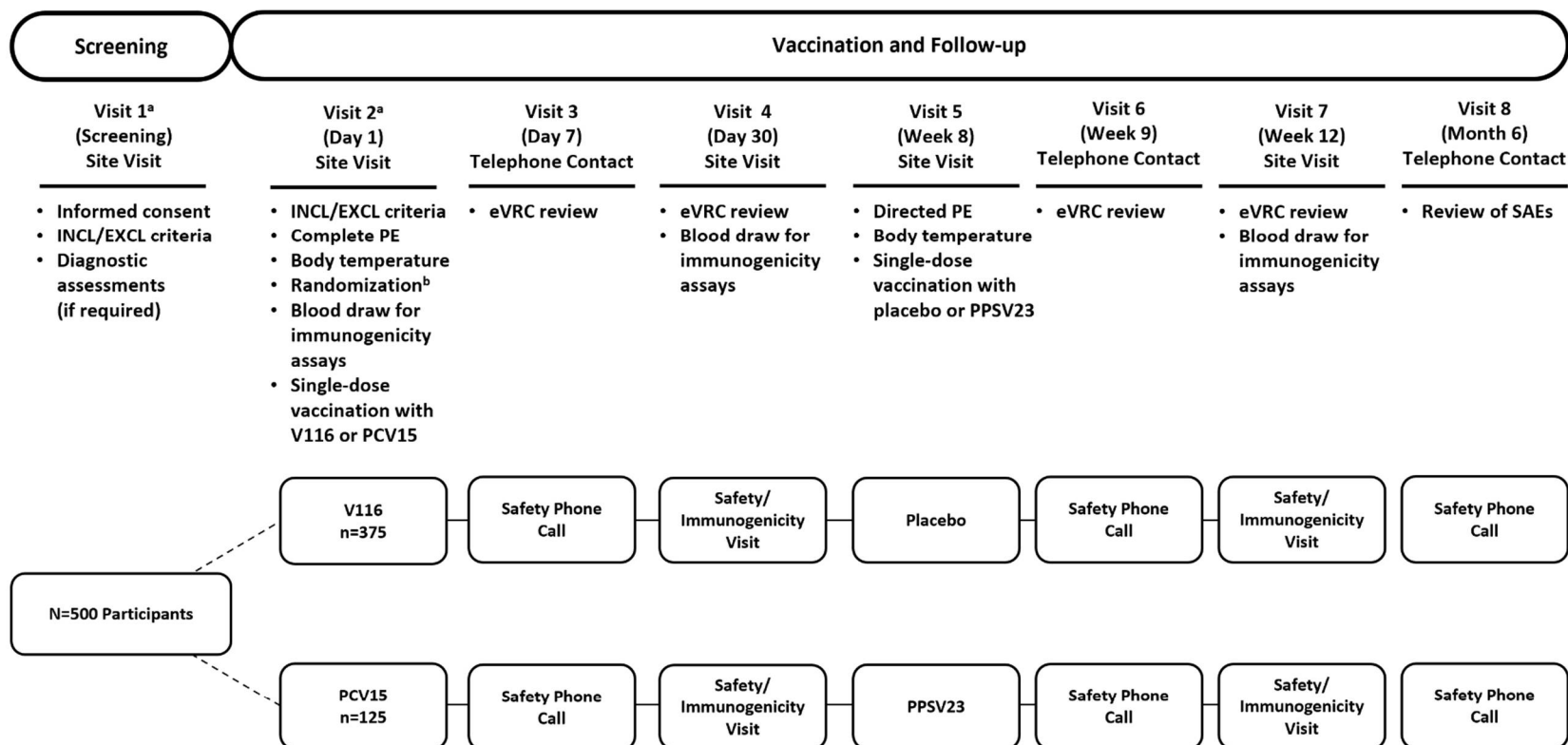
**Study Accepts Healthy Participants:** No

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; PCV15=pneumococcal 15-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent); SAE=serious adverse event.

<sup>a</sup> Visit 2 may occur on the same day as Visit 1 if all INCL/EXCL criteria are satisfied at screening. If Visit 1 and Visit 2 occur on different days, Visit 2 should occur ≤30 days after Visit 1.

<sup>b</sup> Randomization will be stratified by age (18 to 49 years and 50 to 64 years) and type/number of increased-risk conditions for pneumococcal disease (diabetes mellitus only, chronic heart disease only, chronic kidney disease only, chronic liver disease only, chronic lung disease only, and ≥2 increased-risk conditions).



### 1.3 Schedule of Activities

Study Period:	Screening	Intervention and Follow-up							Notes
Visit Number:	1	2	3	4	5	6	7	8	
Visit Type:	Visit	Visit	TC	Visit	Visit	TC	Visit	TC	
Study Day:	Screening	Day 1 (Rand. and Vac. 1)	Day 7 (after Vac. 1)	Day 30 (after Vac. 1)	Week 8 (Vac. 2)	Week 9 (Day 7 after Vac. 2)	Week 12 (Day 30 after Vac. 2)	Month 6 (after Vac. 1)	Visits 1 and 2 may occur on the same day (Section 8.11).
Visit Window:	NA	≤30 days after Visit 1	Day 7 to Day 10 after Visit 2	Day 30 to Day 44 after Visit 2	Day 60 to Day 74 after Visit 2	Day 7 to Day 10 after Visit 5	Day 30 to Day 44 after Visit 5	Day 166 to Day 194 after Visit 2	
Informed Consent	X								Must be obtained before any study procedures are conducted.
Informed Consent for Optional FBR	X								Must be obtained before any sample collection.
Assignment of Screening Number	X								
Participant Identification Card	X	X							
Inclusion/Exclusion Criteria	X	X							
Medical History	X	X							
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	X	X	X	X	X	
Diagnostic Assessments (if required)	X								Performed only if results required for Inclusion Criterion 1 (Section 5.1) are not available.

Study Period:	Screening	Intervention and Follow-up							Notes
Visit Number:	1	2	3	4	5	6	7	8	
Visit Type:	Visit	Visit	TC	Visit	Visit	TC	Visit	TC	
Study Day:	Screening	Day 1 (Rand. and Vac. 1)	Day 7 (after Vac. 1)	Day 30 (after Vac. 1)	Week 8 (Vac. 2)	Week 9 (Day 7 after Vac. 2)	Week 12 (Day 30 after Vac. 2)	Month 6 (after Vac. 1)	Visits 1 and 2 may occur on the same day (Section 8.11).
Visit Window:	NA	≤30 days after Visit 1	Day 7 to Day 10 after Visit 2	Day 30 to Day 44 after Visit 2	Day 60 to Day 74 after Visit 2	Day 7 to Day 10 after Visit 5	Day 30 to Day 44 after Visit 5	Day 166 to Day 194 after Visit 2	
Assignment of Randomization Number		X							
V116 or PCV15 Administration (blinded)		X							
Placebo or PPSV23 Administration (blinded)					X				
Provide Electronic Device or Configure Participant's Own Electronic Device for eVRC Data Collection		X							
Review eVRC Data With Participant			X	X		X	X		
Collect Electronic Device From Participants Who Received an Electronic Device							X		
Complete Telephone Contact Questionnaire								X	
<b>Safety Procedures</b>									
Complete Physical Examination		X							Performed by investigator or medically qualified designee before vaccination.

Study Period:	Screening	Intervention and Follow-up							Notes
Visit Number:	1	2	3	4	5	6	7	8	
Visit Type:	Visit	Visit	TC	Visit	Visit	TC	Visit	TC	
Study Day:	Screening	Day 1 (Rand. and Vac. 1)	Day 7 (after Vac. 1)	Day 30 (after Vac. 1)	Week 8 (Vac. 2)	Week 9 (Day 7 after Vac. 2)	Week 12 (Day 30 after Vac. 2)	Month 6 (after Vac. 1)	Visits 1 and 2 may occur on the same day (Section 8.11).
Visit Window:	NA	≤30 days after Visit 1	Day 7 to Day 10 after Visit 2	Day 30 to Day 44 after Visit 2	Day 60 to Day 74 after Visit 2	Day 7 to Day 10 after Visit 5	Day 30 to Day 44 after Visit 5	Day 166 to Day 194 after Visit 2	
Directed Physical Examination					X				Performed by investigator or medically qualified designee before vaccination.
Pregnancy Test (if applicable)		X			X				POCBP must have a negative urine or serum test (consistent with local requirements and sensitive to ≤25 IU hCG) result before each vaccination.
Prevaccination Body Temperature Measurement		X			X				Reschedule if participant has febrile illness within 72 hours before vaccination.
Postvaccination Observation Period		X			X				Observed by blinded study-site personnel for at least 30 minutes postvaccination.

Study Period:	Screening	Intervention and Follow-up							Notes
Visit Number:	1	2	3	4	5	6	7	8	
Visit Type:	Visit	Visit	TC	Visit	Visit	TC	Visit	TC	
Study Day:	Screening	Day 1 (Rand. and Vac. 1)	Day 7 (after Vac. 1)	Day 30 (after Vac. 1)	Week 8 (Vac. 2)	Week 9 (Day 7 after Vac. 2)	Week 12 (Day 30 after Vac. 2)	Month 6 (after Vac. 1)	Visits 1 and 2 may occur on the same day (Section 8.11).
Visit Window:	NA	≤30 days after Visit 1	Day 7 to Day 10 after Visit 2	Day 30 to Day 44 after Visit 2	Day 60 to Day 74 after Visit 2	Day 7 to Day 10 after Visit 5	Day 30 to Day 44 after Visit 5	Day 166 to Day 194 after Visit 2	
AE Monitoring	X	X	X	X	X	X	X	X	Nonserious AEs collected through 30 days after each vaccination; SAEs and deaths collected through duration of study participation.
<b>Immunogenicity Procedures</b>									
Serum for Immunogenicity Assays		X		X			X		Visit 2 sample should be collected before vaccination.
<b>Future Biomedical Research</b>									
Blood (DNA) for FBR		X							For participants who provided FBR consent, sample should be collected before vaccination at Visit 2, or at a later date as long as FBR consent is obtained before collection.
AE=adverse event; DNA=deoxyribonucleic acid; eVRC=electronic vaccination report card; FBR=future biomedical research; hCG=human chorionic gonadotropin; IU=international units; NA=not applicable; PCV15=pneumococcal 15-valent conjugate vaccine; POCBP= participants of childbearing potential; PPSV23=pneumococcal vaccine, polyvalent (23-valent); SAE=serious adverse event; Rand.=randomization; TC=telephone contact; Vac.=vaccination.									

## 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, called an indirect effect.

An unmet medical need exists as there remains a substantial burden of disease in adults due to serotypes not currently included in licensed pneumococcal vaccines. V116 is an investigational PCV designed to address this unmet need and includes *S pneumoniae* serotypes not included in licensed pneumococcal vaccines, accounting for the majority of IPD currently observed in adults.

Vaccination guidelines generally categorize individuals as having increased risk or high risk for pneumococcal disease. The category of increased risk refers to those individuals with underlying chronic conditions such as diabetes, heart disease, kidney disease, liver disease, lung disease (including COPD and asthma), smoking, and heavy alcohol consumption. These individuals are at increased risk for pneumococcal disease and its complications; the incidence rates of IPD are 2- to 8-fold higher in persons with chronic illnesses relative to healthy individuals, and rates increase with the number of conditions present [Kyaw, M. H., et al 2005] [Weycker, D., et al 2016] [Curcio, D., et al 2015] [Morton, J. B., et al 2017] [Torres, A., et al 2015]. The concern for this population is underscored by the high prevalence of several of these conditions in the adult population, with heart disease, lung disease, and diabetes ranked as some of the top causes of death and disability globally [GBD 2019 Diseases and Injuries Collaborators 2020] [Ward, B. W., et al 2014] [Centers for Medicare and Medicaid Services 2022].

Recommendations for vaccination can vary for each risk condition, and can also vary by country/region. In the most recent updates to recommendations (October 2021), the US ACIP recommends pneumococcal vaccination either with a sequential regimen of PCV15 followed by PPSV23 or with a single dose of PCV20 for adults 19 to 64 years of age with chronic medical conditions or immunocompromising conditions that confer an increased risk of pneumococcal disease [Kobayashi, M., et al 2022]. Many other countries and regions follow similar recommendations (sequential regimen of PCV13 followed by PPSV23 or PPSV23 alone) for adults with certain conditions at increased risk of pneumococcal disease [Castiglia P. 2014] [Bonnave, C., et al 2019].

Adults at increased risk for pneumococcal disease due to underlying conditions may benefit from receiving V116, as V116 has broader protection against pneumococcal disease compared with currently licensed pneumococcal vaccines.

This clinical study is designed to evaluate the safety, tolerability, and immunogenicity of a single dose of V116 in pneumococcal vaccine-naïve individuals at increased risk for pneumococcal disease due to diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, and chronic lung disease.

## 2.2 Background

To date, a Phase 1/2 study (V116-001) and a Phase 1 study in Japan (V116-002) have been conducted with V116 in pneumococcal vaccine-naïve adults. Results from the Phase 1 part of V116-001 were used to select the vaccine formulation for subsequent development. Results from both studies showed that V116 is immunogenic and has acceptable safety and tolerability in healthy 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*) is one of the single largest vaccine-preventable causes of death in children and older adults ( $\geq 65$  years of age) worldwide. PCV use in children has decreased the incidence of disease caused by vaccine serotypes and has led to indirect protection in unvaccinated individuals from other age groups. This has resulted in a decrease in hospital admissions for pneumococcal disease in adults  $\geq 65$  years of age, including estimated decreases of 29% and 34% in admissions due to IPD and noninvasive pneumococcal pneumonia, respectively [Simonsen, L., et al 2014]. In some countries, including the US, the decrease in pneumococcal disease in children vaccinated with PCV has led to the recommendation to vaccinate adults with PCVs. However, surveillance data over the last 5 years does not definitively indicate that the use of PCVs in adults results in a similar reduction in pneumococcal disease after recent vaccination efforts and public health initiatives [Matanock, A. 2018]. There is a residual burden of disease in the US that is estimated at 1.8, 16.6, and 24 cases of IPD per 100,000 in adults 18 to 49, 50 to 64,  $\geq 65$  years of age, respectively, and surveillance data estimates that serotypes included in PCVs licensed during this time account for approximately 23% to 50% of these cases [Centre for Disease Control and Prevention 2016] [Centers for Disease Control and Prevention 2019] [Kobayashi, M., et al 2022] [Zhang, D., et al 2018]. This elevated risk in adults results in a substantial clinical and economic burden to public health.

This residual burden of disease in adults reflects the difference in serotype distribution in adults compared with infants and children. An increasing incidence of disease due to serotypes not included in the licensed PCVs has been observed, particularly in adults [Miller, Elizabeth, et al 2011] [Moore, M. R., et al 2015] [Pilishvili, T. 2015] [van der Linden, M., et al 2015] [Golden, A. R., et al 2016]. Increases in IPD cases due to nonvaccine serotypes (3, 7F, and 19A after implementation of PCV7; 22F and 33F after widespread usage of PCV13) have been observed in both pediatric and older adult ( $\geq 65$  years of age) populations in the US [Hicks, L. A., et al 2007] [Pilishvili, Tamara, et al 2010] [Waight, P. A., et al 2015] [Moore, M. R., et al 2015] [Demczuk, W. H. B., et al 2013]. Similarly, in the EU, serotype

replacement due to nonvaccine serotypes is being observed in older adults and may decrease the potential additional benefit of vaccination with currently available PCVs [European Center for Disease Prevention and Control 2018].

Serotypes were selected for inclusion in V116 based, in part, on available global epidemiology data with a primary focus on older adults ( $\geq 65$  years of age) in the US and EU, regions with an established pediatric vaccination program. V116 includes serotypes that are the largest contributors to adult residual disease, including select serotypes from PPSV23, PCV13, PCV15, and PCV20, as well as unique serotypes not included in any licensed pneumococcal vaccine. The V116 serotypes are responsible for  $>80\%$  of adult IPD in the US, Germany, France, Canada, and Japan, approximately  $90\%$  of IPD in the UK, and approximately  $70\%$  of IPD in Australia, based on data from 2018 [Public Health Agency of Canada 2018] [Demczuk, W. H. B., et al 2018] [Public Health England 2021] [Public Health England 2021] [van der Linden, M., et al 2019] [Batah, J. 2018] [National Institute of Infectious Diseases 2018] [Nakano, S., et al 2016]. In 2019, the most recent year for which serotype-specific data are available in both the EU and US, the serotypes in V116 accounted for  $82\%$  and  $85\%$  of IPD, respectively, in adults  $\geq 65$  years [European Centre for Disease Prevention and Control 2022] (Centers for Disease Control and Prevention, IPD serotype data 2019, as compiled from data provided through Active Bacterial Core surveillance [ABCs]).

V116 is designed to target serotypes that account for the majority of IPD in adults, including serotypes not currently contained in any licensed pneumococcal vaccine, thereby addressing the unmet medical need of preventing residual pneumococcal disease in adults. It is being developed to support an indication for active immunization for the prevention of invasive disease and pneumonia caused by *S pneumoniae* serotypes 3, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older. Note that serotype 15C represents deOAc15B as the molecular structures for deOAc15B and 15C are similar.

## **2.2.2 Information on Other Study-related Therapy**

### **2.2.2.1 PCV15**

Refer to approved labeling for detailed background information on PCV15.

PCV15 is a pneumococcal conjugate vaccine that includes 15 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) individually conjugated to the CRM197 and formulated with aluminum phosphate adjuvant.

### **2.2.2.2 PPSV23**

Refer to 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.

### 2.2.2.3 Pneumococcal Vaccination Guidelines

Many countries have implemented age-based and/or risk-based recommendations for pneumococcal vaccination of adults. Age-based recommendations typically start at 65 years of age due to the increased risk of pneumococcal disease associated with age.

Two expanded valent PCVs (PCV15 and PCV20) have been recently approved in the US, EU, and elsewhere. In the US, the ACIP updated their vaccination guidelines to recommend that adults  $\geq 65$  years of age should receive either PCV15 followed by PPSV23, or PCV20 alone [Kobayashi, M., et al 2022]. It is expected that, globally, vaccination guidelines will be updated to include these newer PCVs. However, PCV13 and PPSV23 are currently the 2 most broadly available vaccines in the majority of countries in the EU and other countries outside the US. While there is variability in the vaccination guidelines, PPSV23 alone, and PCV13 followed by PPSV23 are the 2 most common regimens recommended in European countries that have age-based guidelines for adults [European Centre for Disease Prevention and Control 2021] [Bonnave, C., et al 2019]. Despite national vaccination guidelines and recommendations from institutions such as the European Council and the World Coalition on Adult Vaccination, surveys have estimated that only 20% to 30% of adults  $\geq 65$  years of age in Europe are currently vaccinated [Independent Polling System Of Society 2017].

Recommendations generally address vaccination of individuals who have an increased risk of pneumococcal disease, with the level of risk categorized based on the underlying condition. Conditions associated with increased risk include, but are not limited to, diabetes mellitus, chronic heart disease, chronic liver disease (including cirrhosis), chronic lung disease (including COPD and asthma), chronic kidney disease (without kidney failure), alcoholism, and cigarette smoking. Conditions associated with the highest risk include, but are not limited to, congenital or acquired asplenia, sickle cell disease/other hemoglobinopathies, chronic kidney failure, congenital or acquired immunodeficiencies, generalized malignancy, hematologic malignancy, HIV infection, nephrotic syndrome, solid organ transplant, and hematopoietic stem cell transplant [Kobayashi, M., et al 2022]. Vaccination recommendations for these groups with increased risk or high risk vary across 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.

Despite the public health impact of currently available pneumococcal vaccines, pneumococcal disease in adults remains a significant unmet medical need. *S pneumoniae* is a major cause of vaccine-preventable disease worldwide, resulting in considerable morbidity and mortality [Troeger, C., et al 2018].

Vaccination with PCVs has reduced the incidence of disease caused by vaccine serotypes in the population targeted by the vaccination (primarily children  $< 5$  years of age in most countries) and has had an indirect effect in other age groups. However, in several countries, infant vaccination with PCVs has also led to increases in IPD due to serotypes not included



in the licensed PCVs, particularly in adults. This has resulted in an unmet medical need in this population.

V116 is designed to provide substantially broader pneumococcal disease coverage in adults as compared with currently licensed pneumococcal vaccines and is anticipated to have a generally comparable safety profile. Clinically important safety findings have not been identified to date based on data from early phase clinical studies with V116.

The benefit-risk profile for V116 supports continued evaluation.

In this study, approximately 25% of participants will receive PCV15 followed by PPSV23, a vaccine regimen recommended for the prevention of pneumococcal disease in vaccine-naïve adults 19 to 64 years of age with certain underlying medical conditions for pneumococcal disease [Kobayashi, M., et al 2022]. V116 is expected to provide immune responses comparable to PCV15+PPSV23 for the common serotypes in both regimens while providing additional coverage for the serotypes unique to V116. It is unknown if the investigational V116 will have the same clinical benefit as PCV15+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 documents.

### 3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There is no hypothesis testing in this study.

Objectives and endpoints described below will be evaluated in pneumococcal vaccine-naïve participants 18 to 64 years of age (inclusive) who are at increased risk for pneumococcal disease due to an underlying medical condition.

Primary Objectives	Primary Endpoints
To evaluate the safety and tolerability of V116 as assessed by the proportion of participants with adverse events (AEs).	<ul style="list-style-type: none"><li>Solicited injection-site AEs from Day 1 through Day 5 postvaccination.</li><li>Solicited systemic AEs from Day 1 through Day 5 postvaccination.</li><li>Vaccine-related Serious Adverse Events (SAEs) from Day 1 through the duration of participation in the study.</li></ul>
To evaluate the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) postvaccination with V116 (30 days postvaccination [Day 30]) and PCV15 + PPSV23 (30 days postvaccination with the final dose in the regimen [Week 12]) within each vaccination group separately.	<p>Serotype-specific OPA responses:</p> <ul style="list-style-type: none"><li>13 serotypes common between V116 and PCV15 + PPSV23.</li><li>8 serotypes unique to V116.</li></ul>

Secondary Objectives	Secondary Endpoints
To evaluate the serotype-specific Immunoglobulin G (IgG) geometric mean concentrations (GMCs) postvaccination with V116 (Day 30) and PCV15 + PPSV23 (Week 12) within each vaccination group separately.	Serotype-specific IgG responses: <ul style="list-style-type: none"> <li>13 serotypes common between V116 and PCV15 + PPSV23.</li> <li>8 serotypes unique to V116.</li> </ul>
To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a $\geq 4$ -fold rise from baseline (Day 1) to postvaccination with V116 (Day 30) and from baseline (Day 1) to postvaccination with PCV15 + PPSV23 (Week 12) for both OPA and IgG responses within each vaccination group separately.	Serotype-specific OPA and IgG responses: <ul style="list-style-type: none"> <li>13 serotypes common between V116 and PCV15 + PPSV23.</li> <li>8 serotypes unique to V116.</li> </ul>
Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
To evaluate the ratios of serotype-specific OPA GMTs and IgG GMCs postvaccination with V116 (Day 30) compared with PCV15 + PPSV23 (Week 12).	Serotype-specific OPA and IgG responses: <ul style="list-style-type: none"> <li>13 serotypes common between V116 and PCV15 + PPSV23.</li> <li>8 serotypes unique to V116.</li> </ul>
To evaluate the cross-reactive immune responses to serotypes within a serogroup 30 days postvaccination.	Serotype-specific OPA and IgG responses.

## 4 STUDY DESIGN

### 4.1 Overall Design

This is a randomized, active comparator-controlled, parallel-group, multisite, double-blind study of V116 in adults 18 to 64 years of age with increased risk for pneumococcal disease.

Approximately 500 participants who have not previously received any pneumococcal vaccines other than routine childhood PCVs (vaccine naïve) will be randomized in a 3:1 ratio to receive either V116 on Day 1 followed by placebo at Week 8, or PCV15 on Day 1 followed by PPSV23 at Week 8. Randomization will be stratified by age at time of randomization (18 to 49 years and 50 to 64 years) and the type/number of increased-risk conditions for pneumococcal disease (diabetes mellitus only, chronic heart disease only, chronic kidney disease only, chronic liver disease only, chronic lung disease only, and  $\geq 2$  increased-risk conditions). At least 20% of participants will be 18 to 49 years of age. For participants with a single increased-risk condition, it is expected that at least 5% of participants with each individual condition will be enrolled.

Participants must be on stable treatment for their risk condition for  $\geq 3$  months with no anticipated major change in treatment expected during the study, with a maximum of 1 hospitalization directly related to the risk condition within 3 months before the first study vaccination.

An eVRC will be used by all participants to record solicited injection-site AEs, solicited systemic AEs, and daily body temperature from Day 1 through Day 5 following each vaccination. Unsolicited AEs will be collected through Day 30 following each vaccination. All participants 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 2), Day 30 (Visit 4), and at Week 12 (Visit 7).

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 vaccine-naïve adults 18 to 64 years of age at increased risk for pneumococcal disease.

Adults with stable chronic medical conditions, including diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, and chronic lung disease will be included in this study. These individuals are at 2- to 8-fold increased risk for pneumococcal disease relative to healthy adults [Kyaw, M. H., et al 2005] [Weycker, D., et al 2016] [Curcio, D., et al 2015] [Morton, J. B., et al 2017] [Torres, A., et al 2015]. As it is expected that the number of participants enrolled with each risk condition will vary, this study will be stratified by the type and number of risk conditions to ensure balance between the intervention group.

The randomization ratio of 3:1 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.

Individuals with severe or end-stage 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 confusion of medical treatment effects with the safety and immunogenicity of the vaccine.

Individuals 50 to 64 years of age have been included in this study as older adults with chronic underlying disease are at even greater risk for pneumococcal disease and its associated morbidity and mortality as the incidence of IPD is directly related to age, with over half of all cases occurring in adults  $\geq 50$  years of age [Drijkoningen, J. J 2014] [Imai, K., et al 2018].

#### **4.2.1 Rationale for Endpoints**

##### **4.2.1.1 Immunogenicity Endpoints**

The immunogenicity endpoints are consistent with previous studies evaluating PCVs.

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.

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

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.

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

##### **4.2.1.2 Safety Endpoints**

Safety information will be collected from all participants on an eVRC. The eVRC used to record AEs during the postvaccination periods (Section 8.1.9) is structured as recommended in the final US 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 9.4.2.

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

#### 4.2.1.3 Future Biomedical Research

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

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

#### 4.2.2 Rationale for the Use of Comparator/Placebo

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

The sequential regimen of a PCV followed by PPSV23 8 weeks later is recommended in many countries for individuals at increased risk for pneumococcal disease [Kobayashi, M., et al 2022] [Robert Koch Institut 2017]. Of the approved pneumococcal vaccines, the sequential regimen of PCV15 followed by PPSV23 (PCV15+PPSV23) 1 year later for individuals at increased risk for pneumococcal disease is consistent with US ACIP recommendations [Kobayashi, M., et al 2022] and has the broadest coverage against *S pneumoniae* serotypes. It is expected that many global vaccination guidelines will include this regimen of PCV15+PPSV23.

The sequential regimen of PCV15 + PPSV23 has 13 serotypes in common with V116: 6 serotypes (3, 6A, 7F, 19A, 22F, and 33F) contained in PCV15 and 7 serotypes (8, 9N, 10A, 11A, 12F, 17F, and 20) contained in PPSV23 but not included in PCV15. V116 contains 8 unique serotypes (15A, 15C, 16F, 23A, 23B, 24F, 31, and 35B) not included in any licensed pneumococcal vaccine. Note that serotype 15C represents deOAc15B as the molecular structures for deOAc15B and 15C are similar.

Placebo is used in this study to maintain blinding. The placebo is sterile saline for injection.

#### 4.3 Justification for Dose

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 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 support the selection of the V116 dose of 4 µg/each PnPs for further development in Phase 3.

Refer to the IB for detailed background information on V116.

The doses of PCV15 and PPSV23 selected for use in this study are the approved doses that are consistent with the approved US and EU dosing and product labeling of VAXNEUVANCE™ and PNEUMOVAX™23, respectively.

#### **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 result(s) of  $\geq 1$  of the following risk conditions for pneumococcal disease (Participants who are living with  $\geq 2$  increased-risk conditions listed below must meet the respective diagnostic criteria for each condition to be eligible for enrollment):
  - Diabetes mellitus, receiving treatment with  $\geq 1$  approved antidiabetic medication, with all HbA1c measurements  $\leq 9\%$  within 6 months before first study vaccination (Day 1).



- Compensated chronic liver disease. Participants must meet  $\geq 1$  of the following:
  - Laboratory-confirmed FIB-4 score of  $\geq 1.45$  within 6 months before first study vaccination (Formula: age [years] x AST [IU/L]/platelet count [ $10^9/L$ ] x  $ALT^{1/2}$  [IU/L]) [World Health Organization 2018].
  - Laboratory-confirmed APRI of  $>0.5$  within 6 months before first study vaccination (APRI formula:  $AST \div \text{laboratory ULN for AST} \times 100 \div [\text{platelet count} \div 100]$ ).
  - Prior FibroTest® (FibroSure®) with Fibrosis Score  $>0.25$  performed within 5 years before first study vaccination (Day 1).
  - Prior imaging (including FibroScan® with interpretable score  $>7$  kPa) showing cirrhosis and/or fibrosis within 5 years before first study vaccination (Day 1).
  - Prior biopsy showing cirrhosis and/or fibrosis within 5 years before first study vaccination (Day 1).
- Diagnosis of COPD managed per local guidelines, and confirmed based on  $\geq 1$  of the following:
  - Spirometric data in the 5 years before first study vaccination (Day 1) showing postbronchodilator FEV1/FVC ratio  $<0.7$  and FEV1  $\geq 30\%$  predicted, corresponding to spirometric Global Initiative for Chronic Obstructive Lung Disease Stage 1 to 3 by severity assessment [Global Initiative for Chronic Obstructive Lung Disease 2019].
  - A postbronchodilator improvement in PEFR by  $<20\%$  performed in the 5 years before first study vaccination (Day 1) based on WHO PEN Disease Interventions for Primary Health Care (2020) [World Health Organization 2020].
- Diagnosis of mild or moderate persistent asthma managed per local guidelines, and confirmed based on  $\geq 1$  of the following:
  - Documented reversible airflow obstruction on spirometry consistent with guidelines for the diagnosis of asthma performed within 5 years before first study vaccination (Day 1).
  - A postbronchodilator improvement in PEFR by  $\geq 20\%$  in the 5 years before first study vaccination (Day 1), based on WHO PEN Disease Interventions for Primary Health Care (2020) [World Health Organization 2020].
- Confirmed diagnosis of chronic heart disease managed per local guidelines, including:
  - Cardiomyopathies documented within 5 years before first study vaccination (Day 1)
  - Congestive heart failure documented within 5 years before first study vaccination (Day 1)
  - Noncyanotic congenital heart disease.
- Confirmed diagnosis of chronic kidney disease ( $>3$  months duration) in 1 of the eligible KDIGO-recommended stages of GFR AND albuminuria categories [Kidney Disease: Improving Global Outcomes 2013] specified in [Table 1](#) within 6 months before first study vaccination (Day 1)

Table 1 Eligibility Based on KDIGO-recommended Stages of GFR and Albuminuria

		Albuminuria		
		A1	A2	A3
GFR (mL/min/1.73 m <sup>2</sup> )		<3 mg/mmol or <30 mg/g	3 to 30 mg/mmol or 30 to 300 mg/g	>30 mg/mmol or >300 mg/g
G1	≥90	Not eligible	Eligible	Not eligible
G2	60 to 89	Eligible		
G3a	45 to 59			
G3b	30 to 44	Not eligible		
G4	15 to 29			
G5	<15			

GFR=glomerular filtration rate.

**Note:** Diagnostic assessments specified above may be conducted if not available in medical records.

- 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 first study vaccination (Day 1).

**Note:** The participant may have other comorbidities if they are assessed to be stable as per the investigator's judgment.

### Demographics

- Is an individual of any sex/gender, from 18 years to 64 years of age inclusive, at the time of providing informed consent.

### Female Participants

- 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 before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.2.
- 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**

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

### **Additional Categories**

6. The participant has the ability to complete eVRC data collection without assistance based on judgment of the investigator.

## **5.2 Exclusion Criteria**

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

### **Medical Conditions**

1. Has a history of active hepatitis with elevation in pretreatment AST or ALT values >5 times ULN within 3 months before first study vaccination (Day 1)
2. Has a history of diabetic ketoacidosis or 2 or more episodes of severe, symptomatic hypoglycemia within 3 months before first study vaccination (Day 1).
3. Has a history of myocardial infarction, acute coronary syndrome, transient ischemic attack, or ischemic or hemorrhagic stroke within 3 months before first study vaccination (Day 1).
4. Has a history of severe pulmonary hypertension with WHO functional class  $\geq 3$  or history of Eisenmenger syndrome.
5. Has a history of autoimmune related chronic kidney disease, chronic kidney failure, a reversible cause of kidney disease, nephrotic syndrome, or any ineligible KDIGO-recommended stage of GFR AND Albuminuria specified in [Table 1](#).
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 first study vaccination (Day 1).
7. Has a known hypersensitivity to any component of V116, PCV15, or PPSV23, 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 IM vaccination.
10. \*Had a recent febrile illness (defined as oral or tympanic temperature  $\geq 100.4$  °F [ $\geq 38.0$  °C] or axillary or temporal temperature  $\geq 99.4$  °F [ $\geq 37.4$  °C]) or received antibiotic therapy for any acute illness occurring within 72 hours before receipt of any 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 (eg, breast carcinoma, cervical cancer 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 any prior pneumococcal vaccine or is expected to receive any pneumococcal vaccine during the study outside the protocol. **Exception:** participants with childhood pneumococcal vaccination before the age of 5 will be permitted.
15. \*Received systemic corticosteroids (prednisone equivalent of  $\geq 20$  mg/day) for  $\geq 14$  consecutive days and has not completed intervention  $\geq 14$  days before receipt of study vaccine at Visit 2 (Day 1). **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.
16. 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.
17. \*Received any nonlive vaccine  $\leq 14$  days before receipt of any study vaccine or is scheduled to receive any nonlive vaccine  $\leq 30$  days after receipt of any 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  $\geq 7$  days before or  $\geq 15$  days after receipt of any study vaccine.
18. \*Received any live virus vaccine (including SARS-CoV-2 live virus vaccines)  $\leq 30$  days before receipt of any study vaccine or is scheduled to receive any live virus vaccine  $\leq 30$  days after receipt of any study vaccine.
19. Received a blood transfusion or blood products, including immunoglobulin  $\leq 6$  months before receipt of any study vaccine or is scheduled to receive a blood transfusion or blood product  $\leq 30$  days after receipt of any study vaccine. Autologous blood transfusions are not considered an exclusion criterion.
20. Receiving chronic home oxygen therapy.

### **Prior/Concurrent Clinical Study Experience**

21. 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**

22. In the opinion of the investigator, has a history of clinically relevant drug or alcohol use that interfere with participation in protocol-specified activities.
23. 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.
24. 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 2 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 who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

### **5.5 Participant Replacement Strategy**

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

## **6 STUDY INTERVENTION**

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

Clinical supplies (V116, PCV15, PPSV23, and placebo) 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 2](#).

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin.	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, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B)	0.5 mL	IM	Single dose at Visit 2 (Day 1)	Test Product	IMP	Central
V116	Experimental	Placebo (sterile saline)	Biological/Vaccine	Injection, Solution	N/A	0.5 mL	IM	Single dose at Visit 5 (Week 8)	Placebo	IMP	Central or local
PCV15 + PPSV23	Active Comparator	Pneumococcal 15-valent conjugate vaccine	Biological/Vaccine	Injection, Suspension	2 µg of each PnPs antigen (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) and 4 µg of PnPs antigen 6B	0.5 mL	IM	Single dose at Visit 2 (Day 1)	Comparator	IMP	Central or local

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin.	Vaccination Regimen	Use	IMP or NIMP/AxMP	Sourcing
PCV15 + 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 5 (Week 8)	Comparator	IMP	Central or local

Admin=administration; EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; N/A=not applicable; PCV15=pneumococcal 15-valent conjugate vaccine; PnPs=pneumococcal polysaccharide; PPSV23=pneumococcal vaccine, polyvalent (23-valent); 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 2](#) 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 Medical Devices**

Drug-device combination/combo medicinal product(s) provided as prefilled syringes for use in this study are V116, VAXNEUVANCE™, and PNEUMOVAX™23. 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 3:1 ratio to receive either V116 + placebo or PCV15 + PPSV23, respectively.

#### **6.3.2 Stratification**

Intervention randomization will be stratified according to the following factors:

1. Participant age at time of randomization:
  - 18 to 49 years of age
  - 50 to 64 years of age

At least 20% of participants will be 18 to 49 years of age.
2. Number and type of increased-risk conditions a participant has at the time of randomization:
  - Diabetes mellitus only
  - Chronic heart disease only
  - Chronic kidney disease only
  - Chronic liver disease only
  - Chronic lung disease only
  - $\geq 2$  increased-risk conditions (diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, and/or chronic lung disease).

For participants with a single increased-risk condition, it is expected that at least 5% of participants with each individual condition will be enrolled.

Disease conditions at increased risk for pneumococcal disease include any chronic condition listed under Inclusion Criterion 1 (Section 5.1).

#### **6.3.3 Blinding**

A double-blinding technique will be used. V116, PCV15, PPSV23, and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s)



who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Because V116, PCV15, PPSV23, and placebo 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 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

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

#### 6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (Section 5.2). If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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 vaccines according to the time frames specified in the Exclusion Criteria (Section 5.2).
- Receipt of systemic corticosteroids (prednisone equivalent  $\geq 20$  mg/day) for  $\geq 14$  consecutive days is prohibited from 14 days before each vaccination through 30 days after each 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.

### **6.7 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**

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified vaccination regimen will continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.11 and Section 8.11.3.

A participant must be discontinued from study intervention, but continue to be monitored in the study, for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive urine or serum pregnancy test before vaccination at Visit 5 (Week 8).

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

### **7.2 Participant Withdrawal From the Study**

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in

Section 8.1.11. 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 are outlined in Section 7.3.

### **7.3 Lost to Follow-up**

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

## **8 STUDY ASSESSMENTS AND PROCEDURES**

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

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

#### **8.1.1.1 General Informed Consent**

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

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

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

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

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

#### **8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research**

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

to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

### **8.1.2 Inclusion/Exclusion Criteria**

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

### **8.1.3 Participant Identification Card**

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

The participant 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 the first study vaccination (Day 1) will be obtained to ensure that the participant satisfies the inclusion and exclusion criteria of the study. History of tobacco use will be collected for all participants.

### **8.1.5 Prior and Concomitant Medications Review**

#### **8.1.5.1 Prior Medications**

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

The following must be documented before the first study vaccination and recorded on the appropriate eCRF:

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

#### **8.1.5.2 Concomitant Medications**

The investigator or qualified designee will record vaccinations and medications, if any, taken by the participant through Day 30 after each vaccination. Outside this period, report only concomitant medications related to an SAE.

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

The participant will use their eVRC (Section 8.1.9) to record new and/or concomitant medications taken and nonstudy vaccines received from the day of each vaccination through 30 days postvaccination.

#### **8.1.6 Assignment of Screening Number**

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

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1. 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 the participants 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 study 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 vaccines will be administered as indicated in Section 1.3. The day of the first study vaccination is considered Day 1 of the study. Vaccinations may be administered at any time of day and without regard to timing of meals.

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

Participants must not have a fever reported within 72 hours before each vaccination (Section 1.3 and Section 8.3.3).

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

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

#### **8.1.9 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 investigator or delegate will train the participant in the use of the VRC.

The participant will use the eVRC to record body temperature (Section 8.3.3), solicited injection-site AEs, and solicited systemic AEs (Section 8.4.9.1). Unsolicited AEs (Section 8.4.9.2), concomitant medications (including use of any analgesic or antipyretic medication), and nonstudy vaccinations (Section 8.1.5.2) will also be reported. Participants will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC.

The investigator or delegate will review the data captured on the eVRC with the participant as indicated in Section 1.3. Any differences between data reported by the participant on the eVRC and data entered into the clinical database must be clearly explained in the participant's source documents.

#### **8.1.10 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.



### **8.1.11 Discontinuation and Withdrawal**

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

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

#### **8.1.11.1 Withdrawal From Future Biomedical Research**

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

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

### **8.1.12 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 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 after completion of all study-related immunogenicity testing.

#### **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  $\geq 50\%$  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 and a brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard as indicated in Section 1.3. 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 Pregnancy Testing**

A pregnancy test consistent with local requirements (sensitive to at least 25 IU hCG) must be performed before study vaccination at Visit 2 (Day 1) and Visit 5 in POCBP as described in Section 1.3.

Urine or serum tests can be used, and results must be negative before each 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.

### **8.3.3 Body Temperature Measurements**

Each participant's body temperature must be taken by study-site staff before each 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 oral or tympanic temperature  $\geq 100.4$  °F [ $\geq 38.0$  °C]; axillary or temporal temperature  $\geq 99.4$  °F [ $\geq 37.4$  °C]) within 72 hours before any vaccination must be rescheduled.

Participants will also record oral body temperature measurements using the eVRC (Section 8.1.9) from Day 1 to Day 5 postvaccination.

### **8.3.4 Postvaccination Observation Period**

All participants will be observed by blinded study site personnel 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.

### 8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 to 44 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators 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 provides documented informed consent, but before randomization, must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

All nonserious AEs and other reportable safety events (excluding pregnancy and lactation exposure) must be reported by the investigator from the day of randomization through 30 days after the first vaccination and from the time of each subsequent vaccination 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 throughout the duration of the individual's participation in the study, 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 3](#).

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

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

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

<b>Type of Event</b>	<b><u>Reporting Period:</u> Consent to Randomization/ Allocation</b>	<b><u>Reporting Period:</u> Randomization/ Allocation Through Protocol- specified Follow- up Period</b>	<b><u>Reporting Period:</u> After the Protocol- specified Follow- up Period</b>	<b>Time Frame to Report Event and Follow-up Information to Sponsor</b>
SAE	Report if: – due to protocol- specified intervention – causes exclusion – participant is receiving placebo run-in or other run- in treatment	Report all	Report if: – drug/vaccine related. – any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do 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 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 that the fetus will be



born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

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

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

Not applicable for this study.

#### **8.4.7 Events of Clinical Interest**

There are no ECIs for this study.

#### **8.4.8 Medical Device and Drug–Device Combination Products – PQC/Malfunctions**

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

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

PQCs/malfunctions must be reported to the Sponsor. Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities about certain safety information relating to medical devices and drug-device combination products being used in clinical studies.

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

#### **8.4.9 Adverse Events on the VRC**

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

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

##### **8.4.9.1 Solicited Adverse Event**

Solicited AEs for this study are summarized in [Table 4](#).

Table 4 Solicited Adverse Events

Type of Solicited Adverse Event	Predefined Solicited Adverse Events (Preferred Term)	Solicited Period
Injection site	<ul style="list-style-type: none"><li>• Injection-site pain or tenderness (injection-site pain)</li><li>• Injection-site redness (injection-site erythema)</li><li>• Injection-site swelling (injection-site swelling)</li></ul>	Day 1 to Day 5 postvaccination
Systemic	<ul style="list-style-type: none"><li>• Headache (headache)</li><li>• Muscle aches all over body (myalgia)</li><li>• Tiredness (fatigue)</li></ul>	Day 1 to Day 5 postvaccination

#### 8.4.9.2 Unsolicited Adverse Events

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

PK parameters will not be evaluated in this study.

#### 8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

#### 8.8 Biomarkers

Biomarkers are not evaluated in this study.

#### 8.9 Future Biomedical Research Sample Collection

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

- DNA for future research

#### 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 whether they fulfill the entry requirements in Section 5.

If a participant fulfills all entry requirements at Visit 1, then Visit 2 should occur the same day as Visit 1.

If diagnostic assessments are required to confirm eligibility (Section 5.1) or if Visit 2 needs to be rescheduled (Section 5.2), then Visit 2 should occur  $\leq 30$  days after screening (Visit 1).

### **8.11.2 Treatment Period/Vaccination Visits**

Requirements during the treatment period are outlined in Section 1.3.

If Visit 2 does not occur on the same day as Visit 1, a review of inclusion/exclusion criteria, prior medications/vaccinations, and medical history must be repeated before vaccination. Visit 2 should occur  $\leq 30$  days after Visit 1.

If Visit 2 is rescheduled (see Section 5.2 and Section 8.3.3), 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.

If Visit 5 is rescheduled (see Section 8.3.3), a pregnancy test (if applicable); a body temperature measurement, prior medications/vaccinations, and medical history must be repeated before vaccination

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

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

## 9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

### 9.1 Statistical Analysis Plan Summary

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

<b>Study Design Overview</b>	A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults 18 to 64 years of Age With Increased Risk for Pneumococcal Disease.
<b>Treatment Assignment</b>	Participants will be randomly assigned in a 3:1 ratio to receive V116 + placebo or PCV15 + PPSV23. Randomization will be stratified based on the participant's age (18 to 49 years, and 50 to 64 years), and by the type/number of increased-risk conditions for pneumococcal disease at the time of randomization as defined in Section 6.3.2.
<b>Analysis Populations</b>	<b>Immunogenicity:</b> PP population <b>Safety:</b> APaT population
<b>Primary Endpoint(s)</b>	<b>Immunogenicity:</b> <ul style="list-style-type: none"> <li>Serotype-specific OPA GMTs postvaccination with V116 (30 days postvaccination [Day 30]) or PCV15 + PPSV23 (30 days postvaccination with the final dose in the regimen [Week 12])</li> </ul> <b>Safety:</b> <ul style="list-style-type: none"> <li>Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) from Day 1 through Day 5 postvaccination</li> <li>Proportion of participants with solicited systemic AEs (muscle aches all over body/myalgia, headache, and tiredness/fatigue) from Day 1 through Day 5 postvaccination</li> <li>Proportion of participants with vaccine-related SAEs from Day 1 through the duration of participation in the study</li> </ul>
<b>Key Secondary Endpoints</b>	Serotype-specific IgG GMCs postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12)
<b>Statistical Methods for Key Immunogenicity Analyses</b>	Immunogenicity analyses will be conducted separately for each serotype in V116 within each vaccination group. To address the primary immunogenicity objective, evaluation of the OPA GMTs postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12) will include descriptive summaries and within-group 95% CIs for each vaccination group.

<b>Statistical Methods for Key Safety Analyses</b>	For the overall safety evaluation, safety parameters will be summarized via descriptive statistics. For select safety parameters, point estimates and within-group 95% CIs will be provided.
<b>Interim Analyses</b>	To support the periodic review of safety and tolerability data across the adult V116 Phase 3 program, an external unblinded statistician will provide unblinded interim safety summaries to an independent external DMC for their review. Unblinded immunogenicity data will be made available to the DMC on request to enable a benefit-risk assessment.
<b>Multiplicity</b>	No multiplicity adjustment is planned as there is no hypothesis testing.
<b>Sample Size and Power</b>	This study will randomize approximately 375 participants into the V116 group and 125 participants into the PCV15 + PPSV23 group. It is assumed that approximately 338 participants in the V116 group and 113 in the PCV15 + PPSV23 group will be evaluable for PP immunogenicity analyses (90% evaluability rate). There are no hypotheses to be evaluated. Section 9.9.1 provides information about the expected variability of the OPA GMTs given the sample size.

## 9.2 Responsibility for Analyses/In-house Blinding

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

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

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

Blinding issues related to the planned IAs are described in Section 9.7.

## 9.3 Hypotheses/Estimation

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

## 9.4 Analysis Endpoints

Immunogenicity and safety analysis endpoints that will be summarized are listed below.

### 9.4.1 Immunogenicity Endpoints

Immune responses will be measured for each of the serotypes contained in V116: the 6 serotypes in common with PCV15 (3, 6A, 7F, 19A, 22F, and 33F); 7 additional serotypes in common with PPSV23 but not included in PCV15 (8, 9N, 10A, 11A, 12F, 17F, and 20);

8 unique serotypes in V116 (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 postvaccination with V116 (30 days postvaccination [Day 30]) or PCV15 + PPSV23 (30 days postvaccination with the final dose in the regimen [Week 12])
  - 13 serotypes common between V116 and PCV15 + PPSV23
  - 8 serotypes unique to V116 relative to PCV15 + PPSV23

The secondary immunogenicity endpoints include:

- Serotype-specific IgG GMCs postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12)
  - 13 serotypes common between V116 and PCV15 + PPSV23
  - 8 serotypes unique to V116 relative to PCV15 + PPSV23
- Serotype-specific GMFR and proportion of participants with a  $\geq 4$ -fold rise from baseline (Day 1) to postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12) for both OPA and IgG responses
  - 13 serotypes common between V116 and PCV15 + PPSV23
  - 8 serotypes unique to V116 relative to PCV15 + PPSV23

The exploratory immunogenicity endpoints include:

- Serotype-specific OPA GMTs and IgG GMCs postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12)
  - 13 serotypes common between V116 and PCV15 + PPSV23
  - 8 serotypes unique to V116 relative to PCV15 + PPSV23
- Summaries of the cross-reactive immune responses to serotypes within a serogroup using serotype-specific OPA and IgG responses

#### **9.4.2 Safety Endpoints**

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

- Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) from Day 1 through Day 5 postvaccination
- Proportion of participants with solicited systemic AEs (muscle aches all over body/myalgia, headache, and tiredness/fatigue) from Day 1 through Day 5 postvaccination

- 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 SAE, discontinuation due to an AE, and death from Day 1 through the duration of participation in the study
- Proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 5 postvaccination

## 9.5 Analysis Populations

### 9.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive study vaccine at Visit 2 (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:

- Failure to receive study vaccine at Visit 5 (Week 8)
- 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 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. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the PP population.

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

### **9.5.2 Safety Analysis Populations**

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study vaccination. Participants will be included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. This will be the group to which they are randomized except for participants who receive 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.

## **9.6 Statistical Methods**

### **9.6.1 Statistical Methods for Immunogenicity Analyses**

This section describes the statistical methods that address the primary, secondary, and exploratory immunogenicity objectives. More details for methods related to the exploratory immunogenicity objectives will be further described in the sSAP.

Immunogenicity analyses will be conducted for each of the 21 pneumococcal serotypes in V116 separately. To address the primary immunogenicity objective, evaluation of the OPA GMTs postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12) will include descriptive summaries and within-group 95% CIs for each vaccination group.

For the secondary immunogenicity objectives, to evaluate IgG GMCs postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12), a similar statistical approach described in the primary objective will be used. Also, GMFR and proportions of participants with a  $\geq 4$ -fold rise for both OPA and IgG responses will be calculated for V116 (from Day 1 to Day 30) or PCV15 + PPSV23 (from Day 1 to Week 12). Descriptive statistics with point estimates and within-group 95% CIs will be provided for these 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].

To address the exploratory immunogenicity objective to evaluate the immune responses for V116 (Day 30) compared with PCV15 + PPSV23 (Week 12), the serotype-specific OPA GMTs will be compared between intervention groups through the estimation of serotype-specific OPA GMT ratios. Estimation of the OPA GMT ratios and computation of the corresponding 95% CIs will be calculated using a cLDA method proposed by Liang and



Zeger [Liang, K-Y and Zeger, S. L. 2000]. Details regarding the cLDA models will be included in the sSAP. A similar statistical approach will be used to analyze the IgG GMCs between the 2 intervention groups.

Reverse Cumulative Distribution Curves for OPA titers and IgG concentrations will be graphically displayed by serotype.

A detailed analysis strategy for immunogenicity endpoints is listed in [Table 5](#).

Table 5 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach <sup>a</sup>	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
OPA GMTs postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12)	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints				
IgG GMCs postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12)	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
GMFR and proportion of participants who achieved a ≥4-fold rise from baseline (Day 1) to postvaccination with V116 (Day 30) or PCV15 + PPSV23 (Week 12) for both OPA and IgG responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
CI=confidence interval; 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.				
<sup>a</sup> P=primary approach; S=supportive approach.				

## 9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs and postvaccination temperature measurements. The safety profile will be assessed via point estimates and 95% CIs (for select safety endpoints) across vaccination groups. Summaries on safety parameters will be provided after any vaccination and after each vaccination.

### 9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary (ie, number and percentage) of participants with any AEs, any unsolicited AEs, any vaccine-related AEs, any SAEs, any vaccine-related SAEs, discontinuation due to an AE, and an AE resulting in death. Point estimates and within-group 95% CIs for the percentages of participants will be provided for these events.

The number and percentage of participants with specific AEs will also be provided. Point estimates and within-group 95% CIs for the percentages of participants with specific AEs will be provided for solicited AEs and AEs that occur in  $\geq 5\%$  of participants in any vaccination group.

The number and percentage of participants with maximum temperature measurements categorized by Brighton Collaboration cut points [Marcy, S. M., et al 2004] will be provided along with point estimates and within-group 95% CIs to evaluate elevated temperatures.

Within-group CIs will be calculated using the Clopper Pearson method [CLOPPER, C. J. and PEARSON, E. S. 1934]. CIs should only be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance.

The analysis strategy for safety endpoints is provided in [Table 6](#).

Table 6 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	Within-group 95% CI
Overall Safety Assessment	Solicited injection-site AE (Day 1 through Day 5 postvaccination) <sup>a</sup>	X	X
	Solicited systemic AE (Day 1 through Day 5 postvaccination) <sup>a</sup>	X	X
	Any AE <sup>b</sup>	X	X
	Any unsolicited AE <sup>b</sup>	X	X
	Any vaccine-related AE <sup>b</sup>	X	X
	Any SAE <sup>b</sup>	X	X
	Any vaccine-related SAE <sup>b</sup>	X	X
	Discontinuation due to AE <sup>b</sup>	X	X
	Death <sup>b</sup>	X	X
	Specific AEs by SOC and PT <sup>c</sup>	X	X
	Maximum temperatures (Day 1 through Day 5 postvaccination) <sup>d</sup>	X	X
AE=adverse event; CI=confidence interval; PT=preferred term; SAE=serious adverse event; SOC=system organ class <sup>a</sup> Solicited injection-site AEs include redness/erythema, swelling, and tenderness/pain; solicited systemic AEs include muscle aches all over body/myalgia, headache, and tiredness/fatigue. <sup>b</sup> 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. <sup>c</sup> Descriptive statistics will be provided for specific AEs with incidence $>0\%$ of participants in any vaccination group; additionally within-group 95% CIs will be provided for specific AEs with an incidence $\geq 5\%$ of participants in any vaccination group. <sup>d</sup> Maximum temperature measurements are categorized by Brighton Collaboration cut points.			

### 9.6.3 Demographic and Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed using summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized and discontinued from the study and discontinuation reasons will be displayed. Demographic variables (eg, age, race, ethnicity, sex, and gender), baseline characteristics, and prior and

concomitant vaccinations and medications will be summarized by vaccination group either by descriptive statistics or categorical tables.

## **9.7 Interim Analyses**

A periodic review of safety and tolerability data across the V116 Phase 3 adult program 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. In addition, unblinded immunogenicity data will be made available to the DMC on 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 continuation of the study (with or without protocol modifications) or discontinuation of the study to an executive oversight committee 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 oversight committee (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.

## **9.8 Multiplicity**

No multiplicity adjustment is planned as there is no hypothesis testing.

## **9.9 Sample Size and Power Calculations**

### **9.9.1 Sample Size and Power for Immunogenicity Analyses**

This is a descriptive study. This study will randomize approximately 375 participants into the V116 group and 125 participants into the PCV15 + PPSV23 group. It is assumed that approximately 338 participants in the V116 group and 113 in the PCV15 + PPSV23 group will be evaluable for PP immunogenicity analyses (based on a 90% evaluability rate).

The width of the within-group 95% CIs for the serotype-specific OPA GMTs depend on the sample size, variability of the natural log titers, and the magnitude of the OPA GMTs. The 95% CIs for various hypothetical OPA GMTs and various hypothetical standard deviation estimates for the natural log titers are displayed in [Table 7](#).

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

Standard Deviation of Natural Log Titers <sup>a</sup>	Serotype-specific OPA GMT <sup>a</sup>					
	500		1000		5000	
	V116	PCV15 + PPSV23	V116	PCV15 + PPSV23	V116	PCV15 + PPSV23
1.0	(449, 556)	(415, 602)	(899, 1113)	(830, 1205)	(4493, 5565)	(4150, 6024)
1.5	(426, 587)	(378, 661)	(852, 1174)	(756, 1323)	(4259, 5870)	(3780, 6613)
2.0	(404, 619)	(344, 726)	(807, 1239)	(689, 1452)	(4037, 6193)	(3444, 7259)
2.5	(383, 653)	(314, 797)	(765, 1307)	(628, 1594)	(3827, 6533)	(3138, 7968)
CI=confidence interval; GMT=geometric mean titer; OPA=opsonophagocytic activity; PCV15=pneumococcal 15-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent); V116=pneumococcal 21-valent conjugate vaccine. <sup>a</sup> The estimates of the standard deviation and OPA GMTs are representative of those observed in V116-001. Based on 338 evaluable participants in the V116 group and 113 evaluable participants in the PCV15 + PPSV23 group.						

## 9.9.2 Sample Size and Power for Safety Analyses

The sample size was selected to achieve a reasonably sized safety database in this population exposed to V116. The selected sample size allows for the detection of a minimum level of SAEs with a high degree of confidence for the overall study as described below. The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying incidence of participants with a SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 375 participants in the V116 group if the underlying incidence of an SAE is 0.43% (1 of 234 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 375 participants in the V116 group if the underlying incidence of an SAE is 0.18% (1 of 542 participants receiving the vaccine). If no SAEs are observed among the 375 participants in the V116 group, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.98% (1 of 102 participants) in the V116 group.

## 9.10 Subgroup Analyses

Serotype-specific OPA GMTs and their corresponding within-group 95% CIs for V116 (Day 30) or PCV15 + PPSV23 (Week 12) will be calculated within each vaccination group for each subgroup of the following classification variables:

- Age category (18 to 49, 50 to 64 years of age)
- Sex
- Race
- Ethnicity
- Number of concurrent increased-risk conditions (1 or  $\geq 2$ )

- Type of increased risk-condition (diabetes mellitus only, chronic heart disease only, chronic kidney disease only, chronic liver disease only, chronic lung disease only)

In addition, a summary of AEs and a summary of solicited AEs will be provided for each of the subgroups listed above (point estimates only).

Further details of subgroup analyses will be documented in the sSAP.

### **9.11 Compliance (Medication Adherence)**

Given that participants will receive a single dose of V116 or PCV15 followed by a single dose of placebo or PPSV23, compliance will not be calculated. However, the number and proportion of randomized participants receiving each vaccination will be summarized (Section 9.12).

### **9.12 Extent of Exposure**

The extent of exposure will be summarized by the number and proportion of randomized participants administered V116, placebo, PCV15, or PPSV23.

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



MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

### **III. Participant Protection**

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

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

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations 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 (eg, 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 9.7) 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 trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>, [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu), or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

#### **10.1.7 Compliance with Law, Audit, and Debarment**

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

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

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

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

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

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

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

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Pregnancy Testing	<ul style="list-style-type: none"> <li>• Highly sensitive serum or urine hCG pregnancy test (as needed for POCPBP)</li> </ul>
hCG=human chorionic gonadotropin; POCPBP=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 9](#).

Table 9 Blood Volumes Collected by Visit

	Visit 2	Visit 4	Visit 7	Total
Parameter	Approximate Blood Volume			
Immunogenicity assessment	30 mL	30 mL	30 mL	90 mL
DNA for FBR <sup>a</sup>	8.5 mL	N/A	N/A	8.5 mL
<b>Expected total</b>	<b>38.5 mL</b>	<b>30 mL</b>	<b>30 mL</b>	<b>98.5 mL</b>
DNA=deoxyribonucleic acid; FBR=future biomedical research; N/A=not applicable.				
<sup>a</sup> Samples for FBR will only be obtained from participants who provide separate consent for collection of this optional sample.				



### **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 10 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)
<b>Injection-site AEs occurring Days 1 through 5 following receipt of study vaccine/placebo</b>				
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
<b>Any injection-site reaction that begins ≥6 days after receipt of study vaccine/placebo</b>				
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 11 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
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 12 Other Systemic AE Overall Intensity Grading Scale

Systemic Illness <sup>a</sup>	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4) <sup>b</sup>
Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and required medical intervention	ED visit or hospitalization
AE=adverse event; ED=emergency department; eVRC=electronic Vaccine Report Card; SAE=serious adverse event. The overall intensity grading scales used in this study are adapted from the “FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007” [Food and Drug Administration 2007]. <sup>a</sup> 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. <sup>b</sup> AEs resulting in death will be assessed as Grade 4.				

Table 13 Vital Sign (Temperature) Overall Intensity Grading Scale

Vital Signs <sup>a</sup>	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Fever (°C) <sup>b</sup>	38.0 to 38.4	38.5 to 38.9	39.0 to 40.0	>40.0
(°F) <sup>b</sup>	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]. <sup>a</sup> Participant should be at rest for all vital sign requirements. <sup>b</sup> Oral temperature; no recent hot or cold beverages or smoking.				

### Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based on the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a vaccine-induced effect?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?
  - **Rechallenge:** Was the participant reexposed to the study intervention in the study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose vaccine study; or (3) study intervention(s) is/are used only 1 time.)

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical records.
- 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: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

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

##### 10.4.1 Definitions

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

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

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

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

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

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

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

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

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

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

**Serious Injury** – An injury or illness that:

1. Is life-threatening,
2. Results in permanent impairment of a body function or permanent damage to a body structure, or
3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

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

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

##### **Recording**

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

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

##### **Assessing Causality**

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.

The investigator will use clinical judgment to determine the relationship.

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

### **Follow-up**

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

Country-specific definitions and documenting/reporting requirements can be found in Appendix 7.

## 10.5 Appendix 5: Contraceptive Guidance

### 10.5.1 Definitions

#### Participant of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile and capable of becoming pregnant following menarche and until becoming postmenopausal unless permanently sterile (see below):

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

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

- 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

<b>Contraceptives allowed during the study include:</b>
<b>Highly Effective Contraceptive Methods That Have Low User Dependency<sup>a</sup></b> <i>Failure rate of &lt;1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> <li>• Progestogen- only contraceptive implant<sup>b,c</sup></li> <li>• IUS<sup>b,d</sup></li> <li>• Nonhormonal IUD</li> <li>• Bilateral tubal occlusion</li> </ul>
<ul style="list-style-type: none"> <li>• Azoospermic partner (vasectomized or secondary to medical cause)            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.</li> </ul>
<b>Highly Effective Contraceptive Methods That Are User Dependent<sup>a</sup></b> <i>Failure rate of &lt;1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> <li>• Combined (estrogen- and progestogen- containing) hormonal contraception<sup>b,c</sup> <ul style="list-style-type: none"> <li>- Oral</li> <li>- Intravaginal</li> <li>- Transdermal</li> <li>- Injectable</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• Progestogen-only hormonal contraception<sup>b,c</sup> <ul style="list-style-type: none"> <li>- Oral</li> <li>- Injectable</li> </ul> </li> </ul>
<b>Sexual Abstinence</b> <ul style="list-style-type: none"> <li>• Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) 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.</li> </ul>
<b>Methods That Are Not Considered Highly Effective</b> <i>Failure rate of &gt;1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> <li>• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action</li> <li>• Penile/external or vaginal/internal<sup>e</sup> condom with or without spermicide</li> <li>• Cervical cap, diaphragm, or sponge with spermicide</li> <li>• A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)</li> </ul>
<p><sup>a</sup> Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).</p> <p><sup>b</sup> Penile/external condoms must be used in addition to POCBPs participant hormonal contraception.</p> <p><sup>c</sup> If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.</p> <p><sup>d</sup> IUS is a progestin releasing IUD.</p> <p><sup>e</sup> Vaginal/internal condom used for contraceptive purposes.</p> <p>Note: The following are not acceptable methods of contraception:</p> <ul style="list-style-type: none"> <li>• Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.</li> <li>• Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction).<sup>e</sup></li> </ul>

## **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.<sup>1</sup>
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.<sup>2</sup>
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.<sup>2</sup>
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

### **2. Scope of Future Biomedical Research<sup>3, 4</sup>**

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<sup>3, 4</sup>**

#### **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<sup>3, 4</sup>**

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<sup>3, 4</sup>**

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<sup>3, 4</sup>**

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<sup>3, 4</sup>**

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<sup>3, 4</sup>**

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<sup>3, 4</sup>**

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<sup>3, 4</sup>**

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<sup>3, 4</sup>**

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](mailto:clinical.specimen.management@MSD.com).

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## **10.7 Appendix 7: Country-specific Requirements**

### **10.7.1 Country-specific Requirements for South Korea**

For study sites in South Korea, the following criterion replaces Exclusion Criterion 21 in Section 5.2:

21. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 6 months of participating in this current study.

### **10.7.2 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 17 in Section 5.2:

- 17 \*Received any nonlive vaccine  $\leq 14$  days before receipt of study vaccine or is scheduled to receive any nonlive vaccine  $\leq 30$  days after receipt of any study vaccine. **Exception:** inactivated influenza vaccine may be administered but must be given  $\geq 7$  days before or  $\geq 15$  days after receipt of study vaccine. SARS-CoV-2 mRNA or protein subunit vaccines may be administered but must be given  $\geq 14$  days before or  $\geq 15$  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 17 and 18.

#### **Section 6.1.1 Medical Devices**

Combination Medicinal Product(s) (MSD marketed/MSD investigation medicinal product and medical device or non-MSD marketed/non-MSD investigational product and medical device) provided for use in this study are V116 prefilled syringes, VAXNEUVANCE™ prefilled syringes, and PNEUMOVAX™23 prefilled syringes. Refer to below for instruction on reporting events associated with these devices.

#### **Appendix 4 Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up**

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

#### 10.4.1 Definitions

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

**Combination Medicinal Product** – A product comprised of 2 or more regulated components, ie, a drug and a device; a device and a cellular and tissue-based products; a cellular and tissue-based products and a drug; or a drug, a device, and a cellular and tissue-based products according to Japan regulations.

**Malfunction** – Failure of quality, safety, and performance, etc, of investigational device in a broad sense such as damage or operational failure.

**Serious Adverse Event due to Malfunction** – Any SAE due to malfunction in the characteristics and/or performance of a device (this study is a prefilled syringe) as well as any inadequacy in the labeling or the instructions for use that might lead to or might have led to the death of a participant and/or the associated person or to a serious deterioration in their state of health.

**Malfunction That may Lead to Serious Adverse Events** – Any malfunction of a medical device that might have led to the death of a participant and/or the associated person or to a serious deterioration in their state of health. “That 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 Medical Device/Combination Medicinal Products – Documenting and Reporting

In order to fulfill Japan regulatory reporting obligations, medical device/combination medicinal product information will be collected. SAEs due to malfunction will be reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines. All SAEs due to malfunction will be followed until resolution, stabilization, until the event is otherwise explained, or the participant or associated person is lost to follow-up. Malfunction that may lead to SAEs will be reported to the Sponsor within 5 calendar days of learning of the information via a paper reporting form.

Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities as needed about certain safety information relating to medical devices/combination medicinal products being used in clinical studies.

### **10.4.3 Recording, Assessing Causality, and Follow-up of Adverse Events due to Malfunctions (Serious and Nonserious)**

#### **Recording**

- When AEs due to malfunctions (serious or nonserious) occur, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- Any AEs due to malfunctions (serious or nonserious) occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions in the EDC data entry guidelines (or equivalent).
- It is important that the investigator provides an assessment of causality (relationship to the medical device) at the time of the initial report.

#### **Assessing Causality**

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

#### **Follow-up**

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

## 10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ABCs	Active Bacterial Core Surveillance
ACIP	Advisory Committee on Immunization Practices
ACR	Albumin to creatinine ratio
AE	Adverse event
AER	Albumin excretion rate
ALT	Alanine aminotransferase
APaT	All-Participants-as-Treated
APRI	Aspartate aminotransferase : platelet ratio index
AST	Aspartate aminotransferase
BNP	Brain natriuretic peptide
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CFR	Code of Federal Regulations
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
EF	Ejection fraction
EDC	Electronic data collection
EEA	European Economic Area
EMA	European Medicines Agency

Abbreviation	Expanded Term
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
FEV1	Forced expiratory volume in 1 second
FIB-4	Fibrosis-4
FSH	Follicle-stimulating hormone
FSR	First site ready
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HRT	Hormone-replacement therapy
IA	Interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular(ly)

Abbreviation	Expanded Term
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
KDIGO	Kidney Disease: Improving Global Outcomes
LAM	Lactational amenorrhea method
M&N	Miettinen and Nurminen
MOPA	Multiplexed Opsonophagocytic Assay
mRNA	Messenger RNA
NYHA	New York Heart Association
OPA	Opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
PEFR	Peak expiratory flow rate
PEN	Package of Essential Noncommunicable
PK	pharmacokinetic
Pn ECL	Pneumococcal electrochemiluminescence
PnPs	Pneumococcal polysaccharide
POCBP	Participant/participants of childbearing potential
PP	Per-protocol
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

Abbreviation	Expanded Term
SOC	System organ class
sSAP	Supplemental statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
ULN	Upper limit of normal
US	United States
VRC	Vaccination report card
WHO	World Health Organization



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