

<b>Official Protocol Title:</b>	A Phase 1, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Healthy Japanese Adults.
<b>NCT number:</b>	NCT04665050
<b>Document Date:</b>	20-Oct-2020

## Title Page

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**Protocol Title:** A Phase 1, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Healthy Japanese Adults.

**Protocol Number:** 002-00

**Compound Number:** V116

**Sponsor Name:**

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**Regulatory Agency Identifying Number(s):**

IND	Not Applicable
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**Approval Date:** 20 October 2020

### 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**

<b>Document</b>	<b>Date of Issue</b>	<b>Overall Rationale</b>
Original Protocol	20-OCT-2020	Not applicable



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## 1 PROTOCOL SUMMARY

### 1.1 Synopsis

**Protocol Title:** A Phase 1, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Healthy Japanese Adults.

**Short Title:** Phase 1 Study of a pPCV in Healthy Japanese Adults

**Acronym:** Not applicable

#### Hypotheses, Objectives, and Endpoints:

There are no hypotheses for the study.

The following objectives and endpoints will be evaluated in healthy Japanese pneumococcal vaccine naïve adults  $\geq 20$  years of age who are administered a single dose of Polyvalent Pneumococcal Conjugate Vaccine (pPCV) or PNEUMOVAX™23.

Primary Objectives	Primary Endpoints
- Objective: To evaluate the safety and tolerability of pPCV with respect to the proportion of participants with AEs in the recipients of pPCV and PNEUMOVAX™23.	- Solicited injection-site AEs - Solicited systemic AEs - Vaccine-related SAEs
Secondary Objectives	Secondary Endpoints
- Objective: To describe the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) and Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination in the recipients of pPCV and PNEUMOVAX™23.	- Serotype-specific OPA and IgG responses
- Objective: To describe the serotype-specific Geometric Mean Fold Rises (GMFR) from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses in the recipients of pPCV and PNEUMOVAX™23.	- Serotype-specific OPA and IgG responses

**Overall Design:**

Study Phase	Phase 1
Primary Purpose	Prevention
Indication	Pneumococcal infection
Population	Healthy Japanese adults 20 years of age and older
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 3 months from the time the first participant 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:**

Total approximately 100 participants (approximately 34 participants in 20 to 64 years of age and approximately 66 participants in 65 years of age and older) will be randomized as described in Section 9.9.



**Intervention Groups and Duration:**

Intervention Groups	<table border="1"> <thead> <tr> <th>Intervention Group Name</th> <th>Vaccine</th> <th>Dose Strength</th> <th>Dose Frequency</th> <th>Route of Admin</th> <th>Vaccination Regimen</th> <th>Use</th> </tr> </thead> <tbody> <tr> <td>pPCV</td> <td>pPCV</td> <td>Refer to IB</td> <td>Single Dose</td> <td>IM</td> <td>Single Dose at Visit 1 (Day 1)</td> <td>Experimental</td> </tr> <tr> <td>PNEUMOVAX™23</td> <td>PNEUMOVAX™23</td> <td>Refer to product labeling</td> <td>Single Dose</td> <td>IM</td> <td>Single Dose at Visit 1 (Day 1)</td> <td>Experimental</td> </tr> </tbody> </table>	Intervention Group Name	Vaccine	Dose Strength	Dose Frequency	Route of Admin	Vaccination Regimen	Use	pPCV	pPCV	Refer to IB	Single Dose	IM	Single Dose at Visit 1 (Day 1)	Experimental	PNEUMOVAX™23	PNEUMOVAX™23	Refer to product labeling	Single Dose	IM	Single Dose at Visit 1 (Day 1)	Experimental
	Intervention Group Name	Vaccine	Dose Strength	Dose Frequency	Route of Admin	Vaccination Regimen	Use															
	pPCV	pPCV	Refer to IB	Single Dose	IM	Single Dose at Visit 1 (Day 1)	Experimental															
	PNEUMOVAX™23	PNEUMOVAX™23	Refer to product labeling	Single Dose	IM	Single Dose at Visit 1 (Day 1)	Experimental															
Abbreviations: Admin = administration; IB = Investigator's Brochure; IM = intramuscular; pPCV = polyvalent pneumococcal conjugate vaccine.																						
Total Number of Intervention Groups/ Arms	2 intervention groups																					
Duration of Participation	Each participant will participate in the study for approximately 30 days from the time the participant provides documented informed consent form through the final contact.																					



**Study Governance Committees:**

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
Study governance considerations are outlined in Appendix 1.	

**Study Accepts Healthy Volunteers: Yes**

A list of abbreviations used in this document can be found in Appendix 8.

## 1.2 Schema

The study design is depicted in Figure 1.

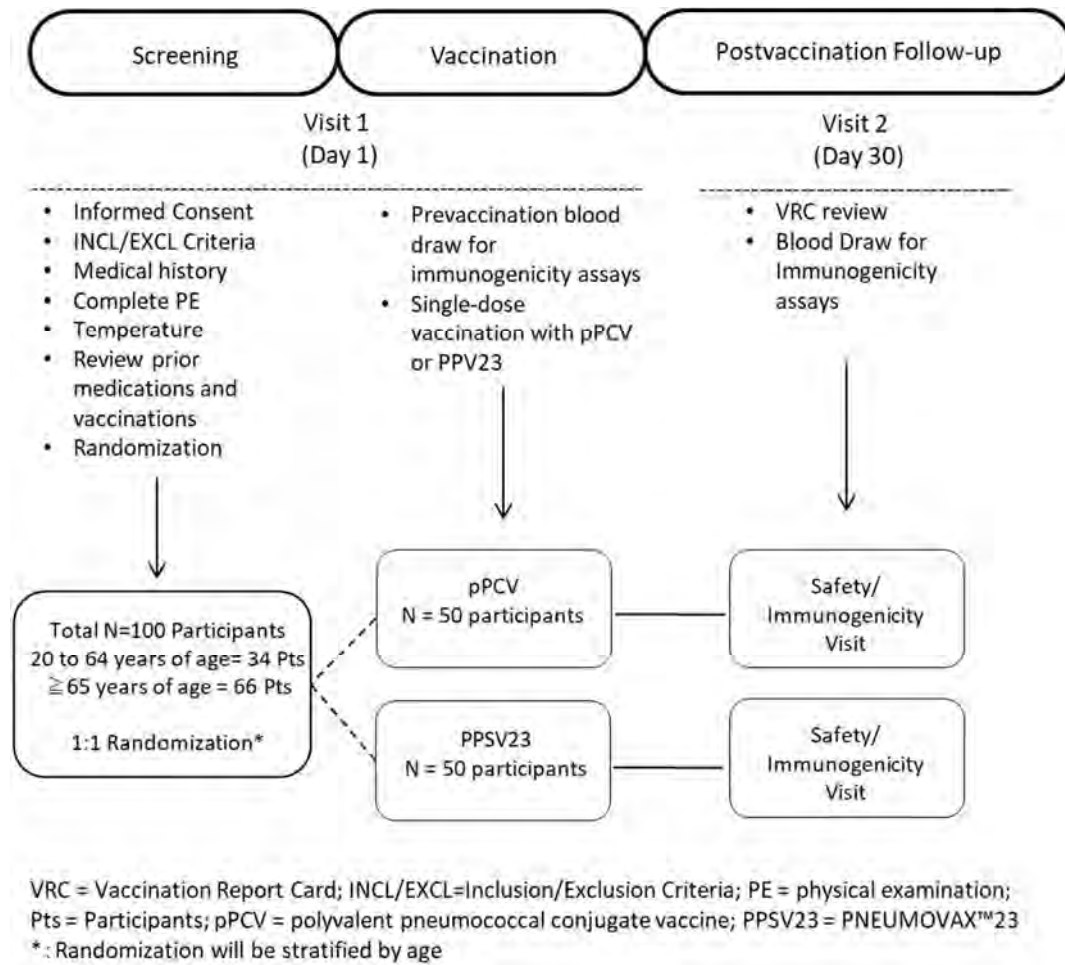


Figure 1 V116-002 Study Design



### 1.3 Schedule of Activities

Study Period:	Screening/Intervention			Notes
	Visit Number:	Telephone Contact	2	
Scheduled Time:	Day 1	Day 15	Day 30	
Visit Window:	-	Day 15 to Day 19	Day 30 to Day 44	
<b>Administrative Procedures</b>				
<b>Screening Procedures</b>				
Informed Consent	X			Consent must be obtained before any study procedures.
Informed Consent for Future Biomedical Research	X			Participation in future biomedical research is optional and consent must be obtained before the blood sample (DNA sample) is collected.
Assignment of Screening Number	X			
Inclusion/Exclusion Criteria	X			Prior to randomization, review of prior medications/vaccinations, medical history, a complete physical examination, and temperature measurement are required at Visit 1 to determine eligibility. If Day 1 is rescheduled (see Section 5.2), these activities must be repeated prior to vaccination.
Medical History	X			The participant's relevant medical history for the 5 years prior to study entry will be reviewed. History of tobacco use will also be collected for all participants.
<b>Post-randomization Procedures</b>				
Assignment of Randomization Number	X			
Participant Identification Card	X			
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	
pPCV/PNEUMOVAX™23 Administration (blinded)	X			Participants will receive a single dose of either pPCV or PNEUMOVAX™23. Study vaccine will be administered by unblinded study site staff (see Section 6.3.3). The unblinded study site staff must not perform any other visit procedures.
Provide Vaccination Report Card (VRC)	X			See Section 8.1.9 for details.
Review VRC Data with Participant		X	X	See Section 8.1.9 for details.
Collect VRC From Participant			X	

Study Period:	Screening/Intervention			Notes
	Visit Number:	1	Telephone Contact 2	
Scheduled Time:	Day 1	Day 15	Day 30	
Visit Window:	-	Day 15 to Day 19	Day 30 to Day 44	
<b>Safety Procedures</b>				
Complete Physical Examination	X			To be performed by the investigator at screening and before vaccine is administered.
Pregnancy Test (if applicable)	X		X	A pregnancy test (sensitive to at least 25 IU $\beta$ -human chorionic gonadotropin [ $\beta$ -hCG]) must be performed before administration of study vaccine in females who are of reproductive potential (see Section 8.3.2 and Appendix 5 for details).
Body Temperature Measurement	X			Each participant's body temperature must be taken before vaccination (see Section 8.3.3 for details). Participants who have febrile illness occurring at or within 72 hours prior to vaccination may have their Day 1 Visit rescheduled (see Section 5.2 for details).
Postvaccination Observation Period	X			Participants will be observed for at least 30 minutes postvaccination (see Section 8.3.4 for details).
AE Monitoring	X	X	X	Nonserious AEs are to be reported from Day 1 through Day 30 following vaccination. SAEs, death and medical device incidents are to be reported from Day 1 through the duration of an individual's study participation (see Section 8.4.1 for details).
<b>Immunogenicity Procedures</b>				
Collect Blood (Serum) for Immunogenicity Assays (Including Retention Serum)	X		X	Day 1 blood samples must be collected before vaccination (see Section 4.1 and Section 8.9 for details).
<b>Future Biomedical Research</b>				
Collect Blood (DNA) for Future Biomedical Research	X			Sample will be collected from randomized participants who provide consent for future biomedical research (see Section 8.9).



## 2 INTRODUCTION

Merck Sharp & Dohme Corp. is developing an investigational polyvalent PCV (V116, hereafter referred to as pPCV) for the prevention of pneumococcal disease caused by the serotypes in the vaccine.

### 2.1 Study Rationale

Pneumococcal disease, in adults, specifically residual disease caused by serotypes not included in the licensed pneumococcal vaccines, remains an unmet medical need. To address the burden of residual pneumococcal disease in adults, pPCV is designed to target serotypes that account for the majority of invasive pneumococcal disease (IPD) in adults and includes serotypes not currently contained in any licensed pneumococcal vaccine.

Especially, the population of adults  $\geq 65$  years of age is at elevated risk for pneumococcal disease and associated morbidity and mortality due to aging related physiological changes in the respiratory system and high prevalence of other medical conditions associated with increased risk for pneumococcal disease [Drijkoningen, J. J 2014] [Janssens, J. P. 2004] [Sunagawa, T., et al 2018].

This study is designed to evaluate the safety, tolerability, and immunogenicity of pPCV compared with PNEUMOVAX™23 in healthy pneumococcal vaccine naïve Japanese adults.

The needs of pneumococcal vaccine for adults aged  $< 65$  years of age exist, especially for those at increased risk for pneumococcal disease (e.g., subjects with co-morbid condition such as chronic heart/lung/hepatic disease, diabetes, and/or acquired/congenital immunosuppression).

Study results will provide useful information about the safety, tolerability and immunogenicity profiles of pPCV in Japanese adults before evaluation in subsequent phases of pPCV clinical development in Japanese adults

### 2.2 Background

Refer to the IB for detailed background information on pPCV, including information on pneumococcal disease burden.

#### 2.2.1 Pharmaceutical and Therapeutic Background

*Streptococcus pneumoniae* causes IPD that may be accompanied by meningitis or bacteremia pneumonia and non-IPD such as pneumonia, otitis media, and sinusitis in children and adults. *S. pneumoniae* accounts for approximately 20% of the causative bacteria in community-onset pneumonia (community-acquired and hospital-acquired pneumonia) in adults.

Currently, many countries worldwide have incorporated licensed PCVs (e.g., Prevnar 13™) into their infant immunization programs. In Japan emergency promotion fund project with Prevnar™ was initiated in November 2010 and introduced into the National Immunization

Program (NIP) for pediatrics in April 2013. Prevnar™ was then replaced by Prevnar 13™ in November 2013. Since PCVs have been introduced into the NIP, the overall burden of IPD in children caused by vaccine serotypes has decreased by 97% in 2017. On the other hand, the proportion of IPD in children caused by serotypes not included in Prevnar 13™ is increasing.

Direct vaccination of children with PCVs under NIP has decreased the incidence of disease caused by vaccine serotypes and has led to herd protection in unvaccinated individuals, referred to as an indirect effect. This indirect effect of childhood vaccination with PCVs has resulted in a decrease in Japanese adults, IPD caused by PCV13 serotypes decreased from 73.8% (2010-2011 years) to 30.9% (2017 years). Additionally, in Japanese individuals ≥15 years of age, and pneumococcal pneumoniae caused by PCV13 serotypes decreased from 53% (2011-2014 years) to 33% (2016-2017 years) [Ubukata, K., et al 2018] [Sando, E., et al 2019]. However, serotype 3 and 19A included in the licensed PCV13 remained major causative serotypes in Japanese adult IPD in 2017.

This residual burden of disease in adults reflects the difference in serotype distribution in adults compared with infants and children. Importantly, infant vaccination with PCVs has led to an increasing incidence of disease due to serotypes not included in the licensed PCVs, particularly in adults [Ubukata, K., et al. 2018] [Sando, E., et al 2019]. Increases in IPD cases due to certain serotypes (3, 7F, and 19A after implementation of Prevnar™; and 22F and 33F following widespread usage of Prevnar 13™) were noted in both pediatric and adult (≥65 years of age) populations in the US [Hicks, L. A., et al 2007] [Pilishvili, T., et al 2010] [Waight, P. A., et al 2015] [Moore, M. R., et al 2015] [Demczuk, W. H. B., et al 2013]. Similarly, in Japan, due to the limited serotype coverage of the currently licensed vaccines, serotype replacement is being observed and may limit the benefit of vaccination with currently available PCVs in the elderly.

To address this residual burden of disease in adults, serotypes were selected for inclusion in pPCV based on available global epidemiology data with a primary focus on data from the elderly (≥65 years of age) in the US and EU. With the intent to provide broad coverage against the leading serotypes associated with pneumococcal disease, the serotypes selected for inclusion in pPCV account for approximately 81% of all cases of IPD in the US in adults ≥65 years of age and approximately 80% of all cases of IPD in Japanese adults based on 2017 surveillance data.

With the above considerations in mind, the investigational pPCV is designed to target serotypes that account for the majority of IPD in adults including serotypes not currently contained in any licensed pneumococcal vaccine, as well as addressing the influence of serotype replacement of circulating strains, thereby addressing the unmet medical need of residual pneumococcal disease in adults.

## 2.2.2 Preclinical and Clinical Studies

Refer to the IB for information on completed preclinical studies conducted with pPCV.

Phase 1/2 study involving healthy adults 18 years of age and older is still ongoing in US. These participants have vaccine administered intramuscularly.

## 2.2.3 Information on Other Study-related Therapy

### 2.2.3.1 PNEUMOVAX™23

The label name of PNEUMOVAX™23 in Japan is PNEUMOVAX® NP.

Refer to the approved labeling for detailed background information on PNEUMOVAX™23.

PNEUMOVAX™23 is comprised of the polysaccharides from 23 of the most important 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. PNEUMOVAX™23 will be US commercial product in this study.

## 2.3 Benefit/Risk Assessment

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

Approximately 50% of participants in this study will receive PNEUMOVAX™23, a pneumococcal vaccine for the prevention of pneumococcal disease that is licensed in Japan. pPCV is expected to provide comparable immune responses to PNEUMOVAX™23 for the serotypes in common while providing additional coverage for the serotypes unique to pPCV. It is unknown if the investigational pPCV will have the same clinical benefit as PNEUMOVAX™23.

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 are no hypotheses for the study.

The following objectives and endpoints will be evaluated in healthy Japanese pneumococcal vaccine naïve adults  $\geq 20$  years of age who are administered a single dose of pPCV or PNEUMOVAX™23.

Objectives	Endpoints
Primary	
- Objective: To evaluate the safety and tolerability of pPCV with respect to the proportion of participants with AEs in the recipients of pPCV and PNEUMOVAX™23.	- Solicited injection-site AEs - Solicited systemic AEs - Vaccine-related SAEs
Secondary	
- Objective: To describe the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) and Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination in the recipients of pPCV and PNEUMOVAX™23.	- Serotype-specific OPA and IgG responses
- Objective: To describe the serotype-specific Geometric Mean Fold Rises (GMFR) from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses in the recipients of pPCV and PNEUMOVAX™23.	- Serotype-specific OPA and IgG responses

## 4 STUDY DESIGN

### 4.1 Overall Design

This is a randomized, active-controlled, parallel-group, multi-site, double-blind (with in-house blinding) study of pPCV in healthy Japanese adults  $\geq 20$  years of age who have not previously received any pneumococcal vaccine.

Approximately 100 participants (approximately 34 participants in 20 to 64 years of age and approximately 66 participants is 65 years of age and older) who have not previously received any pneumococcal vaccine (vaccine naïve) will be randomly assigned in a 1:1 ratio to receive a single dose of pPCV or PNEUMOVAX™23 at Visit 1 (Day 1). Randomization will be stratified by participant age at the time of randomization (20 to 64 years and  $\geq 65$  years) across the 2 vaccination groups. Safety and immunogenicity will be assessed at 30 days postvaccination.

Paper VRC will be used by all participants to record solicited injection site and solicited systemic AEs from Day 1 through Day 5 postvaccination, unsolicited injection site and systemic AEs from Day 1 through Day 30 postvaccination, and daily temperatures from Day 1 through Day 5 postvaccination. Information for SAEs and deaths, regardless of whether the

events are considered to be vaccine related by the investigator, will be collected from the time consent is signed through completion of participation in the study.

Blood samples for immunogenicity assays will be drawn Visit 1 (Day 1) and at Visit 2 (Day 30). Blood samples must be drawn prior to study vaccine administration at Visit 1 (Day 1). After completion of immunogenicity testing to evaluate the study objectives, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. For participants who provide optional consent for future biomedical research, leftover sera from the study may be used for other purposes, such as the development and/or validation of pneumococcal assays after completion of all study related immunogenicity testing.

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

## 4.2 Scientific Rationale for Study Design

This study will assess the safety, tolerability and immunogenicity of pPCV in Japanese healthy adults  $\geq 20$  years of age. The healthy adults  $\geq 20$  years of age who are in general population in Phase 1 study and elderly  $\geq 65$  years of age who are at elevated risk for pneumococcal disease are included in this study. Participants will be stratified by age group (20 to 64 years of age and  $\geq 65$  years of age).

### 4.2.1 Rationale for Endpoints

#### 4.2.1.1 Immunogenicity Endpoints

The immunogenicity endpoints are consistent with previous early phase studies evaluating PCVs.

Sera from participants will be used to measure vaccine induced, anti-pneumococcal polysaccharide (PnP) serotype-specific OPA and IgG responses for all serotypes included in pPCV using the Multiplexed Opsonophagocytic Assay (MOPA) and pneumococcal electrochemiluminescence (PnECL) assay, respectively.

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

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

#### **4.2.1.2 Safety Endpoints**

The safety endpoints (i.e., AEs and temperature) evaluated in this study were selected based on the anticipated product safety profile and published data from marketed PCVs.

The paper VRC will be used to collect participant-reported events during the postvaccination period, as detailed in Section 8.1.9.

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

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

#### **4.2.1.3 Future Biomedical Research**

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

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

#### **4.2.2 Rationale for the Use of Comparator**

PNEUMOVAX™23 was selected as the comparator for this study based on the following rationale. Of the currently licensed pneumococcal vaccines, PNEUMOVAX™23 has the most serotypes in common with pPCV, and antibody responses to PNEUMOVAX™23 are generally comparable to Prevnar 13™ for the common serotypes. PNEUMOVAX™23 has been previously evaluated in healthy Japanese adults 20 to 40 years of age. In Japan, PNEUMOVAX®NP (PNEUMOVAX™23) is approved for use in the population who are at least 2 years of age and at high risk of developing severe pneumococcal infections.

Additionally, PNEUMOVAX®NP (PNEUMOVAX™23) is the only pneumococcal vaccine currently included in the NIP in Japan and is recommended for a) adults 65 years of age or older, and b) adults who are 60 to under 65 years old with heart, kidney and respiratory dysfunction, and with immunocompromised adults with HIV infection.



### **4.3 Justification for Dose**

#### **4.3.1 Starting Dose for This Study**

The dose of each serotype contained in pPCV was based on prior dose-ranging clinical trials (Phase I part of V116-001 study).

The dose of PNEUMOVAX™23 selected for use in this trial is the approved dose in Japan.

### **4.4 Beginning and End of Study Definition**

The overall study begins when the first participant provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

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

#### **4.4.1 Clinical Criteria for Early Study Termination**

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

## **5 STUDY POPULATION**

Healthy Japanese male and female participants  $\geq 20$  years of age will be enrolled in this study.

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

### **5.1 Inclusion Criteria**

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

1. In the opinion of the investigator, is in good health. Any underlying chronic condition must be documented to be in stable condition according to the investigator's judgment.

#### **Demographics**

2. Is male or female  $\geq 20$  years of age at the time of randomization.

### Male Participants

3. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 30 days after the last dose of study intervention:
- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

### Female Participants

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

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 30 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (e.g., 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 located in Appendix 2.

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

### **Informed Consent**

5. The participant has provided documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

### **5.2 Exclusion Criteria**

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

#### **Medical Conditions**

1. 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 of Visit 1 (Day 1).
2. Has a known hypersensitivity to any component of the pneumococcal polysaccharide vaccine, PCV, or any diphtheria toxoid-containing vaccine.
3. Has a known or suspected impairment of immunological function including, but not limited to, a history of congenital or acquired immunodeficiency, documented HIV infection, functional or anatomic asplenia, or history of autoimmune disease.
4. Has a coagulation disorder contraindicating intramuscular vaccination.
5. \*Had a recent febrile illness (defined as axillary temperature  $\geq 37.5^{\circ}\text{C}$  or equivalent) or received antibiotic therapy for any acute illness occurring within 72 hours before receipt of study vaccine.
6. Has a known malignancy that is progressing or has required active treatment within the 3 years prior to signing the informed consent. (**Note:** participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ [e.g., breast carcinoma, cervical cancer in situ] that have undergone potentially curative therapy are not excluded).
7. A WOCBP who has a positive urine or serum pregnancy test before vaccination at Visit 1 (Day 1).

#### **Prior/Concomitant Therapy**

8. Has received any pneumococcal vaccine or is expected to receive any pneumococcal vaccine during the study, outside of the protocol.

9. \*Has received systemic corticosteroids (prednisone equivalent of  $\geq 20$  mg/day) for  $\geq 14$  consecutive days and has not completed intervention at least 30 days prior to study vaccination.
10. \*Has received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) starting from 14 days prior to study vaccination. (**Note:** Topical, ophthalmic, intra-articular or soft-tissue [e.g., bursa, tendon steroid injections], and inhaled/nebulized steroids are permitted).
11. Is receiving immunosuppressive therapy, including chemotherapeutic agents used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease.
12. \*Has received any non-live vaccine starting from 14 days prior to study vaccination or is scheduled to receive any non-live vaccine through 30 days following study vaccination. **Exception:** Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of study vaccine or at least 15 days after receipt of study vaccine.
13. \*Has received any live vaccine starting from 30 days before study vaccination or is scheduled to receive any live vaccine through 30 days following study vaccination.
14. Has received a blood transfusion or blood products, including immunoglobulin, starting from 6 months before study vaccination or is scheduled to receive a blood transfusion or blood product until the Visit 2 postvaccination blood draw is complete. Autologous blood transfusions are not considered an exclusion criterion.

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

15. 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**

16. In the opinion of the investigator, has a history of clinically relevant drug or alcohol use that would interfere with participation in protocol-specified activities.
17. 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.
18. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

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

### **5.3 Lifestyle Considerations**

No lifestyle restrictions are required.

### **5.4 Screen Failures**

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

### **5.5 Participant Replacement Strategy**

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

## **6 STUDY INTERVENTION**

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

Clinical supplies (pPCV and PNEUMOVAX™23) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

### **6.1 Study Intervention(s) Administered**

The study intervention(s) to be used in this study are outlined in [Table 1](#).

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin	Vaccination Regimen	Use	IMP/NIMP	Sourcing
pPCV	Experimental	pPCV	Biological/Vaccine	Sterile Solution	Refer to IB	1.0 mL	IM	Single dose at Visit 1 (Day 1)	Experimental	IMP	Central
PNEUMOVAX™23	Active Comparator	PNEUMOVAX™23*	Biological/Vaccine	Sterile Solution	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Experimental	IMP	Central
<p>Admin = administration; IB = Investigator's Brochure; IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; pPCV = polyvalent pneumococcal conjugate vaccine.</p> <p>Definition of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.</p> <p>*: Pneumococcal vaccine polyvalent, US commercial product</p>											

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

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

### **6.1.1 Medical Devices**

Combination Medicinal Product(s) (MSD marketed/MSD investigation medicinal product and medical device or nonMSD marketed/nonMSD investigational product and medical device) provided for use in this study are pPCV and PNEUMOVAX™23, a single-dose pre-filled syringe. Refer to Appendix 4 for instruction on reporting events associated with these combination medicinal products.

## **6.2 Preparation/Handling/Storage/Accountability**

### **6.2.1 Dose Preparation**

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

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

### **6.2.2 Handling, Storage, and Accountability**

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

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

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

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

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

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

### **6.3 Measures to Minimize Bias: Randomization and Blinding**

#### **6.3.1 Intervention Assignment**

Intervention allocation/randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive either pPCV or PNEUMOVAX™23.

#### **6.3.2 Stratification**

Intervention allocation/randomization will be stratified according to the following factors:

Age at time of randomization

- Participants 20 to 64 years of age
- Participants  $\geq 65$  years of age.
- Enrollment into the age groups will be restricted to approximately 34 participants in the 20 to 64 years of age, and approximately 66 participants in the  $\geq 65$  years of age.

#### **6.3.3 Blinding**

A double-blinding technique will be used. pPCV and PNEUMOVAX™23 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 clinical evaluation of the participants are unaware of the intervention assignments.

Because pPCV and PNEUMOVAX™23 have a different appearance, a member of the study site staff will be unblinded for the purposes of receiving, maintaining, preparing and/or dispensing, and administering these study vaccines. Procedures for handling, preparing, and administering the unblinded vaccines are located in the Investigator Study File Binder.

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



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

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

#### 6.4 Study Intervention Compliance

Given that a single dose of pPCV or PNEUMOVAX™23 will be administered in this study, intervention compliance will not be assessed.

#### 6.5 Concomitant Therapy

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

If the participant is scheduled to receive any nonstudy vaccine, the investigator should discuss this with the Sponsor Clinical Director as soon as possible. All nonstudy vaccinations should be recorded on the appropriate eCRF.

Listed below are specific restrictions for concomitant therapy or vaccination:

- Any administration of a nonstudy pneumococcal vaccine is prohibited during the study.
- Live and non-live vaccines may only be administered prior to or following the receipt of study vaccine according to the time frames specified in Exclusion Criteria (Section 5.2).  
**Exception:** Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of any study vaccine or at least 15 days after receipt of any study vaccine.
- Participants should not receive systemic corticosteroids (prednisone equivalent of  $\geq 20$  mg/day for  $\geq 14$  consecutive days) starting from 30 days prior to vaccination through 30 days following vaccination.
- Participants should not receive systemic corticosteroids exceeding physiologic replacement doses (prednisone equivalent dose  $> 5$  mg/day) starting from 14 days prior to vaccination.

**Note:** Topical, ophthalmic, intra-articular or soft-tissue (e.g., 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.

### **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 following the end of the study.

### **6.8 Clinical Supplies Disclosure**

This study is blinded, but supplies are provided open label; therefore, an unblinded pharmacist or unblinded qualified study site personnel will be used to maintain the blinding of study staff who are directly involved in the clinical evaluation of participants in the study. Study intervention identity (name, strength, or potency) is included in the label text.

The emergency unblinding call center will use the intervention allocation/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). 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.

## **7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL**

### **7.1 Discontinuation of Study Intervention**

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

Participants who receive a single-dose intervention cannot discontinue study intervention.

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

A participant must be withdrawn from the study if the participant 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 future biomedical research, 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.

Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

## **8 STUDY ASSESSMENTS AND PROCEDURES**

Study procedures and their timing are summarized in the SoA.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

All study-related medical decisions must be made by an investigator who is a qualified physician.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met 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 at each study visit will not exceed 40 mL, and the total amount of blood collected over the duration of the study will not exceed 70 mL (Table 2).

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

Table 2 Approximate Blood Volumes Drawn by Study Visit and by Sample Type

	Visit 1 Day 1	Visit 2 Day 30	Total
<b>Parameter</b>	<b>Approximate Blood Volume (mL)</b>		
Blood (serum) for Immunogenicity assessment (including retention samples)	30 mL	30 mL	60 mL
Blood (DNA) for Future Biomedical Research <sup>a</sup>	8.5 mL	N/A	8.5 mL
Expected total (mL)	38.5 mL	30 mL	68.5 mL

DNA = deoxyribonucleic acid.

<sup>a</sup> Blood for future biomedical research will only be obtained from participants who provide separate consent for collection of the optional sample.

## 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 prior to participating in this clinical study or future biomedical research. 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 must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and /agreement of the participant and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant 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 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 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 future biomedical research consent to the participant, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

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

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

### **8.1.3 Participant Identification Card**

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

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare 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 prior to Visit 1 (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 prior medication use and record prior medication taken by the participant within 30 days before the study vaccination at Visit 1 (Day 1).

##### **8.1.5.2 Concomitant Medications**

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

The participant will use their paper VRC (Section 8.1.9) to record new and/or concomitant medications taken after Visit 1 (Day 1) and nonstudy vaccines received since Visit 1 through Day 30 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 prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

#### **8.1.7 Assignment of Treatment/Randomization Number**

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

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

### **8.1.8 Study Intervention Administration**

Unblinded study personnel not otherwise involved in the conduct of the study will prepare and administer pPCV or PNEUMOVAX™23. Study vaccines should be administered by appropriately qualified members of the study personnel (physician or nurse). Procedures for handling, preparing, and administering the unblinded vaccines are provided in the Investigator Study File Binder. Unblinded study personnel should follow the preparation and administration instructions for PNEUMOVAX™23 as specified in the product label.

Study vaccines should be removed from the refrigerator no more than 1 hour before vaccination. The time of removal and time of vaccination should be documented in the participant's chart.

Study vaccine will be administered as a single IM injection, preferably in the deltoid region of the participant's arm. Adequate treatment provision, including epinephrine and equipment for maintaining an airway, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

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

#### **8.1.8.1 Timing of Dose Administration**

Vaccinations may be administered at any time of day and without regard to timing of meals.

Each participant's body temperature must be taken before vaccine administration. Individuals who present with fever (axillary temperature  $\geq 99.5^{\circ}\text{F}$  [ $\geq 37.5^{\circ}\text{C}$ ]) or equivalent) will have the vaccination delayed until fever is resolved for at least 72 hours.

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

All participants will be observed for at least 30 minutes after vaccination for any immediate reactions. This observation must be performed by blinded site personnel for all study vaccines (Section 1.3 and Section 6.3.3).

### **8.1.9 Vaccination Report Card (VRC)**

Participants in this study will use a paper VRC as indicated in Section 1.3. The investigator or delegate will train the participant in the use of the paper VRC at Visit 1 (Day 1).

The participant will use the paper VRC to record body temperature (Section 8.3.3); concomitant medications and nonstudy vaccinations (Section 8.1.5.2); and injection-site reactions, vaccine-specific complaints, and other complaints or illnesses (Section 8.4.8).

The investigator or delegate will discuss information entered into the paper VRC with the participant at the telephone Contact on Day 15 (Section 8.1.10). A full review of the completed paper VRC will occur at Visit 2 (Day 30).

Any differences between paper VRC data and the clinical database must be documented in the participant's source record.

### **8.1.10 Telephone Contact on Day 15**

The investigator or delegate will discuss any information entered into the paper VRC with the participant at the telephone contact on Day 15. A full review of the completed paper will occur at Visit 2 (Day 30).

### **8.1.11 Discontinuation and Withdrawal**

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

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit (Visit 2) 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 future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox ([clinical.specimen.management@merck.com](mailto:clinical.specimen.management@merck.com)). Subsequently, the participant's consent for future biomedical research 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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. Prior to 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 of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

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

### **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.

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.

Serotype-specific IgG will be measured using the V116 PnECL assay to assess the concentration of binding antibodies to capsular polysaccharide of *S. pneumoniae*.

### 8.2.1 Multiplexed Opsonophagocytic Assay (MOPA)

The MOPA, developed and published by Professor Moon Nahm (Director of the US World Health Organization pneumococcal serology reference laboratory and National Institutes of Health pneumococcal reference laboratories) [Burton, Robert L. and Nahm, Moon H. 2006], is a multiplexed OPA assay capable of measuring 4 serotypes at a time, against a total of 24 serotypes of pneumococci. 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. The ability of the assay to simultaneously test 4 serotypes/run 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 MOPA assay for pPCV will be qualified. The qualification studies will evaluate various performance parameters of the assay including precision, ruggedness, specificity, and relative accuracy/dilutional linearity.

### 8.2.2 Pneumococcal Electrochemiluminescence (PnECL)

The Sponsor has developed and optimized a multiplex, ECL-based detection method for the quantitation of IgG serotype-specific antibodies to PnP serotypes contained in pPCV. The V116 PnECL assay is based on the Meso-Scale Discovery technology, which employs disposable multi-spot microtiter plates. Pneumococcal polysaccharide (PnP) 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 is detected using a ruthenium labeled anti-human IgG. Chemiluminescent signal emitted from the ruthenium tag upon electrochemical stimulation initiated at the electrode surfaces of the microplates is measured. Antibodies to the PnP serotypes can be measured in mass units ( $\mu\text{g/mL}$ ) read from a standard curve generated from a reference standard. The V116 PnECL assay for pPCV will be qualified. The qualification studies will evaluate various performance parameters of the assay including precision, ruggedness, specificity, relative accuracy/dilutional linearity, and the limit of detection of the assay.

## 8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Section 8.

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

### **8.3.1 Physical Examinations**

A complete physical examination will be conducted by an investigator before vaccination at Visit 1 (Day 1).

A complete physical examination includes, but is not limited to, the assessment of general appearance, vital signs (e.g., heart rate, respiratory rate, blood pressure, and body temperature), eyes, throat, mouth, cardiovascular, respiratory, gastrointestinal, skin, neurologic, and psychiatric systems, and other organ systems as indicated.

In the source documents, investigators should document physical examination data and the status of all active medical conditions.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### **8.3.2 Pregnancy Test**

A pregnancy test (sensitive to at least 25 IU  $\beta$ -hCG) must be performed before vaccination at Visit 1 (Day 1) and Visit 2 (Day 30) in WOCBP as described in Section 1.3. Urine or serum tests can be used, and results must be negative before vaccination can occur. A detailed definition of WOCBP is provided in Appendix 5.

### **8.3.3 Body Temperature Measurement**

Each participant's body temperature must be taken before vaccination as described in Section 1.3.

Participants will also record axillary body temperatures using their paper VRC (Section 8.1.9) from Day 1 to Day 5 postvaccination.

For this study, any axillary temperature  $\geq 99.5^{\circ}\text{F}$  [ $\geq 37.5^{\circ}\text{C}$ ] or equivalent will be considered an AE of fever. All fevers must be reported Day 1 through Day 30, unless the fever is a symptom of another reported AE.

### **8.3.4 Postvaccination Observation Period**

All participants will be observed for at least 30 minutes following 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, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before randomization must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-

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

From the time of randomization through 30 days following the study vaccination, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

All SAEs must be reported by the investigator throughout the duration of the individual's participation in the study, regardless of whether or not related to the Sponsor's product.

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

A death that occurs prior to the participant completing the study, but outside the time period specified in the previous paragraph.

OR

An SAE that is considered by an investigator, who is a qualified physician, to be vaccine related.

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

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

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

Type of Event	<u>Reporting Time Period:</u> Consent to Randomization/ Allocation	<u>Reporting Time Period:</u> Randomization/ Allocation through Protocol- specified Follow-up Period	<u>Reporting Time 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
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)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	There are no ECIs in this study.			
ECI (do not require regulatory reporting)	There are no ECIs in this study.			
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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



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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

#### **8.4.4 Regulatory Reporting Requirements for SAE**

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards 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 SAE) 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, a pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

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

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

This is not applicable to this study.

#### 8.4.7 Events of Clinical Interest

There are no events of clinical interest in this study

#### 8.4.8 Adverse Events Reported on the VRC

Participants will use a paper VRC (Section 8.1.9) to report solicited and unsolicited AEs.

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

##### 8.4.8.1 Solicited Adverse Events

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

Table 4 Solicited Adverse Events for V116-002

Type of Solicited Adverse Event	Predefined Solicited Adverse Events	Solicited Time Period
Injection site	Injection-site tenderness/pain Injection-site redness/erythema Injection-site swelling	Day 1 to Day 5 postvaccination
Systemic	Headache Muscle pain/myalgia Joint pain/arthralgia Tiredness/fatigue	Day 1 to Day 5 postvaccination

All solicited injection-site AEs will be considered related to study intervention. The investigator will assess all solicited systemic AEs for causality (Appendix 3).

##### 8.4.8.2 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 of the solicited time period.

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



## **8.5 Treatment of Overdose**

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

The Sponsor does not recommend specific treatment for an overdose.

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

## **8.6 Pharmacokinetics**

PK parameters will not be evaluated in this study.

## **8.7 Pharmacodynamics**

Pharmacodynamic parameters will not be evaluated in this study.

## **8.8 Biomarkers**

Biomarkers are not evaluated in this study.

## **8.9 Future Biomedical Research Sample Collection**

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

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

## **8.10 Medical Resource Utilization and Health Economics**

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

## **8.11 Visit Requirements**

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

### **8.11.1 Screening**

Screening procedures will be conducted at Visit 1 (Day 1) as outlined in Section 1.3.

In the event that Day 1 is rescheduled (see Section 5.2), a review of prior medications/ vaccinations and medical history, a complete physical examination, and a body temperature measurement must be repeated prior to vaccination.

### **8.11.2 Treatment Period/Vaccination Visit**

Requirements during the treatment period are outlined in Section 1.3.

## **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 a supplemental SAP (sSAP) and referenced in the Clinical Study Report (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 9.2-9.12. This is an estimation/exploratory study, no hypothesis testing will be performed (and therefore no multiplicity adjustments will be made).

<b>Study Design Overview</b>	A Phase 1, Randomized, Double-blind Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Healthy Japanese Adults.
<b>Treatment Assignment</b>	Approximately 100 participants will be randomly assigned in a 1:1 ratio to receive either Polyvalent Pneumococcal Conjugate Vaccine (pPCV) or PNEUMOVAX™23 (PPSV23). Randomization will be stratified by age at study entry (20 to 64 years and ≥65 years).
<b>Analysis Populations</b>	Safety: All Participants as Treated (APaT) Primary Immunogenicity: Per Protocol (PP) Supportive Immunogenicity: Full Analysis Set (FAS)
<b>Primary Endpoint(s)</b>	The primary safety endpoints include: <ul style="list-style-type: none"> <li>• Proportion of participants with solicited injection-site AEs</li> <li>• Proportion of participants with solicited systemic AEs</li> <li>• Proportion of participants with vaccine-related SAEs</li> </ul>
<b>Secondary Endpoints</b>	The key secondary immunogenicity endpoints include: <ul style="list-style-type: none"> <li>• Ratio of serotype-specific OPA GMTs at 30 days postvaccination for the common serotypes in pPCV and PPSV23</li> <li>• Ratio of serotype-specific OPA GMTs at 30 days postvaccination for the serotypes unique to pPCV</li> <li>• Ratio of serotype specific IgG GMCs at 30 days postvaccination for the common serotypes in pPCV and PPSV23</li> <li>• Ratio of serotype specific IgG GMCs at 30 days postvaccination for the serotypes unique to pPCV</li> <li>• Serotype-specific GMFRs from prevaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses</li> <li>• Serotype-specific GMFRs from prevaccination (Day 1) to 30 days postvaccination (Day 30) for IgG responses</li> </ul>
<b>Statistical Methods for Key Safety Analyses</b>	The analysis of safety will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. No Tier 1 events are defined in this study. For Tier 2 events, 95% CIs will be provided for between-group differences in the proportion of participants with events; these analyses will be performed using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985].
<b>Statistical Methods for Key Immunogenicity Analyses</b>	Immunogenicity analyses will be conducted separately for each serotype. Immunogenicity endpoints will be analyzed at 30 days postvaccination to describe the antibody concentrations in response to the vaccination. The ratio of OPA GMTs and IgG GMCs (pPCV/PPSV23) will be presented along with 95% CIs. The OPA GMT ratio estimation and 95% CI will be calculated using a cLDA method. IgG GMCs will be analyzed in the same way.
<b>Interim Analyses</b>	No interim analyses are planned for this study.
<b>Multiplicity</b>	No multiplicity adjustment is planned in this study.
<b>Sample Size and Power</b>	A total of 100 participants will be enrolled. Assuming a 90% evaluability rate, 90 participants are expected to be included the immunogenicity analysis.



## 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.

## 9.3 Hypotheses/Estimation

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

## 9.4 Analysis Endpoints

### 9.4.1 Immunogenicity Endpoints

There are no primary immunogenicity analysis endpoints.

Secondary immunogenicity analysis endpoints include:

- Ratio (pPCV/PPSV23) of serotype-specific OPA GMTs for the common serotypes in pPCV and PNEUMOVAX™23 at 30 days postvaccination.
- Ratio (pPCV/PPSV23) of serotype-specific OPA GMTs of pPCV and PNEUMOVAX™23 for the serotypes unique to pPCV at 30 days postvaccination.
- Ratio (pPCV/PPSV23) of serotype-specific IgG GMCs for the common serotypes in pPCV and PNEUMOVAX™23 at 30 days postvaccination.
- Ratio (pPCV/PPSV23) of serotype-specific IgG GMCs of pPCV and PNEUMOVAX™23 for the serotypes unique to pPCV at 30 days postvaccination.
- Serotype-specific GMFRs from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses.

### 9.4.2 Safety Endpoints

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

The safety analysis endpoints 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 pain/myalgia, joint pain/arthralgia, 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.
- Proportions of participants with the broad AE categories consisting of any AE and any vaccine-related AE from Day 1 through Day 30 postvaccination
- Proportions of participants with the broad AE categories consisting of any SAE and death from Day 1 through the duration of participation in the study.
- Proportion of participants with maximum axillary temperature measurements which is less than 37.5°C, more than or equal 37.5°C by 0.5°C intervals 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 those participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s).

Potential deviations include but are not limited to:

- Failure to receive correct clinical material as per the randomization schedule at Visit 1 (Day 1) (i.e., participants who were cross-treated)
- Having no valid serology results (i.e., participants who are missing serology results for both Day 1 and Day 30 [30 to 44 days following vaccination]).

The final determination on major 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.

The FAS population will be used for supplementary analysis of the immunogenicity data.

The FAS population consists of all randomized participants who received at least 1 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.

Details on the approach to handling missing data are provided in Section 9.6

## 9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who receive study vaccine. Participants will be included in the group corresponding to the clinical material they actually received for the analysis of safety data using the APaT population. For most participants, this will be the group to which they are randomized. Participants who receive incorrect clinical material will be included in the group corresponding to the clinical material actually received.

## 9.6 Statistical Methods

### 9.6.1 Statistical Methods for Immunogenicity Analyses

The immunogenicity analyses will be conducted for each serotype separately.

The geometric mean ratios and 95% CIs of IgG GMCs and OPA GMTs will be calculated using a cLDA method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000] utilizing data from all vaccination groups. In this model, the response vector consists of the log-transformed prevaccination (Day 1) and postvaccination (Day 30) antibody titers. The repeated measures model will include terms for time, age stratification, the interaction of time-by-vaccination group and age stratification-by-time. The treatment difference in terms of a geometric mean ratio at a given postvaccination time point will be estimated from this model. The term for time will be treated as a categorical variable. An unstructured covariance matrix will be used to model the correlation among repeated measurements. This model allows the inclusion of participants who are missing either the baseline or postbaseline measurements, thereby increasing efficiency. IgG GMCs will be analyzed in the same way. The GMFRs from prevaccination to 30 days postvaccination for both OPA and IgG response will be estimated by vaccination group, and the corresponding 95% CIs will be based on the sample t-distribution. For titers and concentrations that are smaller than the lower bound of the assay's detectable range, half of the lower bound will be used as the value of them.

The analysis strategy for key immunogenicity variables is listed in [Table 5](#).

Table 5 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
<b>Secondary Endpoints</b>			
Ratio of the serotype-specific OPA GMTs at 30 days postvaccination.	cLDA † (point estimate, 95% CI)	PP/FAS	Model-based
Ratio of the serotype-specific IgG GMCs at 30 days postvaccination.	cLDA † (point estimate, 95% CI)	PP/FAS	Model-based
The serotype specific GMFR from prevaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses	Descriptive Statistics (point estimate, 95% CI)	PP/FAS	Observed data
The serotype specific GMFR from prevaccination (Day 1) to 30 days postvaccination (Day 30) for IgG responses	Descriptive Statistics (point estimate, 95% CI)	PP/FAS	Observed data
cLDA = constrained longitudinal data analysis; FAS = Full Analysis Set; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; IgG = immunoglobulin G; OPA = opsonophagocytic activity; PP = Per-protocol. † : cLDA model with terms for time, age stratification, the interaction of time-by-vaccination group and age stratification-by-time.			

### 9.6.2 Statistical Methods for Safety Analyses

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

The analysis of AEs and temperature measurements will follow a tiered approach (Table 6). The tiers differ with respect to the analyses that will be performed. Events are either prespecified as Tier 1 events or will be classified as belonging to Tier 2 or Tier 3 based on the number of events observed.

#### **Tier 1 Events**

Safety events or AEs of special interest that are identified a priori constitute Tier 1 events that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-treatment differences in the proportion of participants with events.

No Tier 1 events are defined for this study.

#### **Tier 2 Events**

Tier 2 events will be assessed via point estimates and risk differences with 95% CIs provided for differences in the proportion of participants with events; these analyses will be performed

using the M&N method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method.

For this study, solicited injection-site AEs from Day 1 through Day 5 postvaccination, solicited systemic AEs from Day 1 through Day 5 postvaccination, and axillary temperature measurements collected from Day 1 through Day 5 postvaccination are considered Tier 2 events. In addition, the broad AE categories consisting of the percentage of participants with any AE, any vaccine-related AE, any solicited injection-site AE, any solicited systemic AE, any SAE, any vaccine-related SAE, and death will be considered Tier 2 events. Nonserious AEs will be followed for 30 days postvaccination, while SAEs will be followed through the duration of participation in the study.

AEs (specific terms as well as SOC terms) will be classified as belonging to Tier 2 if at least 4 participants in any vaccination group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when vaccination groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences.

Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

### **Tier 3 Events**

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



Table 6 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoints	95% CI for Between group Comparison <sup>a</sup>	Descriptive Statistics
Tier 2	Injection-site redness/erythema (Days 1 to 5)	X	X
	Injection-site swelling (Days 1 to 5)	X	X
	Injection-site tenderness/pain (Days 1 to 5)	X	X
	Muscle pain/myalgia (Days 1 to 5)	X	X
	Joint Pain/arthritis (Days 1 to 5)	X	X
	Headache (Days 1 to 5)	X	X
	Tiredness/fatigue (Days 1 to 5)	X	X
	Any AE <sup>b</sup>	X	X
	Any vaccine-related AE <sup>b</sup>	X	X
	Any solicited injection-site AE (Days 1 to 5) <sup>b</sup>	X	X
	Any solicited systemic AE (Days 1 to 5) <sup>b</sup>	X	X
	Any serious AE <sup>b</sup>	X	X
	Any vaccine-related SAE <sup>b</sup>	X	X
	Death <sup>b</sup>	X	X
	Maximum axillary temperature measurements which is less than 37.5°C, more than or equal 37.5°C by 0.5°C intervals (Days 1 to 5)	X	X
Specific AEs by SOC and PT <sup>c</sup> (incidence ≥4 participants in at least 1 of the vaccination groups)	X	X	
Tier 3	Specific AEs by SOC and PT <sup>c</sup> (incidence <4 participants in all of the vaccination groups)		X

AE = adverse event; CI = confidence interval; M&N = Miettinen and Nurminen; PT = preferred term; SAE = serious adverse event; SOC = system organ class; X = results will be provided.

<sup>a</sup> These analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].

<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> Includes only those endpoints not prespecified as Tier 2 endpoints.

### 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 vaccinated, and the reasons for discontinuation, will be displayed by group.

Demographic variables (e.g., age) and prior and concomitant therapies and vaccines will be summarized by group.

### 9.7 Interim Analyses

No interim analyses are planned for this study.

### 9.8 Multiplicity

No multiplicity adjustment is planned in this study.

### 9.9 Sample Size and Power Calculations

#### 9.9.1 Immunogenicity Analyses

Approximately 100 participants (approximately 34 participants in the 20 to 64 years of age, and approximately 66 participants in the  $\geq 65$  years of age) will be enrolled, with approximately 50 participants in each of the 2 vaccination groups. Assuming 90% evaluability (approximately 45 participants per group), the half width of 95%CI for the ratios between vaccination groups with respect to IgG and OPA is 0.524, 0.842, respectively, in natural log scale based on the following assumptions:

- The overall standard deviation of natural log-transformed IgG results is 1.25, OPA results is 2.01. This assumption is based on observations from V114 PN015 study.
- 90% evaluability rate (approximately 45 participants per group).

#### 9.9.2 Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants enrolled and the incidence rate of SAEs in the general population. If the incidence rate of an SAE is 1 of every 50 recipients of the vaccine (2%), then there is a 63.6% chance of observing at least 1 such SAE among 50 participants in the pPCV group.

### 9.10 Subgroup Analyses

Serotype-specific OPA and IgG responses will be summarized by vaccination group in each age subgroup (i.e., 20-64 years and  $\geq 65$  years).

Following safety endpoints will be summarized by vaccination group in each age subgroup (i.e., 20-64 years and  $\geq 65$  years).

- Solicited injection-site AEs (redness/erythema, swelling, tenderness/pain) (Days 1 to 5)
- Solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, tiredness/fatigue) (Days 1 to 5)
- Any AE, Any vaccine-related AE, Any serious AE, Any vaccine-related SAE, Death
- Maximum axillary temperature measurements which is less than 37.5°C, more than or equal 37.5°C by 0.5°C intervals (Days 1 to 5)

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

Given that participants will receive a single dose of pPCV or PNEUMOVAX™23, compliance will not be calculated. However, the number and proportion of randomized participants receiving pPCV or PNEUMOVAX™23 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 pPCV or PNEUMOVAX™23.

## 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

#### 10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

##### Code of Conduct for Interventional Clinical Trials

#### I. Introduction

##### A. Purpose

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

##### B. Scope

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

#### II. Scientific Issues

##### A. Trial Conduct

##### 1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

##### 2. Site Selection

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.

##### 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 fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

### **B. Publication and Authorship**

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

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

## **III. Participant Protection**

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

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

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

### **B. Safety**

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

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

### **C. Confidentiality**

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

### **D. Genomic Research**

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

#### **IV. Financial Considerations**

##### **A. Payments to Investigators**

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

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

##### **B. Clinical Research Funding**

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

##### **C. Funding for Travel and Other Requests**

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

#### **V. Investigator Commitment**

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

##### **10.1.2 Financial Disclosure**

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

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

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

#### **10.1.3.3 Confidentiality of IRB/IEC Information**

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

#### **10.1.4 Publication Policy**

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with

standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

### **10.1.5 Compliance with Study Registration and Results Posting Requirements**

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>, [www.clinicaltrialsregister.eu](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 trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

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

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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



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

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

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

#### **10.1.7 Data Quality Assurance**

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

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

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

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

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

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

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

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

#### **10.1.8 Source Documents**

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

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

#### **10.1.9 Study and Site Closure**

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

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

## 10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 7](#) will be performed by the local laboratory.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum) should be conducted at Visit 1 (Day 1) and Visit 2 (Day 30).
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Other Screening Tests	<ul style="list-style-type: none"><li>• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only)</li><li>• Serum or urine <math>\beta</math>-human chorionic gonadotropin (<math>\beta</math>-hCG) pregnancy test (for WOCBP)</li><li>• All study-required laboratory assessments will be performed by a central laboratory, with the exception of pregnancy tests.</li></ul>

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

#### **10.3.1 Definition of AE**

##### **AE definition**

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

##### **Events meeting the AE definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing 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 who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant in their VRC.

### 10.3.2 Definition of SAE

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

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

**a. Results in death**

**b. Is life-threatening**

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

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

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

**d. Results in persistent or significant disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

In offspring of participant taking the product regardless of time to diagnosis.

**f. Other important medical events**

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

**10.3.3 Additional Events Reported**

**Additional events that require reporting**

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

Is a cancer

Is associated with an overdose

**10.3.4 Recording AE and SAE**

**AE and SAE recording**

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

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

### **Assessment of intensity**

- An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies definitely acting like something is wrong).
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).
- Injection site erythema/redness or swelling from the day of vaccination through Day 5 postvaccination will be evaluated by maximum size.

### **Assessment of causality**

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product 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 upon the available information.
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product 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 Sponsor's product? 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 re-exposed to the Sponsor's product 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, or (2) the study is a single-dose vaccine study; or (3) Sponsor's product(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 SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT 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 Sponsor's product or drug class pharmacology or toxicology?



- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:

There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:

Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

### **Follow-up of AE and SAE**

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

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

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

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

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

Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

#### **SAE reporting to the Sponsor via paper CRF**

- If the EDC tool is not operational, facsimile transmission or secure e-mail 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/combination medicinal products as described below. For purposes of this section, medical devices/combination medicinal products in scope for device information collection include medical devices/combination medicinal products 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

**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 two or more regulated components, i.e., a drug and a device; a device and a cellular and tissue-based product; a cellular and tissue-based product and a drug; or a drug, a device, and a cellular and tissue-based product according to 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 serious adverse event due to malfunction in the characteristics and/or performance of a device (this study is a pre-filled syringe) as well as any inadequacy in the labeling or the instructions for use which has led to the death of a participant and/or the associated person or to a serious deterioration in his/her state of health.

**Malfunction which may lead to Serious Adverse Events** - Any malfunction of a medical device which might have led to the death of a participant and/or the associated person or to a serious deterioration in his/her state of health. "Which might have led to" means that there is the possibility that death or a serious deterioration might have occurred in a participant and/or the associated person, although these cases have not actually occurred.

### 10.4.2 Medical Device/Combination Medicinal Products – Documenting and Reporting

In order to fulfill regulatory reporting obligations, medical device/combination medicinal product information will be collected. Serious adverse event 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 serious adverse events due to malfunctions will be followed until resolution, stabilization, until the event is otherwise explained, or the

participant or associated person is lost to follow-up. Malfunction which may lead to serious adverse events 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 adverse event due to malfunction (serious or nonserious) occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- Any serious adverse event due to malfunction 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 EDC data entry guidelines (or equivalent).
- It is important that the investigator provides his/her 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 the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

## 10.5 Appendix 5: Contraceptive Guidance

### 10.5.1 Definitions

#### Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

## 10.5.2 Contraception Requirements

<p><b>Contraceptives allowed during the study include<sup>a</sup>:</b></p>
<p><b>Highly Effective Contraceptive Methods That Have Low User Dependency<sup>b</sup></b>  <i>Failure rate of &lt;1% per year when used consistently and correctly.</i></p>
<p>Progestogen-only subdermal contraceptive implant<sup>c,d</sup>          IUS<sup>c,e</sup>          Non-hormonal IUD          Bilateral tubal occlusion</p>
<p>Azoospermic partner (vasectomized or secondary to medical cause)          This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.</p> <p>Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.</p>
<p><b>Highly Effective Contraceptive Methods That Are User Dependent<sup>b</sup></b>  <i>Failure rate of &lt;1% per year when used consistently and correctly.</i></p>
<p>Combined (estrogen- and progestogen- containing) hormonal contraception<sup>c,d</sup></p> <ul style="list-style-type: none"> <li>- Oral</li> <li>- Intravaginal</li> <li>- Transdermal</li> <li>- Injectable</li> </ul>
<p>Progestogen-only hormonal contraception<sup>c,d</sup></p> <ul style="list-style-type: none"> <li>- Oral</li> <li>- Injectable</li> </ul>
<p>Sexual Abstinence</p> <p>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</p>
<p>a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.</p> <p>b Typical use failure rates are higher than perfect-use failure rates (i.e., when used consistently and correctly).</p> <p>c Male condoms must be used in addition to female participant hormonal contraception.</p> <p>d If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.</p> <p>e IUS is a progestin releasing IUD.</p> <p>Note: The following are not acceptable methods of contraception:</p> <ul style="list-style-type: none"> <li>- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.</li> <li>- Male condom with cap, diaphragm, or sponge with spermicide.</li> <li>- Male and female condom should not be used together (due to risk of failure with friction).</li> </ul>

## Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.
    - Male condom with cap, diaphragm, or sponge with spermicide.
    - Male and **female** condom cannot be used together.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

## 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

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

#### 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

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 are 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 which 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

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing 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

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

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

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main 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 utilized 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**

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**

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**

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**

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

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

Not applicable.

## 10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
APaT	All Participants as Treated
β-hCG	β-human chorionic gonadotropin
CFR	Code of Federal Regulations
CI	confidence interval
cLDA	constrained longitudinal data analysis
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
CTFG	Clinical Trials Facilitation Group
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	events of clinical interest
ECL	electrochemiluminescence
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular
IPD	invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
IU	intersection-union
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
M&N	Miettinen and Nurminen
MOPA	multiplexed opsonophagocytic assay
MSD	Merck Sharp & Dohme Corp.
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
PK	pharmacokinetic
PnECL	pneumococcal electrochemiluminescence
PnP	pneumococcal polysaccharide
PP	Per protocol

<b>Abbreviation</b>	<b>Expanded Term</b>
pPCV	polyvalent pneumococcal conjugate vaccine
RNA	ribonucleic acid
SAE	serious adverse event
SLAB	supplemental laboratory test
SoA	Schedule of Activities
SOC	system organ class
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
US	United States
VRC	vaccination report card
WOCBP	woman (or women) of childbearing potential

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Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal  
Conjugate Vaccine in Healthy Japanese Adults.**

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## Supplemental Statistical Analysis Plan (sSAP)

### 1 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP will provide additional sensitivity statistical analysis details, data derivations and documents modifications or additions to the analysis plan that are not “principal” in nature and result from information that was not available at the time of protocol finalization.

### 2 SUMMARY OF CHANGES

A summary of changes is provided in the table below.

Section	Description of change	Rationale
3.6.1	Add text around analysis of cross-reactive serotypes and RCDC	Addition for clarity
3.6.1	Added [Table 2] that lists serotype-specific limits of quantitation for OPA and IgG responses and text around them	Addition for clarity

### 3 ANALYTICAL AND METHODOLOGICAL DETAILS

#### 3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in [Sec. 3.2] to [Sec. 3.12].

<b>Study Design Overview</b>	A Phase 1, Randomized, Double-blind Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Healthy Japanese Adults.
<b>Treatment Assignment</b>	Approximately 100 participants will be randomly assigned in a 1:1 ratio to receive either Polyvalent Pneumococcal Conjugate Vaccine (pPCV) or PNEUMOVAX™23 (PPSV23). Randomization will be stratified by age at study entry (20 to 64 years and ≥65 years).
<b>Analysis Populations</b>	Safety: All Participants as Treated (APaT) Primary Immunogenicity: Per Protocol (PP) Supportive Immunogenicity: Full Analysis Set (FAS)
<b>Primary Endpoint(s)</b>	The primary safety endpoints include: <ul style="list-style-type: none"> <li>· Proportion of participants with solicited injection-site AEs</li> <li>· Proportion of participants with solicited systemic AEs</li> <li>· Proportion of participants with vaccine-related SAEs</li> </ul>



<b>Secondary Endpoints</b>	<p>The key secondary immunogenicity endpoints include:</p> <ul style="list-style-type: none"> <li>• Ratio of serotype-specific OPA GMTs at 30 days postvaccination for the common serotypes in pPCV and PPSV23</li> <li>• Ratio of serotype-specific OPA GMTs at 30 days postvaccination for the serotypes unique to pPCV</li> <li>• Ratio of serotype specific IgG GMCs at 30 days postvaccination for the common serotypes in pPCV and PPSV23</li> <li>• Ratio of serotype specific IgG GMCs at 30 days postvaccination for the serotypes unique to pPCV</li> <li>• Serotype-specific GMFRs from prevaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses</li> <li>• Serotype-specific GMFRs from prevaccination (Day 1) to 30 days postvaccination (Day 30) for IgG responses</li> </ul>
<b>Statistical Methods for Key Safety Analyses</b>	<p>The analysis of safety will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. No Tier 1 events are defined in this study. For Tier 2 events, 95% CIs will be provided for between-group differences in the proportion of participants with events; these analyses will be performed using the Miettinen and Nurminen (M&amp;N) method [Ref. 5.4: 04J96G].</p>
<b>Statistical Methods for Key Immunogenicity Analyses</b>	<p>Immunogenicity analyses will be conducted separately for each serotype. Immunogenicity endpoints will be analyzed at 30 days postvaccination to describe the antibody concentrations in response to the vaccination. The ratio of OPA GMTs and IgG GMCs (pPCV/PPSV23) will be presented along with 95% CIs. The OPA GMT ratio estimation and 95% CI will be calculated using a cLDA method. IgG GMCs will be analyzed in the same way.</p>
<b>Interim Analyses</b>	<p>No interim analyses are planned for this study.</p>
<b>Multiplicity</b>	<p>No multiplicity adjustment is planned in this study.</p>
<b>Sample Size and Power</b>	<p>A total of 100 participants will be enrolled. Assuming a 90% evaluability rate, 90 participants are expected to be included the immunogenicity analysis.</p>

### 3.2 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.

### 3.3 Hypotheses/Estimation

Objectives and hypotheses are stated in Section 3 in protocol.

### 3.4 Analysis Endpoints

#### 3.4.1 Immunogenicity Endpoints

There are no primary immunogenicity analysis endpoints.

Secondary immunogenicity analysis endpoints include:

- Ratio (pPCV/PPSV23) of serotype-specific OPA GMTs for the common serotypes in pPCV and PNEUMOVAX™23 at 30 days postvaccination.
- Ratio (pPCV/PPSV23) of serotype-specific OPA GMTs of pPCV and PNEUMOVAX™23 for the serotypes unique to pPCV at 30 days postvaccination.
- Ratio (pPCV/PPSV23) of serotype-specific IgG GMCs for the common serotypes in pPCV and PNEUMOVAX™23 at 30 days postvaccination.
- Ratio (pPCV/PPSV23) of serotype-specific IgG GMCs of pPCV and PNEUMOVAX™23 for the serotypes unique to pPCV at 30 days postvaccination.
- Serotype-specific GMFRs from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses.

### 3.4.2 Safety Endpoints

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

The safety analysis endpoints 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 pain/myalgia, joint pain/arthralgia, 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.
- Proportions of participants with the broad AE categories consisting of any AE and any vaccine-related AE from Day 1 through Day 30 postvaccination.
- Proportions of participants with the broad AE categories consisting of any SAE and death from Day 1 through the duration of participation in the study.
- Proportion of participants with maximum axillary temperature measurements which is less than 37.5°C, more than or equal 37.5°C by 0.5°C intervals from Day 1 through Day 5 postvaccination.



## **3.5 Analysis Populations**

### **3.5.1 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 those participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s).

Potential deviations include but are not limited to:

- Failure to receive correct clinical material as per the randomization schedule at Visit 1 (Day 1) (i.e., participants who were cross-treated)
- Having no valid serology results (i.e., participants who are missing serology results for both Day 1 and Day 30 [30 to 44 days following vaccination]).

The final determination on major 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.

The FAS population will be used for supplementary analysis of the immunogenicity data.

The FAS population consists of all randomized participants who received at least 1 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.

Details on the approach to handling missing data are provided in [Sec. 3.6].

### **3.5.2 Safety Analysis Population**

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who receive study vaccine. Participants will be included in the group corresponding to the clinical material they actually received for the analysis of safety data using the APaT population. For most participants, this will be the group to which they are randomized. Participants who receive incorrect clinical material will be included in the group corresponding to the clinical material actually received.

## **3.6 Statistical Methods**

### **3.6.1 Statistical Methods for Immunogenicity Analyses**

The immunogenicity analyses will be conducted for each serotype separately.

The geometric mean ratios and 95% CIs of IgG GMCs and OPA GMTs will be calculated using a cLDA method proposed by Liang and Zeger [Ref. 5.4: 03RS5G] utilizing data from all vaccination groups. In this model, the response vector consists of the log-transformed

prevaccination (Day 1) and postvaccination (Day 30) antibody titers. The repeated measures model will include terms for time, age stratification, the interaction of time-by-vaccination group and age stratification-by-time. The treatment difference in terms of a geometric mean ratio at a given postvaccination time point will be estimated from this model. The term for time will be treated as a categorical variable. An unstructured covariance matrix will be used to model the correlation among repeated measurements. This model allows the inclusion of participants who are missing either the baseline or postbaseline measurements, thereby increasing efficiency. IgG GMCs will be analyzed in the same way. The GMFRs from prevaccination to 30 days postvaccination for both OPA and IgG response will be estimated by vaccination group, and the corresponding 95% CIs will be based on the sample t-distribution. For titers and concentrations that are smaller than the lower bound of the assay’s detectable range, half of the lower bound will be used as the value of them.

A similar statistical approach will be used to estimate the treatment effect for each cross-reactive serotype in an exploratory manner.

Reverse Cumulative Distribution Curves (RCDC) for both OPA titers and IgG concentrations at Day 1 (Baseline) and Day 30 (30 days postvaccination) will be graphically displayed by serotype. The analysis strategy for key immunogenicity variables is listed in [Table 1].

Table 1 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
<b>Secondary Endpoints</b>			
Ratio of the serotype-specific OPA GMTs at 30 days postvaccination.	cLDA <sup>†</sup> (point estimate, 95% CI)	PP/FAS	Model-based
Ratio of the serotype-specific IgG GMCs at 30 days postvaccination.	cLDA <sup>†</sup> (point estimate, 95% CI)	PP/FAS	Model-based
The serotype specific GMFR from prevaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses	Descriptive Statistics (point estimate, 95% CI)	PP/FAS	Observed data
The serotype specific GMFR from prevaccination (Day 1) to 30 days postvaccination (Day 30) for IgG responses	Descriptive Statistics (point estimate, 95% CI)	PP/FAS	Observed data
cLDA = constrained longitudinal data analysis; FAS = Full Analysis Set; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; IgG = immunoglobulin G; OPA = opsonophagocytic activity; PP = Per-protocol. †: cLDA model with terms for time, age stratification, the interaction of time-by-vaccination group and age stratification-by-time.			

The detectable ranges for OPA and IgG response differ for each serotype. The limits of quantitation define the range of responses over which the assay provides precise and accurate measurements. For all serotypes measured using the multiplex opsonophagocytic assay (MOPA), the laboratory reports OPA titers down to the limits of detection (LOD) of 8, and titers below 8 will be reported as <8. The MOPA lab does not apply the lower limit of

quantitation (LLOQ) or upper limit of quantitation (ULOQ). For IgG responses, the serotype-specific LLOQ and ULOQ are applied. [Table 2] displays the limits of quantitation and limits of detection defined for each serotype for IgG and OPA responses, respectively. For responses smaller than LLOQ(LOD), half of the LLOQ(LOD) will be used for the analysis when calculating OPA GMTs, IgG GMCs. Again, for responses smaller than LLOQ (LOD), the value equal to the LLOQ(LOD) will be used for analysis when calculating the GMFR and proportion of participants with a  $\geq 4$ -fold rise for OPA and IgG. For responses larger than ULOQ, a value equal to ULOQ+1 will be used for the IgG analysis. A similar approach to addressing the out of detectable range responses in the OPA and IgG will be used for the RCDCs.

Table 2 Limits of Quantitation for OPA and IgG Serotype-specific Responses

Serotype	OPA		IgG	
	LOD (1/dil)	ULOQ (1/dil)	LLOQ ( $\mu\text{g/mL}$ ) <sup>b</sup>	ULOQ ( $\mu\text{g/mL}$ ) <sup>b</sup>
3	8	N/A		
6A	8	N/A		
6C	8	N/A		
7F	8	N/A		
8	8	N/A		
9N	8	N/A		
10A	8	N/A		
11A	8	N/A		
12F	8	N/A		
15A	8	N/A		
15B	8	N/A		
15C <sup>a</sup>	8	N/A		
16F	8	N/A		
17F	8	N/A		
19A	8	N/A		
20A	8	N/A		
22F	8	N/A		
23A	8	N/A		
23B	8	N/A		
24F	8	N/A		
31	8	N/A		
33F	8	N/A		
35B	8	N/A		

IgG=immunoglobulin G; LLOQ = the lower limit of quantitation; OPA= opsonophagocytic activity; ULOQ = upper limit of quantitation; MOPA= multiplex opsonophagocytic killing assay ; LOD = limit of detection  
<sup>a</sup>15C = deOAc 15B .  
<sup>b</sup>1:1,000 dilution corrected.  
<sup>c</sup>Serotype 20B was tested using OPA only.

### **3.6.2 Statistical Methods for Safety Analyses**

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

The analysis of AEs and temperature measurements will follow a tiered approach [Table 3]. The tiers differ with respect to the analyses that will be performed. Events are either prespecified as Tier 1 events or will be classified as belonging to Tier 2 or Tier 3 based on the number of events observed.

#### **Tier 1 Events**

Safety events or AEs of special interest that are identified a priori constitute Tier 1 events that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-treatment differences in the proportion of participants with events.

No Tier 1 events are defined for this study.

#### **Tier 2 Events**

Tier 2 events will be assessed via point estimates and risk differences with 95% CIs provided for differences in the proportion of participants with events; these analyses will be performed using the M&N method [Ref. 5.4: 04J96G], an unconditional, asymptotic method.

For this study, solicited injection-site AEs from Day 1 through Day 5 postvaccination, solicited systemic AEs from Day 1 through Day 5 postvaccination, and axillary temperature measurements collected from Day 1 through Day 5 postvaccination are considered Tier 2 events. In addition, the broad AE categories consisting of the percentage of participants with any AE, any vaccine-related AE, any solicited injection-site AE, any solicited systemic AE, any SAE, any vaccine-related SAE, and death will be considered Tier 2 events. Nonserious AEs will be followed for 30 days postvaccination, while SAEs will be followed through the duration of participation in the study.

AEs (specific terms as well as SOC terms) will be classified as belonging to Tier 2 if at least 4 participants in any vaccination group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when vaccination groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences.

Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

#### **Tier 3 Events**

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



Serious Adverse Event due to Malfunction ,and malfunction which may lead to Serious Adverse Events, if any, will be listed.

Table 3 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoints	95% CI for Between group Comparison <sup>a</sup>	Descriptive Statistics
Tier 2	Injection-site redness/erythema (Days 1 to 5)	X	X
	Injection-site swelling (Days 1 to 5)	X	X
	Injection-site tenderness/pain (Days 1 to 5)	X	X
	Muscle pain/myalgia (Days 1 to 5)	X	X
	Joint Pain/arthritis (Days 1 to 5)	X	X
	Headache (Days 1 to 5)	X	X
	Tiredness/fatigue (Days 1 to 5)	X	X
	Any AE <sup>b</sup>	X	X
	Any vaccine-related AE <sup>b</sup>	X	X
	Any solicited injection-site AE (Days 1 to 5) <sup>b</sup>	X	X
	Any solicited systemic AE (Days 1 to 5) <sup>b</sup>	X	X
	Any serious AE <sup>b</sup>	X	X
	Any vaccine-related SAE <sup>b</sup>	X	X
	Death <sup>b</sup>	X	X
Maximum axillary temperature measurements which is less than 37.5°C, more than or equal 37.5°C by 0.5°C intervals (Days 1 to 5)	X	X	
Specific AEs by SOC and PT <sup>c</sup> (incidence ≥4 participants in at least 1 of the vaccination groups)	X	X	
Tier 3	Specific AEs by SOC and PT <sup>c</sup> (incidence <4 participants in all of the vaccination groups)		X

AE = adverse event; CI = confidence interval; M&N = Miettinen and Nurminen; PT = preferred term; SAE = serious adverse event; SOC = system organ class; X = results will be provided.

<sup>a</sup> These analyses will be performed using the M&N method [Ref. 5.4: 04J96G].

<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> Includes only those endpoints not prespecified as Tier 2 endpoints.

### 3.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

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 vaccinated, and the reasons for discontinuation, will be displayed by group.

Demographic variables (e.g., age) and prior and concomitant therapies and vaccines will be summarized by group.

### 3.7 Interim Analyses

No interim analyses are planned for this study.

### 3.8 Multiplicity

No multiplicity adjustment is planned in this study.

### 3.9 Sample Size and Power Calculations

#### 3.9.1 Immunogenicity Analyses

Approximately 100 participants (approximately 34 participants in the 20 to 64 years of age, and approximately 66 participants in the  $\geq 65$  years of age) will be enrolled, with approximately 50 participants in each of the 2 vaccination groups. Assuming 90% evaluability (approximately 45 participants per group), the half width of 95%CI for the ratios between vaccination groups [REDACTED], in natural log scale based on the following assumptions:

- The [REDACTED] [REDACTED] This assumption is based on observations from V114 PN015 study.
- 90% evaluability rate (approximately 45 participants per group).

#### 3.9.2 Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants enrolled and the incidence rate of SAEs in the general population. If the incidence rate of an SAE is 1 of every 50 recipients of the vaccine (2%), then there is a 63.6% chance of observing at least 1 such SAE among 50 participants in the pPCV group.

### 3.10 Subgroup Analyses

Serotype-specific OPA (GMTs, GMFRs) and IgG (GMCs, GMFRs) responses will be summarized by vaccination group in each age subgroup (i.e., 20-64 years and  $\geq 65$  years). The point estimate and 95%CI will be provided.

Following safety endpoints will be summarized by vaccination group in each age subgroup (i.e., 20-64 years and  $\geq 65$  years). The counts and risk difference with 95%CI will be provided.

- Solicited injection-site AEs (redness/erythema, swelling, tenderness/pain) (Days 1 to 5)
- Solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, tiredness/fatigue) (Days 1 to 5)
- Any AE, Any vaccine-related AE, Any serious AE, Any vaccine-related SAE, Death
- Maximum axillary temperature measurements which is less than 37.5°C, more than or equal 37.5°C by 0.5°C intervals (Days 1 to 5)

### **3.11 Compliance (Medication Adherence)**

Given that participants will receive a single dose of pPCV or PNEUMOVAX™23, compliance will not be calculated. However, the number and proportion of randomized participants receiving pPCV or PNEUMOVAX™23 will be summarized [Sec. 3.12].

### **3.12 Extent of Exposure**

The extent of exposure will be summarized by the number and proportion of randomized participants administered pPCV or PNEUMOVAX™23.

## **4 LIST OF REFERENCES**

- [Ref. 5.4: 03RS5G] Liang K-Y, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. *Sankhya: The Indian Journal of Statistics* 2000;62(Series B, Pt 1):134-48.
- [Ref. 5.4: 04J96G] Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med.* 1985 Apr-Jun;4(2):213-26.