Official Protocol Title:	A Phase 1/Phase 2, Randomized, Double-blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Adults.
NCT number:	NCT04168190
Document Date:	11-May-2020

Title Page

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Protocol Title: A Phase 1/Phase 2, Randomized, Double-blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Adults.

Protocol Number: 001-01

Compound Number: V116

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	19316

Approval Date: 11 May 2020

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 1	11-MAY-2020	The primary purpose of this amendment is to include definitions for solicited and unsolicited adverse events.
Original Protocol	20-AUG-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

The primary purpose of this amendment is to include definitions for solicited and unsolicited adverse events.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
8.1.9 Vaccination Report Card (VRC) 8.3.4 Postvaccination Observation Period 8.4.8 Adverse Events Reported on the VRC 10.3.1 Definition of AE	Details related to AEs reported on the VRC were moved from Section 8.1.9 to Section 8.4.8. The previous Section 8.3.4 (Safety Assessments and Use of the VRC/eVRC) was split into 2 sections: Section 8.3.4 was renamed and retains details of the postvaccination observation period. Text related to AEs reported on the VRC was moved to Section 8.4.8. Section 8.4.8 is a new section containing details of solicited and unsolicited AEs reported on the VRC. The definitions of solicited and unsolicited AEs were added to Section 10.3.1.	The text was updated to include definitions for solicited and unsolicited AEs reported by the participant using the VRC.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria 10.5.2 Contraception Requirements	Updated inclusion criterion No. 4 to include different contraception requirements for Phase 1 and Phase 2. Added subsections to Appendix 3 (Section 10.5.2) to define different contraception requirements for Phase 1 (Section 10.5.2.1) and Phase 2 (Section 10.5.2.2).	Based on assessment of additional nonclinical data, contraception requirements for Phase 2 were made less restrictive compared with Phase 1.
1.2.2 Schema for Phase 2 1.3.2 Schedule of Activities for Phase 2 8 Study Assessments and Procedures (Table 4: Approximate Blood Volumes Drawn by Study Visit and Sample Type [Phase 2])	Added visit numbers for the telephone contacts in Phase 2: • Visit 2 (Day 15 telephone contact) • Visit 4 (Day 90 telephone contact) • Visit 5 (Day 180 telephone contact) The Day 30 site visit in Phase 2 (previously Visit 2) was renumbered to Visit 3	Visit numbers were added for telephone contacts.
1.3.1 Schedule of Activities for Phase 1 1.3.2 Schedule of Activities for Phase 2	Updated the Notes column for the provision and review of the VRC to refer to Section 8.1.9 for additional details.	Revision was made for clarity.

Section # and Name	Description of Change	Brief Rationale
4.2.1.3 Future Biomedical Research 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Removed the word "substudy" from the description of future biomedical research.	Future biomedical research is not a separate substudy.
8.1.13 Participant Blinding/Unblinding	Added the following text to clarify emergency unblinding procedures: Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.	Revisions were made for clarity.
Throughout	Editorial revisions.	Minor editorial changes to the text.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/Phase 2, Randomized, Double-blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Adults.

Short Title: Phase 1/Phase 2 Study of a pPCV in Adults

Acronym:

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for Phase 1 of this study. For Phase 2, hypotheses are aligned with objectives in the Objectives and Endpoints table.

In Phase 1, objectives and endpoints will be evaluated in pneumococcal vaccine-naïve adults 18 to 49 years of age who are administered a single dose of pPCV-1, pPCV-2, or PNEUMOVAX™23.

In Phase 2, objectives and endpoints will be evaluated in pneumococcal vaccine-naïve adults ≥50 years of age who are administered a single dose of pPCV or PNEUMOVAX™23.

Primary Objectives	Primary Endpoints
Phase 1 - Objective: To evaluate the safety and tolerability of pPCV-1 and pPCV-2 with respect to the proportion of participants with AEs.	- Solicited injection-site AEs - Solicited systemic AEs - Vaccine-related SAEs
Phase 2 - Objective: To evaluate the safety and tolerability of pPCV with respect to the proportion of participants with AEs.	- Solicited injection-site AEs - Solicited systemic AEs - Vaccine-related SAEs

Phase 2 - Objective: To evaluate the serotype-specific OPA GMTs at 30 days postvaccination. Hypothesis (H1): pPCV is noninferior to PNEUMOVAX™23 as measured by the serotype-specific OPA GMTs for the common serotypes at 30 days postvaccination. Hypothesis (H2): The serotype-specific OPA GMTs for the unique serotypes in pPCV at 30 days postvaccination are statistically significantly greater following vaccination with pPCV than those following vaccination with PNEUMOVAX™23.	- Serotype-specific OPA responses
Secondary Objectives	Secondary Endpoints
Phase 1 - Objective: To describe the serotype-specific OPA GMTs and IgG GMCs as measured at 30 days postvaccination.	- Serotype-specific OPA and IgG responses
Phase 1 - Objective: To describe the serotype-specific GMFR from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses	- Serotype-specific OPA and IgG responses
Phase 2 - Objective: To evaluate serotype-specific IgG GMCs at 30 days postvaccination. Hypothesis (H3): pPCV is noninferior to PNEUMOVAX™23 as measured by the serotype-specific IgG GMCs for the common serotypes at 30 days postvaccination. Hypothesis (H4): The serotype-specific IgG GMCs for the unique serotypes in pPCV at 30 days postvaccination are statistically significantly greater following vaccination with pPCV than those following vaccination with PNEUMOVAX™23.	- Serotype-specific IgG responses
Phase 2 - Objective: To evaluate serotype-specific GMFR from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses	- Serotype-specific OPA and IgG responses.

Phase 2 - Objective: To evaluate the proportion of participants who achieve a ≥4-fold increase in serotype-specific OPA responses from prevaccination (Day 1) to 30 days postvaccination (Day 30)	- Serotype-specific OPA responses

Overall Design:

Study Phase	Phase 1/Phase 2
Primary Purpose	Prevention
Indication	Pneumococcal infection
Population	Phase 1: Adults 18 to 49 years of age Phase 2: Adults 50 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 18 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 590 total participants (90 participants in Phase 1 and 500 participants in Phase 2) will be enrolled as detailed in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Study Interventions for Phase 1:

Intervention Group Name	Vaccine	Dose Strength	Dose Frequency	Route of Admin	Vaccination Regimen	Use
pPCV-1	pPCV	Refer to IB	Single Dose	IM	Single Dose at Visit 1 (Day 1)	Experimental
pPCV-2	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.

Study Interventions for Phase 2:

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

5 total intervention groups (3 groups in Phase 1 and 2 groups in Phase 2)

Duration of Participation

Each participant will participate in the study for approximately 6 months from the time the participant signs the Informed Consent Form through the final contact.

Study Governance Committees:

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

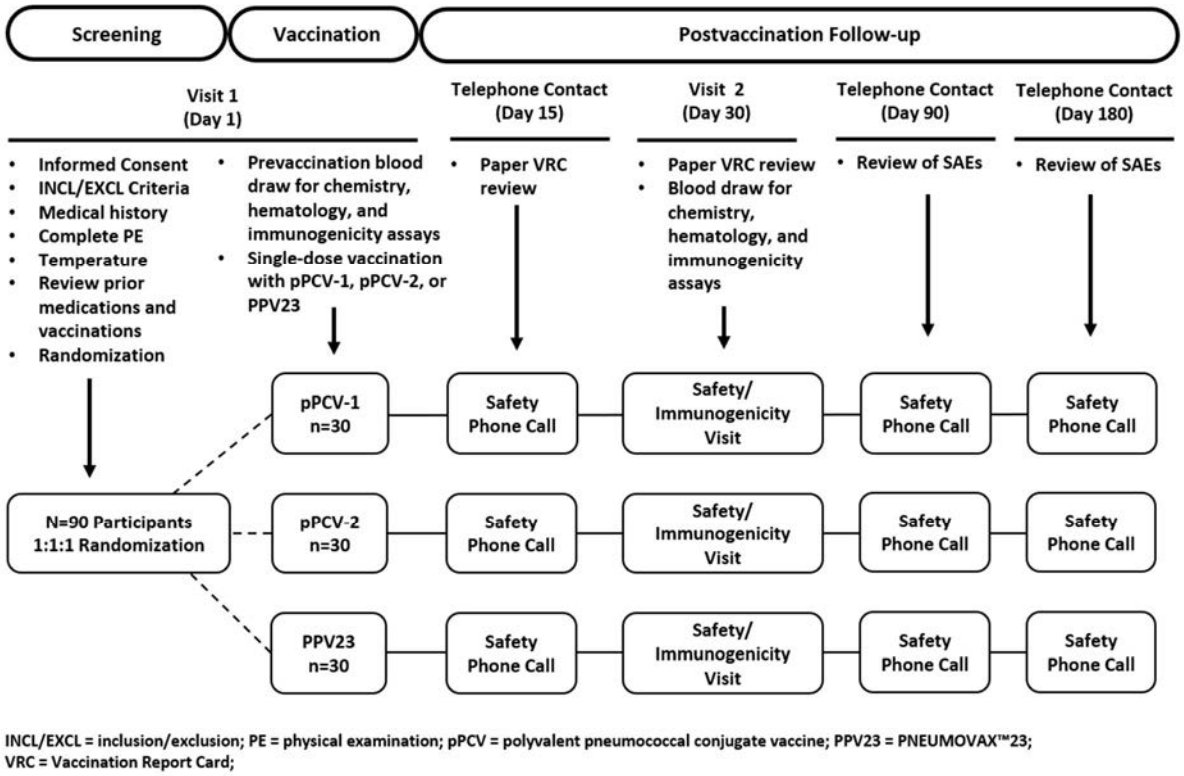
Study Accepts Healthy Volunteers: Yes

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

1.2 Schema

1.2.1 Schema for Phase 1

The Phase 1 study design is depicted in Figure 1.

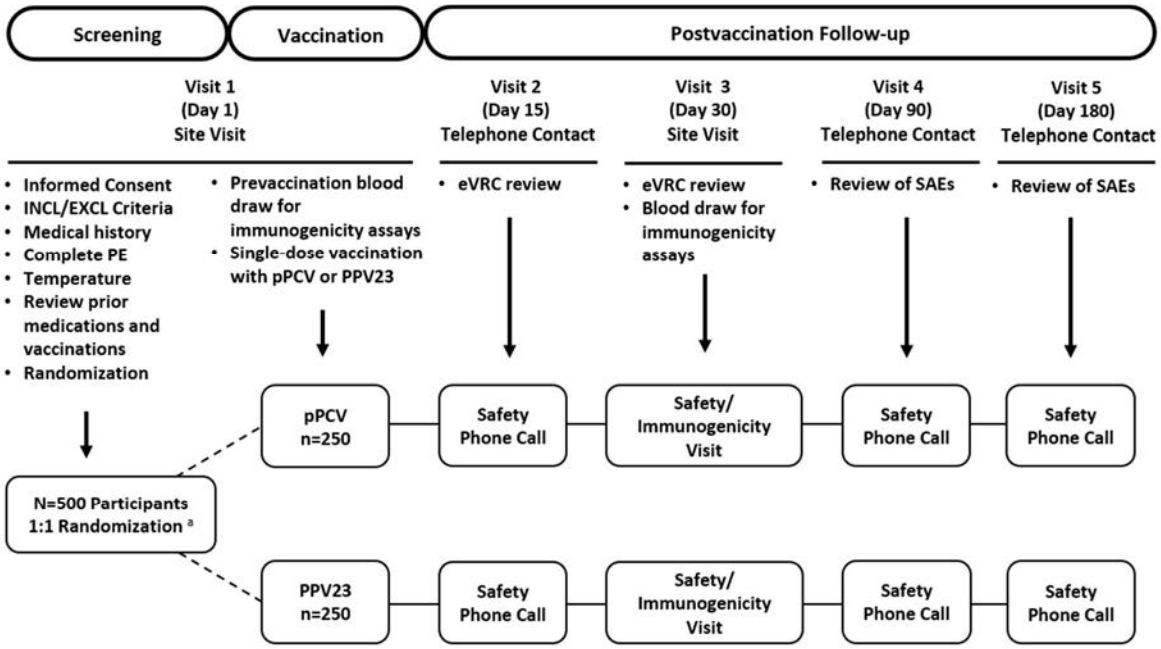


INCL/EXCL = inclusion/exclusion; PE = physical examination; pPCV = polyvalent pneumococcal conjugate vaccine; PPV23 = PNEUMOVAX™23; VRC = Vaccination Report Card;

Figure 1 V116-001 Study Design: Phase 1

1.2.2 Schema for Phase 2

The Phase 2 study design is depicted in Figure 2.



eVRC = electronic Vaccination Report Card; INCL/EXCL = inclusion/exclusion; PE = physical examination; pPCV = polyvalent pneumococcal conjugate vaccine; PPV23 = PNEUMOVAX™23; SAE = serious adverse event

[a] Randomization will be stratified by age.

Figure 2 V116-001 Study Design: Phase 2

1.3 Schedule of Activities

1.3.1 Schedule of Activities for Phase 1

Study Period:	**Intervention**					**Notes**
Visit Number:	**1**	**Telephone Contact**	**2**	**Telephone Contact**	**Telephone Contact**	
Scheduled Time:	**Day 1**	**Day 15**	**Day 30**	**Day 90**	**Day 180**	
Visit Window:	-	Day 15 to Day 19	Day 30 to Day 44	Day 76 to Day 104	Day 166 to Day 194	
Administrative Procedures						
Screening Procedures						
Informed Consent	X					Consent must be obtained before any study procedures.
Informed Consent for Optional Assay Development Blood Samples	X					Consent for optional assay development blood samples must be obtained before any of these samples are collected from the participant.
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.
Postrandomization Procedures						
Assignment of Randomization Number	X					
Participant Identification Card	X					
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X			

Study Period:	**Intervention**					**Notes**
Visit Number:	**1**	**Telephone Contact**	**2**	**Telephone Contact**	**Telephone Contact**	
Scheduled Time:	**Day 1**	**Day 15**	**Day 30**	**Day 90**	**Day 180**	
Visit Window:	-	Day 15 to Day 19	Day 30 to Day 44	Day 76 to Day 104	Day 166 to Day 194	
pPCV-1/pPCV-2/PNEUMOVAX™23 Administration (blinded)	X					Participants will receive a single dose of either pPCV-1, pPCV-2, 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 Paper Vaccination Report Card (VRC)	X					See Section 8.1.9 for details.
Review Paper VRC Data With Participant		X	X			See Section 8.1.9 for details.
Collect Paper VRC From Participant			X			
Complete Telephone Contact Questionnaire				X	X	See Section 8.1.11 for details.
Safety Procedures						
Complete Physical Examination	X					To be performed by the investigator or medically qualified designee to determine study eligibility at screening and before vaccine is administered.
Pregnancy Test (if applicable)	X		X			A pregnancy test consistent with local requirements (sensitive to at least 25 IU beta human chorionic gonadotropin [β-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).
Hematology	X		X			Day 1 blood samples should be collected before vaccination.

Study Period:	**Intervention**					**Notes**
Visit Number:	**1**	**Telephone Contact**	**2**	**Telephone Contact**	**Telephone Contact**	
Scheduled Time:	**Day 1**	**Day 15**	**Day 30**	**Day 90**	**Day 180**	
Visit Window:	-	Day 15 to Day 19	Day 30 to Day 44	Day 76 to Day 104	Day 166 to Day 194	
Chemistry	X		X			Day 1 blood samples should be collected before vaccination.
AE Monitoring	X	X	X	X	X	Nonserious AEs are to be reported from Day 1 through Day 30 following vaccination. Serious adverse events (SAEs) and deaths are to be reported from Day 1 through the duration of an individual's study participation (see Section 8.4.1 for details).
Immunogenicity Procedures						
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).
Future Biomedical Research						
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). The sample should be obtained at Day 1 before vaccine is administered, or at a later date as soon as the informed consent is obtained.
Assay Development Samples						
Serum for Optional Assay Development	X		X			Samples will be collected from randomized participants who provide consent for assay development sample collection (see Section 8.10). Day 1 blood samples must be collected before vaccination.

1.3.2 Schedule of Activities for Phase 2

Study Period:	**Intervention**					**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	
Visit Type	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Telephone Contact**	
Scheduled Time:	**Day 1**	**Day 15**	**Day 30**	**Day 90**	**Day 180**	
Visit Window:	-	Day 15 to Day 19	Day 30 to Day 44	Day 76 to Day 104	Day 166 to Day 194	
Administrative Procedures						
Screening Procedures						
Informed Consent	X					Consent must be obtained before any study procedures.
Informed Consent for Optional Assay Development Blood Samples	X					Consent for optional assay development blood samples must be obtained before any of these samples are collected from the participant.
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.
Postrandomization Procedures						
Assignment of Randomization Number	X					
Participant Identification Card	X					

Study Period:	**Intervention**					**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	
Visit Type	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Telephone Contact**	
Scheduled Time:	**Day 1**	**Day 15**	**Day 30**	**Day 90**	**Day 180**	
Visit Window:	-	Day 15 to Day 19	Day 30 to Day 44	Day 76 to Day 104	Day 166 to Day 194	
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 electronic Vaccination Report Card (eVRC)	X					See Section 8.1.9 for details.
Review eVRC Data With Participant		X	X			See Section 8.1.9 for details.
Collect eVRC From Participant			X			
Complete Telephone Contact Questionnaire				X	X	See Section 8.1.11 for details.
Safety Procedures						
Complete Physical Examination	X					To be performed by the investigator or medically qualified designee at screening and before vaccine is administered.
Pregnancy Test (if applicable)	X		X			A pregnancy test consistent with local requirements (sensitive to at least 25 IU beta human chorionic gonadotropin [β-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).

Study Period:	**Intervention**					**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	
Visit Type	**Site Visit**	**Telephone Contact**	**Site Visit**	**Telephone Contact**	**Telephone Contact**	
Scheduled Time:	**Day 1**	**Day 15**	**Day 30**	**Day 90**	**Day 180**	
Visit Window:	-	Day 15 to Day 19	Day 30 to Day 44	Day 76 to Day 104	Day 166 to Day 194	
AE Monitoring	X	X	X	X	X	Nonserious AEs are to be reported from Day 1 through Day 30 following vaccination. Serious adverse events (SAEs) and deaths are to be reported from Day 1 through the duration of an individual's study participation (see Section 8.4.1 for details).
Immunogenicity Procedures						
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).
Future Biomedical Research						
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). The sample should be obtained at Day 1 before vaccine is administered, or at a later date as soon as the informed consent is obtained.
Assay Development Samples						
Serum for Optional Assay Development	X		X			Samples will be collected from randomized participants who provide consent for assay development sample collection (see Section 8.10). Day 1 blood samples must be collected before vaccination.

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, specifically residual disease in adults, 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 IPD in adults and includes serotypes not currently contained in any licensed pneumococcal vaccine.

This Phase 1/Phase 2 clinical study is designed to evaluate the safety, tolerability, and immunogenicity of pPCV compared with PNEUMOVAX™23 in adults.

The Phase 1 portion of this study will be conducted in a population of adults 18 to 49 years of age. This population is in general good health and, based on age, is not at increased risk for pneumococcal disease.

The Phase 2 portion of this study will be conducted in a population of adults ≥50 years of age. This population 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].

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

Pneumococcal disease (ie, disease caused by *Streptococcus pneumoniae)* is the single largest vaccine-preventable cause of death in children and older adults (≥65 years of age) worldwide. Direct vaccination of children with PCVs has decreased the incidence of disease caused by vaccine serotypes and has led to herd protection in unvaccinated individuals from other age groups, referred to as an indirect effect. This indirect effect of childhood vaccination with PCVs has resulted in a decrease in hospital admissions for pneumococcal disease in adults ≥65 years of age, with an estimated 29% and 34% reduction in IPD and non-invasive pneumococcal pneumonia admissions, respectively [Simonsen, L., et al 2014]. Additionally, in some countries, including the US, this indirect effect led to the recommendation to vaccinate adults with PCVs. However, current surveillance does not definitively support that a reduction of disease has been observed due to direct vaccination of adults with currently licensed PCVs. A significant burden of pneumococcal disease remains with an estimated 24 cases of IPD per 100,000 in adults >65 years of age in the US, and surveillance data estimates serotypes included in currently licensed PCVs account for only

approximately 20% of these cases [Centre for Disease Control and Prevention 2016] [Centers for Disease Control and Prevention 2019].

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 [Miller, Elizabeth, et al 2011] [Moore, M. R., et al 2015] [Pilishvili, T. 2015] [van der Linden, M., et al 2015] [Golden, A. R., et al 2016]. Increases in IPD cases due to certain serotypes (3, 7F, and 19A after implementation of Prevnar™; 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, Tamara, et al 2010] [Waight, P. A., et al 2015] [Moore, M. R., et al 2015] [Demczuk, W. H. B., et al 2013]. Similarly, in the EU, due to the limited serotype coverage of the currently licensed vaccines, serotype replacement is being observed and may decrease the potential additional benefit of vaccination with currently available PCVs in the elderly [European Center for Disease Prevention and Control 2018].

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 based on 2017 surveillance data. [redacted]

With the above considerations in mind, 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.

This is the first clinical study conducted with pPCV.

2.2.3 Information on Other Study-related Therapy

2.2.3.1 PNEUMOVAX™23

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.

In the US, PNEUMOVAX™23 is recommended by the ACIP for routine use in immunocompetent adults ≥65 years of age [Kobayashi, M., et al 2015]. PNEUMOVAX™23 is also recommended in the US for use in adults aged 19 to 64 years of age with underlying medical conditions that increase the risk for serious pneumococcal infection [Centers for Disease Control and Prevention 2010] and in immunocompromised adults ≥19 years of age as part of a sequential regimen with Prevnar 13™ [Kobayashi, M., et al 2015]. Children 2 to 18 years of age with underlying medical conditions are recommended to receive PNEUMOVAX™23 after completing all recommended Prevnar 13™ doses [Centers for Disease Control and Prevention (CDC) 2013].

Many countries follow similar age-based and/or risk-based recommendations for the use of PNEUMOVAX™23 [Castiglia P. 2014].

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 33% of participants in Phase 1 and 50% of participants in Phase 2 will receive PNEUMOVAX™23, a pneumococcal vaccine for the prevention of pneumococcal disease that is licensed in the US, EU, and other regions. 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 Phase 1 of this study. For Phase 2, hypotheses are aligned with objectives in the Objectives and Endpoints table.

In Phase 1, objectives and endpoints will be evaluated in pneumococcal vaccine-naïve adults 18 to 49 years of age who are administered a single dose of pPCV-1, pPCV-2, or PNEUMOVAX™23.

In Phase 2, objectives and endpoints will be evaluated in pneumococcal vaccine-naïve adults ≥50 years of age who are administered a single dose of pPCV or PNEUMOVAX™23.

Objectives	Endpoints
Primary	
Phase 1 • **Objective**: To evaluate the safety and tolerability of pPCV-1 and pPCV-2 with respect to the proportion of participants with AEs.	• Solicited injection-site AEs • Solicited systemic AEs • Vaccine-related SAEs
Phase 2 • **Objective**: To evaluate the safety and tolerability of pPCV with respect to the proportion of participants with AEs.	• Solicited injection-site AEs • Solicited systemic AEs • Vaccine-related SAEs
Phase 2 • **Objective**: To evaluate the serotype-specific OPA GMTs at 30 days postvaccination. **Hypothesis (H1)**: pPCV is noninferior to PNEUMOVAX™23 as measured by the serotype-specific OPA GMTs for the common serotypes at 30 days postvaccination. **Hypothesis (H2)**: The serotype-specific OPA GMTs for the unique serotypes in pPCV at 30 days postvaccination are statistically significantly greater following vaccination with pPCV than those following vaccination with PNEUMOVAX™23.	• Serotype-specific OPA responses
Secondary	
Phase 1 • **Objective**: To describe the serotype-specific OPA GMTs and IgG GMCs as measured at 30 days postvaccination.	• Serotype-specific OPA and IgG responses

Objectives	Endpoints
Phase 1 • **Objective:** To describe the serotype-specific GMFR from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses	• Serotype-specific OPA and IgG responses
Phase 2 • **Objective**: To evaluate serotype-specific IgG GMCs at 30 days postvaccination. **Hypothesis (H3)**: pPCV is noninferior to PNEUMOVAX™23 as measured by the serotype-specific IgG GMCs for the common serotypes at 30 days postvaccination. **Hypothesis (H4)**: The serotype-specific IgG GMCs for the unique serotypes in pPCV at 30 days postvaccination are statistically significantly greater following vaccination with pPCV than those following vaccination with PNEUMOVAX™23.	• Serotype-specific IgG responses
Phase 2 • **Objective:** To evaluate serotype-specific GMFR from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses	• Serotype-specific OPA and IgG responses.
Phase 2 • **Objective:** To evaluate the proportion of participants who achieve a ≥4-fold increase in serotype-specific OPA responses from prevaccination (Day 1) to 30 days postvaccination (Day 30)	• Serotype-specific OPA responses

4 STUDY DESIGN

4.1 Overall Design

This is a 2-part, randomized, active-controlled, parallel-group, multi-site, double-blind (with in-house blinding) study of pPCV in adults who have not previously received any pneumococcal vaccine.

In the Phase 1 portion of the study, approximately 90 participants 18 to 49 years of age (inclusive) who have not previously received any pneumococcal vaccine (vaccine naïve) will be randomly assigned in a 1:1:1 ratio to receive a single dose of either pPCV-1 (30 participants), pPCV-2 (30 participants), or PNEUMOVAX™23 (30 participants) at Visit 1 (Day 1). pPCV-1 and pPCV-2 are the 2 different dosage levels of pPCV that will be evaluated. Safety will be assessed via telephone contact 15 days postvaccination, and safety and immunogenicity will be assessed at 30 days postvaccination. Additional safety assessments via telephone contact will occur at 90 and 180 days postvaccination. An siDMC will review the safety and tolerability data throughout Phase 1 and Phase 2. The siDMC is a standing, internal Sponsor committee established to monitor early phase clinical studies. Additional details are provided in Appendix 1 and in the siDMC charter.

An interim analysis will be performed once the primary 30-day postvaccination safety and immunogenicity data are available for all Phase 1 participants. At this point, the database will be locked and an analysis will be performed to summarize the safety and immunogenicity data. The siDMC will review all safety and immunogenicity data to evaluate the benefit risk profile and to make a recommendation regarding proceeding to Phase 2. The Sponsor study team will also review the unblinded aggregate data and, in conjunction with the recommendation of the siDMC, a decision will be made whether to proceed to Phase 2, and which dose should be selected for further evaluation. If the decision is made to proceed to Phase 2, enrollment will commence immediately.

In the Phase 2 portion of the study, approximately 500 participants ≥50 years of age 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 either pPCV (250 participants) or PNEUMOVAX™23 (250 participants) on Day 1. Randomization will be stratified by participant age at enrollment (50 to 64 years, 65 to 74 years, and ≥75 years) across the 2 vaccination groups. Safety will be assessed via telephone contact 15 days postvaccination, and safety and immunogenicity will be assessed at 30 days postvaccination. Additional safety assessments via telephone contact will occur at 90 and 180 days postvaccination.

An interim analysis will be performed prior to the completion of Phase 2 once the primary 30-day postvaccination safety and immunogenicity data are available for all Phase 2 participants and the 6-month safety data are available for at least 50% of Phase 2 participants. This interim analysis will be performed to support clinical development decisions.

In both phases, a 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 immediately before vaccine administration (Day 1) and at 30 days postvaccination (Day 30). After completion of immunogenicity testing to evaluate the study objectives and hypotheses, serum samples will be stored to conduct any additional study-related testing as 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 be conducted in 2 parts.

The first-in-human Phase 1 portion of the study will assess the safety and tolerability of 2 different dosage levels of pPCV (pPCV-1 and pPCV-2) in adults 18 to 49 years of age. Two different doses are being evaluated to assess antibody concentrations related to polysaccharide antigen dose in a polyvalent pneumococcal vaccine and to ensure confidence in the dose selected for further evaluation in Phase 2. The population in Phase 1 includes adults who are in general good health and, based on age, are not at increased risk for pneumococcal disease.

The dose selection for Phase 2 will be based on Phase 1 safety and immunogenicity data.

The Phase 2 portion of the study will assess safety, tolerability, and immunogenicity of pPCV in adults ≥50 years of age. As the incidence of IPD is directly related to age, with over half of all cases occurring in adults 50 years of age or older [Drijkoningen, J. J 2014], this population is at increased risk for pneumococcal disease and its associated morbidity and mortality.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

The immunogenicity endpoints and associated comparative statistical criteria are consistent with previous early phase studies evaluating PCVs.

Sera from participants will be used to measure vaccine-induced, anti-PnP serotype-specific OPA GMTs and IgG GMCs for all serotypes included in pPCV using the MOPA and 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.

In the Phase 1 portion of this study, anti-PnP serotype-specific OPA GMTs and IgG GMCs will be evaluated as secondary endpoints.

In the Phase 2 portion of this study, anti-PnP serotype-specific OPA GMTs will be evaluated as a primary endpoint and serotype-specific IgG GMCs will be evaluated as a secondary endpoint.

Details on the immunogenicity endpoints evaluated in this study can be found in Section 9.4.1 and Section 9.4.2.

4.2.1.2 Safety Endpoints

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

Vaccination report cards will be used to collect participant-reported events during the postvaccination period, as detailed in Section 8.1.9. Participants in Phase 1 will use paper VRCs and participants in Phase 2 will use eVRCs. The VRCs were structured as recommended in the final US Food and Drug Administration Patient-reported Outcome Guidance [U.S. Food and Drug Administration 2009].

Details on the safety endpoints evaluated in this study can be found in Section 9.4.3.

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

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

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. Globally, PNEUMOVAX™23 is the primary pneumococcal vaccine recommended for adults 65 years of age and older, and thus its use as a comparator in this study will provide useful information for many key regions. In the US, PNEUMOVAX™23 is indicated for use in persons 50 years of age or older, which is consistent with the population to be enrolled in Phase 2. Additionally, as of June 2019, ACIP changed their guideline to recommend that all adults 65 years of age and older should receive PNEUMOVAX™23, and that vaccination with Prevnar 13™ as part of a sequential regimen with PNEUMOVAX™23 is not routinely recommended for adults who do not have an immunocompromising condition, but rather should be based on shared clinical decision between the health care provider and the patient.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

A dose of 2 µg/each PnP is proposed for clinical development of pPCV, which is consistent with the dose used in other PCVs. The proposed human dose of pPCV is based on dose-ranging evaluation of pPCV in animal studies, as well as evaluation of other pneumococcal vaccines in humans. To gain confidence in the safety and immunogenicity of pPCV and to confirm the proposed human dose for pPCV clinical development, 2 different doses will be evaluated in Phase 1: a 1.0x dose with 2 µg/each PnP, and a 2.0x dose with 4 µg/each PnP. For additional information related to dose, refer to the IB.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, 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 male and female participants between the ages of 18 and 49 years (inclusive) will be enrolled in Phase 1 of this study.

Healthy male and female participants ≥50 years of age will be enrolled in Phase 2 of 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. For Phase 1:

   - Is male or female, from 18 years to 49 years of age inclusive, at the time of signing the informed consent.

   For Phase 2:

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

Male Participants

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

3. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 3 months (90 days [a spermatogenesis cycle]) after the last dose of study intervention:

- Refrain from donating sperm

  PLUS either:

- 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

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

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

   - For Phase 1:

     - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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 6 months after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should

evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

For Phase 2:

- 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 6 months after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

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

- Additional requirements for pregnancy testing during and after study intervention are 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 provides written informed consent for the study. The participant may also provide consent for future biomedical research and/or assay development sample collection. However, the participant may participate in the main study without participating in future biomedical research or assay development sample collection.

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 (including but not limited to the autoimmune conditions outlined in the Investigator Trial File Binder for this study).

4. Has a coagulation disorder contraindicating intramuscular vaccination.

5. *Had a recent febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C] or axillary or temporal temperature ≥99.4°F [≥37.4°C]) 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 [eg, 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 ≥20 mg/day) for ≥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 [eg, 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 Day 30 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.

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 interventions to be used in this study are outlined in Table 1 (Phase 1) and Table 2 (Phase 2).

Table 1 Study Interventions for Phase 1

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-1	Experimental	pPCV	Biological /Vaccine	Sterile Solution	Refer to IB	0.5 mL	IM	Single dose at Visit 1 (Day 1)	Experimental	IMP	Central
pPCV-2	Experimental	pPCV	Biological /Vaccine	Sterile Solution	Refer to IB	1.0 mL	IM	Single dose at Visit 1 (Day 1)	Experimental	IMP	Central
PNUEMOVAX™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

Admin = administration; IB = Investigator's Brochure; IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; pPCV = polyvalent pneumococcal conjugate vaccine.

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.

Table 2 Study Interventions for Phase 2

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	Based on Phase 1 Results	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

Admin = administration; IB = Investigator's Brochure; IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; pPCV = polyvalent pneumococcal conjugate vaccine.

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.

All supplies indicated in Table 1 and Table 2 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.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

The rationale for selection of doses to be used in this study is provided in Section 4.3.

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

As detailed in Section 6.3.3, study 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

In Phase 1, intervention allocation/randomization will occur centrally using an IRT system. There are 3 study intervention arms. Participants will be assigned randomly in a 1:1:1 ratio to receive either pPCV-1, pPCV-2, or PNEUMOVAX™23.

In Phase 2, 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 in Phase 1 will not be stratified.

Intervention allocation/randomization in Phase 2 will be stratified according to the following factors:

- Participant age at time of randomization (50 to 64, 65 to 74, and ≥75 years of age).

6.3.3 Blinding

In both Phase 1 and Phase 2, 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 study intervention administration or 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 Trial File Binder.

To avoid bias, the unblinded study personnel will have no further contact with study participants for any study-related procedures/assessments after administration of study vaccines, which includes all safety follow-up procedures. 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) and Merck Research Laboratories employees directly involved with the conduct of this study will remain blinded to the participant-level intervention assignment.

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

6.4 Study Intervention Compliance

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 ≥20 mg/day for ≥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 (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.

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

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

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

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 8.1.12. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

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

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

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

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

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be 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.

In Phase 1, the maximum amount of blood collected from each participant at each study visit will not exceed 105 mL, and the total amount of blood collected over the duration of the study will not exceed 195 mL (Table 3).

In Phase 2, the maximum amount of blood collected from each participant at each study visit will not exceed 80 mL, and the total amount of blood collected over the duration of the study will not exceed 150 mL (Table 4).

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

Table 3 Approximate Blood Volumes Drawn by Study Visit and by Sample Type (Phase 1)

	Visit 1 Day 1	**Visit 2 Day 30**	**Total**
Parameter	**Approximate Blood Volume (mL)**		
Immunogenicity assessment (including retention samples)	30 mL	30 mL	60 mL
Blood chemistry and hematology	13 mL	13 mL	26 mL
DNA for future biomedical research[a]	8.5 mL	N/A	8.5 mL
Assay development[a]	50 mL	50 mL	100 mL
Expected total (mL)	101.5 mL	93 mL	194.5 mL

DNA = deoxyribonucleic acid.

[a] Samples for future biomedical research and assay development will only be obtained from participants who provide separate consent for collection of these optional samples.

Table 4 Approximate Blood Volumes Drawn by Study Visit and by Sample Type (Phase 2)

	Visit 1 Day 1	**Visit 3 Day 30**	**Total**
Parameter	**Approximate Blood Volume (mL)**		
Immunogenicity assessment (including retention samples)	30 mL	30 mL	60 mL
DNA for Future Biomedical Research[a]	8.5 mL	N/A	8.5 mL
Assay development[a]	40 mL	40 mL	80 mL
Expected total (mL)	78.5 mL	70 mL	148.5 mL

DNA = deoxyribonucleic acid.

[a] Samples for future biomedical research and assay development will only be obtained from participants who provide separate consent for collection of these optional samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant prior to participating in a 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written 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 a study and the study population will be added to the consent form template at the protocol level.

The 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 written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

8.1.1.3 Consent and Collection of Blood Samples for Optional Assay Development

The investigator or medically qualified designee will explain the consent for the optional assay development blood samples to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the optional assay development blood samples collection. A copy of the informed consent will be given to the participant.

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 written 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 (Phase 1) or eVRC (Phase 2) (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 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 prepared and administered by appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance. Procedures for handling, preparing, and administering the unblinded vaccines are provided in the Investigator Trial File Binder. 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 (oral or tympanic temperature ≥100.4°F [≥38.0°C] or axillary or temporal temperature ≥99.4°F [≥37.4°C]) 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 Phase 1 will use a paper VRC and participants in Phase 2 will use an eVRC. The information collected on the paper VRC will be consistent with the information collected on the eVRC.

The paper VRCs/eVRCs are structured as recommended in the final Food and Drug Administration Patient-Reported Outcome Guidance [U.S. Food and Drug Administration 2009]. The investigator or delegate will train the participant in the use of the paper VRC (Phase 1) or eVRC (Phase 2) at Visit 1 (Day 1).

The participant will use the paper VRC/eVRC 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/eVRC with the participant at the telephone contact on Day 15 (Section 8.1.10). A full review of the completed paper VRC/eVRC will occur at the Day 30 postvaccination visit.

Any differences between paper VRC/eVRC 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 (Phase 1) or eVRC (Phase 2) with the participant at the telephone contact on Day 15. Any differences between the paper VRC/eVRC data and the clinical database must be documented in the participant's source record. A full review of the completed paper VRC/eVRC will occur at the Day 30 postvaccination visit.

8.1.11 Telephone Contact Questionnaire on Day 90 and Day 180

Site personnel will contact the participant approximately 3 months and 6 months after the last dose of study vaccine to collect additional information based on a Telephone Contact Questionnaire provided by the Sponsor. Data to be reported from this discussion will include SAEs and/or any updates to previously reported safety information.

8.1.12 Discontinuation and Withdrawal

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.12.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for 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 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.

8.1.13 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. 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 and toxicity grade 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 (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

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

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

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

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.14 Calibration of Equipment

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

8.2 Immunogenicity Assessments

Sera from participants will be used to measure 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 PnECL v2.0 assay to assess the concentration of binding antibodies to capsular polysaccharide of S. pneumoniae.

8.2.1 Multiplex 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 ≥50% bacterial killing, as determined by comparison to assay background controls. MSD has developed and optimized the MOPA in a high throughput microcolony platform. The MOPA assay for pPCV will be qualified. The qualification studies will evaluate various performance parameters of the assay including precision, ruggedness, relative accuracy/dilutional linearity, and the limit of detection of the assay.

8.2.2 Pneumococcal Electrochemiluminescence (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 PnECL v2.0 assay is based on the Meso-Scale Discovery technology, which employs disposable multi-spot microtiter plates. The benefits of the ECL multiplex technology over the prior enzyme-linked immunosorbent assay methodology include speed, equivalent or better sensitivity, increased dynamic range, the ability to multiplex, and reduction in required serum sample and reagent volumes. The measurement of immune responses to the serotypes contained in pPCV is performed using an assay format consisting of 3 groups of 8, 9, and 7 serotypes each. The PnECL v2.0 assay for pPCV will be qualified. The qualification studies will evaluate various performance parameters of the assay including precision, ruggedness, 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 or medically qualified designee (consistent with local requirements) before vaccination at Visit 1 (Day 1).

A complete physical examination includes, but is not limited to, the assessment of general appearance, vital signs (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 consistent with local requirements (sensitive to at least 25 IU β-hCG) must be performed before vaccination at Visit 1 (Day 1) 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 oral body temperatures using their paper VRC (Phase 1) or eVRC (Phase 2) (Section 8.1.9) from Day 1 to Day 5 postvaccination.

For this study, any oral or tympanic temperature ≥100.4°F (≥38.0°C) or axillary or temporal temperature ≥99.4°F (≥37.4°C) 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 consent form is signed 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 treatment, or a procedure.

- All nonserious AEs and other reportable safety events (excluding pregnancy and lactation exposure) must be reported by the investigator from the day of randomization through 30 days postvaccination.

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

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

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.

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 5.

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

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (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
Serious Adverse Event (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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest in Phase 1 (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest in Phase 2 (do not require regulatory reporting)	There are no ECIs in Phase 2 of this study.			Not applicable
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

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, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

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

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for Phase 1 of this study include:

a. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

There are no ECIs for Phase 2 of this study.

8.4.8 Adverse Events Reported on the VRC

Participants will use a paper VRC (Phase 1) or eVRC (Phase 2) (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 6.

Table 6 Solicited Adverse Events for V116-001

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 injection-site AEs for toxicity, and all solicited systemic AEs for both toxicity and causality (Appendix 3).

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

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

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

Phase 1:
Solicited injection-site AEs and solicited systemic AEs reported by the participant using the paper VRC will be entered by study site personnel on the appropriate eCRF.

Phase 2:
Solicited injection-site AEs and solicited systemic AEs reported by the participant using the eVRC will be transferred directly to the Sponsor database.

8.4.8.2 Unsolicited Adverse Events

Unsolicited AEs for this study are events that are 1) not predefined in Table 6, or 2) predefined in Table 6 but reported at any time outside of the solicited time period. In Phase 1 and Phase 2, unsolicited AEs reported by the participant will be entered by study site personnel on the appropriate eCRF.

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/toxicity, 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 Trial 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 signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- DNA for future research
- Leftover study serum after completion of immunogenicity testing stored for future research

8.10 Optional Assay Development Blood Sample Collection

If the participant signs the consent for the optional assay development blood samples, these additional blood samples will be obtained at Day 1 and Day 30. These blood samples will be used to support future development work on improving bioanalytical measurements, which requires high-volume single-donor samples to monitor performance of the assay over time.

Sample collection, storage, and shipment instructions for the optional assay development blood samples will be provided in the operations/laboratory manual.

8.11 Medical Resource Utilization and Health Economics

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

8.12 Visit Requirements

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

8.12.1 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.

8.12.2 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. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 1/Phase 2, Randomized, Double-blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Adults.
Treatment Assignment	In Phase 1, participants will be randomly assigned in a 1:1:1 ratio to receive either pPCV-1, pPCV-2, or PNEUMOVAX™23. In Phase 2, participants will be randomly assigned in a 1:1 ratio to receive either pPCV or PNEUMOVAX™23. Randomization in Phase 2 will be stratified by age at study entry (50 to 64 years, 65 to 74 years, and ≥75 years).
Analysis Populations	**Safety**: APaT population **Primary Immunogenicity:** PP population **Supportive Immunogenicity:** FAS population

Primary Endpoints in Phase 1	The primary **safety** endpoints in Phase 1 include: • Proportion of participants with solicited injection-site AEs • Proportion of participants with solicited systemic AEs • Proportion of participants with vaccine-related SAEs
Key Secondary Endpoints in Phase 1	The key secondary **immunogenicity** endpoints in Phase 1 include: • Ratio of serotype-specific OPA GMTs for the common serotypes in pPCV and PNEUMOVAX™23 • Ratio of serotype-specific OPA GMTs of pPCV and PNEUMOVAX™23 for the serotypes unique to pPCV • Ratio of serotype-specific IgG GMCs for the common serotypes in pPCV and PNEUMOVAX™23
Primary Endpoints in Phase 2	The primary **safety** endpoints in Phase 2 include: • Proportion of participants with solicited injection-site AEs • Proportion of participants with solicited systemic AEs • Proportion of participants with vaccine-related SAEs. The primary **immunogenicity** endpoints in Phase 2 include: • Ratio of serotype-specific OPA GMTs for the common serotypes in pPCV and PNEUMOVAX™23 • Ratio of serotype-specific OPA GMTs of pPCV and PNEUMOVAX™23 for the serotypes unique to pPCV
Key Secondary Endpoints in Phase 2	The key secondary **immunogenicity** endpoints in Phase 2 include: • Ratio of serotype-specific IgG GMCs for the common serotypes in pPCV and PNEUMOVAX™23 • Ratio of serotype-specific IgG GMCs of pPCV and PNEUMOVAX™23 for the serotypes unique to pPCV
Statistical Methods for Key Immunogenicity Analyses in Phase 1	Immunogenicity analyses will be conducted separately for each serotype. Immunogenicity endpoints will be analyzed at 30 days postvaccination compared with prevaccination (Day 1) to describe the IgG antibody concentrations in response to the vaccination. The ratio of OPA GMTs and IgG GMCs (pPCV-1/PNEUMOVAX™23 and pPCV-2/PNEUMOVAX™23) will be presented along with 95% CIs by vaccination group. The OPA GMT ratio estimation and 95% CI will be calculated using a cLDA method.
Statistical Methods for Key Immunogenicity Analyses in Phase 2	Immunogenicity analyses will be conducted separately for each serotype. To address the primary noninferiority hypothesis (H1), a noninferiority test comparing OPA GMTs for the common serotypes in pPCV and PNEUMOVAX™23 (control group) will be conducted. A noninferiority margin of 0.33 corresponding to a 3.0-fold lower OPA GMT in the pPCV group compared with the control group will be used. Rejecting the null hypothesis at the 1-sided α=0.025 level corresponds to the lower bound of

	the 2-sided 95% CI on the GMT ratio (pPCV/control) being >0.33 and would lead to the conclusion that the OPA GMT for pPCV is noninferior to that of the control vaccine, for the given common serotype. To address the second primary hypothesis (H2), a test comparing OPA GMTs for the serotypes unique to pPCV will be conducted. Rejecting the null hypothesis at the 1-sided α=0.025 level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (pPCV/control) being >1.0 and would lead to the conclusion that the OPA GMT for pPCV is statistically significantly greater than that of the control vaccine, for the given unique serotype. The statistical margins specified for H1 and H2 are consistent with previous early phase comparative studies [Jackson, L. A., et al 2013]. The OPA GMT ratio estimation, 95% CI, and the hypothesis test (ie, 1-sided p-value) will be calculated using a cLDA method.
Statistical Methods for Key Safety Analyses in Phase 1 and Phase 2	The analysis of safety will follow a tiered approach. 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 M&N method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses (IA)	There are 2 interim analyses planned for this study: **Phase 1 Interim Analysis:** An interim analysis will be performed once the primary 30-day postvaccination safety and immunogenicity data are available for all Phase 1 participants. At this point, the database will be locked and an analysis will be performed to summarize the safety and immunogenicity data. The siDMC will review unblinded Phase 1 safety and immunogenicity data reports and evaluate the benefit and risk profile to make a recommendation regarding proceeding to Phase 2. The Sponsor study team will review the Phase 1 safety and immunogenicity aggregate data reports to inform the clinical development decision to proceed to Phase 2. The study team will not be unblinded to participant-level data. The unblinded Phase 1 data will be provided by an unblinded statistician who is not part of the blinded study team, and the clinical database will remain blinded to both the Sponsor study team and participating sites throughout the duration of the Phase 1/Phase 2 study. **Phase 2 Interim Analysis:** An interim analysis is planned to support clinical development decisions prior to the completion of the Phase 2 portion of this study. This analysis will be conducted once the primary 30-day postvaccination safety and immunogenicity data are available for all Phase 2 participants and the 6-month safety data are available for at least 50% of Phase 2 participants. This analysis will represent the final analysis of the primary immunogenicity endpoints and will be considered a preliminary analysis of the safety data. These analyses will be conducted by an unblinded statistician who is not part of the blinded study team. The siDMC will review unblinded Phase 2 safety and immunogenicity data reports and evaluate the benefit and risk profile. The Sponsor study team will review the Phase 2 safety and immunogenicity aggregate data reports to inform further clinical development. The Sponsor study team will not be

	unblinded to participant-level data, and the clinical database will remain blinded to both the Sponsor study team and participating sites throughout the duration of the Phase 1/Phase 2 study.
Multiplicity	This study will be considered to have met its primary immunogenicity objectives if success is demonstrated for all common and unique serotypes included in each primary immunogenicity hypothesis. The intersection-union test controls the overall type I error at the 1-sided 0.025 level within each group; therefore, no multiplicity adjustment will be required. The overall alpha level for the secondary immunogenicity objectives, relating to both the set of common and unique serotypes, as measured by IgG, is also controlled at the 1-sided 0.025 level. No multiplicity adjustments will be made for the safety comparisons.
Sample Size and Power	In Phase 1, approximately 90 participants will be enrolled, with approximately 30 participants in each of the 3 vaccination groups. In Phase 2, Approximately 500 participants will be enrolled, with approximately 250 participants in each of the 2 vaccination groups. Assuming 90% evaluability (approximately 225 participants per group), there is 98.7% power to declare primary noninferiority to PNEUMOVAX™23 for the common serotypes and 99.2% power to declare pPCV is statistically significantly greater than PNEUMOVAX™23 for the unique serotypes based on OPA GMT ratios. The overall estimate of power for the primary hypothesis, as the product of the powers for the set of noninferiority hypotheses and the set of superiority (ie, statistically significantly greater) hypotheses, is 98%. This sample size also provides adequate power for the secondary hypotheses. Specifically, there is 87% power for the secondary noninferiority hypothesis and 92% power for the secondary superiority (ie, statistically significantly greater) hypothesis. The overall power for the secondary hypotheses is 80%.

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. At the time of the interim analyses, the unblinded Phase 1 and Phase 2 data will be provided by an unblinded statistician who is not part of the blinded study team, and the clinical database will remain blinded to both the Sponsor study team and participating sites throughout the duration of the Phase 1/Phase 2 study.

Section 6.3.3 specifies the roles and responsibilities of the site and Sponsor personnel who will be unblinded during the study.

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

Blinding details related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Immunogenicity and safety analysis endpoints are listed below.

9.4.1 Immunogenicity Endpoints in Phase 1

There are no primary immunogenicity analysis endpoints in Phase 1.

Secondary immunogenicity analysis endpoints in Phase 1 include:

- Ratio of serotype-specific IgG GMCs for the common serotypes in pPCV and PNEUMOVAX™23 at 30 days postvaccination.
- Ratio of serotype-specific OPA GMTs for the common serotypes in pPCV and PNEUMOVAX™23 at 30 days postvaccination.
- Ratio of serotype-specific OPA GMTs 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.

The specific sets of serotypes described as common or unique will be clearly defined in the sSAP to be written prior to database lock.

9.4.2 Immunogenicity Endpoints in Phase 2

Primary immunogenicity analysis endpoints in Phase 2 include:

- Ratio of serotype-specific OPA GMTs for the common serotypes in pPCV and PNEUMOVAX™23 at 30 days postvaccination.
- Ratio of serotype-specific OPA GMTs of pPCV and PNEUMOVAX™23 for the serotypes unique to pPCV at 30 days postvaccination.

Secondary immunogenicity analysis endpoints in Phase 2 include:

- Ratio of serotype-specific IgG GMCs for the common serotypes in pPCV and PNEUMOVAX™23 at 30 days postvaccination.
- Ratio 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.

- Difference in the proportion of participants who achieve a ≥4-fold increase in serotype-specific OPA responses from prevaccination (Day 1) to 30 days postvaccination.

The specific sets of serotypes described as common or unique will be clearly defined in the sSAP to be written prior to database lock.

9.4.3 Safety Endpoints in Phase 1 and Phase 2

Safety analyses will be conducted separately for Phase 1 and Phase 2. Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs and postvaccination body temperature measurements.

The safety analysis endpoints that address the primary objective include:

- Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) from Day 1 through Day 5 postvaccination

- Proportion of participants with solicited systemic AEs (muscle 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.

Additional Safety analysis endpoints include:

- 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 temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 5 postvaccination.

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of 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) (ie, participants who were cross-treated)

- Having no valid serology results (ie, participants who are missing serology results for both Day 1 and Day 30 [30 to 44 days following vaccination]).

Determinations on protocol deviations will be made by blinded study team members prior to the planned Phase 1 interim analysis (Section 9.7.1), prior to the planned Phase 2 interim analysis (Section 9.7.2), and prior to the final unblinding of the database. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the PP population.

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 Populations

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.

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

9.6 Statistical Methods

No statistical hypothesis testing is planned for Phase 1, but rather estimation will be performed for both the safety and immunogenicity data.

For immunogenicity analyses in Phase 2, unless otherwise specified, all statistical tests will be conducted at the α=0.05 level (2-sided). Results that will be considered statistically significant (versus nominally significant) after consideration of the strategy for controlling type-I errors are described in Section 9.8.

9.6.1 Statistical Methods for Immunogenicity Analyses in Phase 1

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 3 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, the interaction of time-by-vaccination group (with a restriction of the same baseline mean across groups). The treatment difference in terms of a geometric mean ratio at a given postvaccination time point will be estimated and tested 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. 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.

The analysis strategy for key immunogenicity variables in Phase 1 is listed in Table 7.

Table 7 Analysis Strategy for Key Immunogenicity Variables in Phase 1

Endpoint/Variable (Description, Time point)	Statistical Method	Analysis Population	Missing Data Approach
Secondary Endpoints			
Ratio of IgG GMCs at 30 days postvaccination for common serotypes	cLDA[a] (point estimate, 95% CI)	PP/FAS	Model-based
Ratio of OPA GMTs at 30 days postvaccination for common serotypes	cLDA[a] (point estimate, 95% CI)	PP/FAS	Model-based
Ratio of OPA GMTs at 30 days postvaccination for unique serotypes in pPCV	cLDA[a] (point estimate, 95% CI)	PP/FAS	Model-based
GMFRs from prevaccination to 30 days postvaccination for both OPA and IgG responses	Descriptive Statistics (point estimate, 95% CI)	PP/FAS	Missing data will not be imputed

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

[a] cLDA model with terms for time and the interaction of time-by-vaccination group.

9.6.2 Statistical Methods for Immunogenicity Analyses in Phase 2

This section describes the statistical methods that address the primary and secondary Phase 2 immunogenicity objectives. The margins of noninferiority and superiority (ie, statistically significantly greater) presented below are consistent with previous early phase comparative studies [Jackson, L. A., et al 2013].

The immunogenicity analyses will be conducted for each serotype separately.

Primary Endpoints/Hypotheses

For the common serotypes, the primary noninferiority hypotheses (H1) regarding OPA GMT levels between recipients of pPCV and PNEUMOVAX™23 is:

H_0: $GMT_1/GMT_2 \leq 0.33$ versus
H_1: $GMT_1/GMT_2 > 0.33$

where GMT_1 is the serotype-specific OPA GMT for the pPCV group and GMT_2 is the serotype-specific OPA GMT for the PNEUMOVAX™23 group. A ratio of 0.33 corresponds to a 3.0-fold lower OPA GMT in the pPCV group compared with the PNEUMOVAX™23 group. Rejecting the null hypothesis (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (pPCV/PNEUMOVAX™23) being >0.33 and would lead to the conclusion that the OPA response to pPCV for the common serotype is noninferior to that of PNEUMOVAX™23.

For the serotypes that are unique to pPCV, the primary superiority (ie, statistically significantly greater) hypotheses (H2) regarding OPA levels between recipients of pPCV group and PNEUMOVAX™23 group is:

H_0: $GMT_1/GMT_2 \leq 1.0$ versus
H_1: $GMT_1/GMT_2 > 1.0$

where GMT_1 is the OPA GMT for the pPCV group and GMT_2 is the OPA GMT for the PNEUMOVAX™23 group. Rejecting the null hypothesis (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (pPCV/PNEUMOVAX™23) being >1.0 and would lead to the conclusion that the OPA response to pPCV for the unique serotype is statistically significantly greater than that of PNEUMOVAX™23.

The GMT ratio estimation, 95% CI, and the hypothesis test (ie, 1-sided p-value) will be calculated using a cLDA method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000] utilizing data from both 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, the interaction of time-by-vaccination group (with a restriction of the same baseline mean across groups), age stratum (ie, 50 to 64 years, 65 to 74 years, and ≥75 years) at vaccination, and age stratum-by-time interaction. This model will allow for different baseline means for each age stratum, but restrict the baseline mean within each age stratum to be the same for all vaccination groups. The treatment difference in terms of a geometric mean ratio at a given postvaccination time point will be estimated and tested 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. The Kenward-Roger adjustment will be used with REML to make proper statistical inference. This model allows the inclusion of

participants who are missing either the baseline or postbaseline measurements, thereby increasing efficiency.

For titer measurements 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 the titer.

Secondary Endpoints/Hypotheses

The same statistical approach as used for the primary endpoints will be used to address the secondary immunogenicity hypotheses (H3 and H4) that compare the IgG GMC responses of pPCV with PNEUMOVAX™23, except that a noninferiority margin of 0.5 will be used to evaluate noninferiority of the common serotypes, which corresponds to a 2.0-fold lower IgG GMC in the pPCV group compared with the PNEUMOVAX™23 group. 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 sample t-distribution. The difference between the pPCV group and the PNEUMOVAX™23 group in the proportion of participants with ≥4-fold increase in serotype-specific OPA responses from prevaccination (Day 1) to 30 days postvaccination will be estimated. The corresponding 95% CIs about these differences will be calculated using the M&N method, stratifying by age at enrollment (50 to 64 years, 65 to 74 years, and ≥75 years) [Miettinen, O. and Nurminen, M. 1985].

The analysis strategy for key immunogenicity variables in Phase 2 is listed in Table 8.

Table 8 Analysis Strategy for Key Immunogenicity Variables in Phase 2

Endpoint/Variable (Description, Time point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints			
Ratio of OPA GMTs at 30 days postvaccination for common serotypes	cLDA[a] (point estimate, 95% CI, p-value[b])	PP/FAS	Model-based
Ratio of OPA GMTs at 30 days postvaccination for unique serotypes	cLDA[a] (point estimate, 95% CI, p-value[b])	PP/FAS	Model-based
Secondary Endpoints			
Ratio of IgG GMCs at 30 days postvaccination for common serotypes	cLDA[a] (point estimate, 95% CI, p-value[b])	PP/FAS	Model-based
Ratio of IgG GMCs at 30 days postvaccination for unique serotypes	cLDA[a] (point estimate, 95% CI, p-value[b])	PP/FAS	Model-based
GMFRs from prevaccination to 30 days postvaccination for both OPA and IgG responses	Descriptive Statistics (point estimate, 95% CI)	PP/FAS	Missing data will not be imputed
Difference in proportion of participants with a ≥4-fold increase in serotype-specific OPA responses from prevaccination to 30 days postvaccination	Descriptive Statistics (point estimate, 95% CI)	PP/FAS	Missing data will not be imputed

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

[a] cLDA model with terms for time, the interaction of time-by-vaccination group, age stratum, and the interaction of age stratum-by-time.

[b] p-values for noninferiority or superiority (ie, statistically significantly greater) hypothesis.

9.6.3 Statistical Methods for Safety Analysis (Phase 1 and Phase 2)

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, postvaccination temperature measurements, and laboratory measurements (Phase 1 only). Safety analyses will be conducted separately for Phase 1 and Phase 2.

The analysis of AEs and temperature measurements will follow a tiered approach (Table 9). 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.

Laboratory measurements collected during Phase 1 (see Appendix 2) will be summarized separately. Details regarding the analysis of laboratory measurements will be provided in the sSAP.

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.

This study will solicit for predefined injection-site and systemic AEs. However, as this is the first clinical study of pPCV, no data exists around which a comparative, data-driven safety hypothesis can be formulated and tested. As a result, the solicited injection-site and systemic AEs reported in this study will be analyzed as Tier 2 events.

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 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.

Adverse events (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 treatment group will be provided for Tier 3 events.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoints	95% CI for Between-group Comparison [a]	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/arthralgia (Days 1 to 5)	X	X
	Headache (Days 1 to 5)	X	X
	Tiredness/fatigue (Days 1 to 5)	X	X
	Any AE[b]	X	X
	Any vaccine-related AE[b]	X	X
	Any solicited injection-site AE (Days 1 to 5)[b]	X	X
	Any solicited systemic AE (Days 1 to 5)[b]	X	X
	Any serious AE[b]	X	X
	Any vaccine-related SAE[b]	X	X
	Death[b]	X	X
	Maximum temperature measurements meeting the Brighton Collaboration cut points (Days 1 to 5)	X	X
	Specific AEs by SOC and PT[c] (incidence ≥4 participants in at least 1 of the vaccination groups)	X	X
Tier 3	Specific AEs by SOC and PT[c] (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.
Note: AEs includes both clinical and laboratory AEs (laboratory AEs will be collected in Phase 1 only).
[a] These analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].
[b] These endpoints are broad AE categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least 1 AE.
[c] Includes only those endpoints not prespecified as Tier 2 endpoints.

9.6.4 Summaries of 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 (eg, age) and prior and concomitant therapies and vaccines will be summarized by group. Separate summaries will be provided for Phase 1 and Phase 2.

No other analyses are planned for this study.

9.7 Interim Analyses

A review of Phase 1 and Phase 2 safety and tolerability data will be conducted by an unblinded siDMC. Immunogenicity data will also be provided to the siDMC to enable a benefit-risk assessment. A description of the structure and function of the siDMC, along with the timing and content of the safety review, will be outlined in the siDMC charter. Information regarding the composition of the siDMC is provided in Appendix 1.

Blinding to intervention assignment will be maintained at all investigational sites. Participant-level unblinding will be restricted to an internal unblinded statistician and statistical programmer performing any planned or requested safety reviews by the siDMC. Any safety reviews conducted while the study is ongoing will be provided by the internal unblinded statistician to the siDMC. Prior to final study unblinding, the internal unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the safety reviews.

Two prespecified analyses are planned prior to the completion of this study, as described below.

9.7.1 Phase 1 Interim Analysis

An interim analysis will be performed once the primary 30-day postvaccination safety and immunogenicity data are available for all Phase 1 participants. At this point, the database will be locked and an analysis will be performed to summarize the safety and immunogenicity data. This analysis will not occur until medical/scientific review of the data has been performed and protocol deviations have been identified. The siDMC will review unblinded Phase 1 safety and immunogenicity data reports and evaluate the benefit and risk profile to make a recommendation regarding proceeding to Phase 2. The Sponsor study team will review the Phase 1 safety and immunogenicity aggregate data reports to inform the clinical development decision to proceed to Phase 2. The Sponsor study team will not be unblinded to participant-level data. The unblinded Phase 1 data will be provided by an unblinded statistician who is not part of the blinded study team, and the clinical database will remain blinded to both the Sponsor study team and participating sites throughout the duration of the Phase 1/Phase 2 study. Additionally, based on the analysis of this Phase 1 data, power and sample size assumptions for Phase 2 will be examined and the sample size may be adjusted.

9.7.2 Phase 2 Interim Analysis

An interim analysis is planned to support clinical development decisions prior to the completion of the Phase 2 portion of this study. This analysis will be conducted once the primary 30-day postvaccination safety and immunogenicity data are available for all Phase 2 participants and the 6-month safety data are available for at least 50% of Phase 2 participants. This analysis will represent the final analysis of the primary immunogenicity endpoints and will be considered a preliminary analysis of the safety data. These analyses will be conducted by an unblinded statistician who is not part of the blinded study team. The siDMC will review unblinded Phase 2 safety and immunogenicity data reports and evaluate the benefit and risk profile. The Sponsor study team will review the Phase 2 safety and immunogenicity aggregate data reports to inform further clinical development. The Sponsor study team will not be unblinded to participant-level data.

9.8 Multiplicity

As described in Section 9.6.2, there are 2 types of hypothesis tests for the Phase 2 immunogenicity analysis: (1) a separate noninferiority test for each of the common serotypes between pPCV and PNEUMOVAX™23, and (2) a separate superiority (ie, statistically significantly greater) test for each of the serotypes that are unique to pPCV. This study will be considered to have met its primary immunogenicity objective if success is demonstrated for all common serotypes and all unique serotypes included in the primary immunogenicity hypotheses. The intersection-union test controls the overall type I error at the 1-sided 0.025 level within each group; therefore, no multiplicity adjustment will be required within each group [Berger, R. L. 1982]. The intersection-union test refers to the fact that the set of statistical null hypotheses to be tested can be expressed as a union, and the set of statistical alternative hypotheses as an intersection. Thus, the overall statistical null hypothesis can only be rejected if each of the set of statistical null hypotheses are rejected.

The same multiplicity strategy will be applied to the 2 secondary study hypotheses for which there is also a noninferiority hypothesis for the common serotypes between pPCV and PNEUMOVAX™23, and a superiority (ie, statistically significantly greater) hypothesis for the serotypes unique to pPCV, as measured by IgG. In this way, for the secondary hypotheses to be supported by the data, all statistical tests will have to be statistically significant. This approach controls the type I error at 0.025 (1-sided) for the set of primary hypothesis tests and separately at 0.025 (1-sided) for the set of secondary hypothesis tests.

No multiplicity adjustments will be made for the safety comparisons.

9.9 Sample Size and Power Calculations

9.9.1 Immunogenicity Analyses

In Phase 1, approximately 90 participants will be enrolled, with approximately 30 participants in each of the 3 vaccination groups.

In Phase 2, Approximately 500 participants will be enrolled, with approximately 250 participants in each of the 2 vaccination groups. Assuming 90% evaluability (approximately 225 participants per group), there is 98.7% power to declare primary noninferiority to PNEUMOVAX™23 for the common serotypes and 99.2% power for superiority (ie, statistically significantly greater) for the unique serotypes based on OPA GMT ratios. The overall estimate of power for the primary hypothesis, as the product of the powers for the set of noninferiority hypotheses and the set of superiority (ie, statistically significantly greater) hypotheses, is 98%. This sample size also provides adequate power for the secondary hypotheses. Specifically, there is 87% power for the secondary noninferiority hypothesis and 92% power for the secondary superiority (ie, statistically significantly greater) hypothesis. The overall power for the secondary hypotheses is 80%. The sample size and power calculations are based on the following assumptions:

- The standard deviation of natural log-transformed OPA assay and IgG results are 2.2 and 1.73, respectively. These assumptions are based on observations from previous studies with PNEUMOVAX™23.

- For the common serotypes, the assumed true geometric mean ratios of OPA GMTs and IgG GMCs are 1.

- For the unique serotypes, the assumed true geometric mean ratios of OPA GMTs and IgG GMCs are 3 and 2, respectively.

- 90% evaluability rate (approximately 225 participants per group).

9.9.2 Safety Analyses

For safety comparisons, all participants are expected to be evaluable.

In Phase 1, if no SAEs are observed among the 30 participants in each vaccination group, this study provides 68.7% confidence that the true SAE rate is <1.2% (1 out of every 83 participants). In Phase 2, if no SAEs are observed among the 250 participants in each vaccination group, this study provides 97.9% confidence that the true SAE rate is <1.5% (1 out of every 67 participants).

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. In Phase 2, if the incidence rate of an SAE is 1 of every 143 recipients of the vaccine (0.7%), then there is an 80% chance of observing at least 1 such SAE among 250 participants in the pPCV group. If the incidence rate is 1 of every 332 recipients of the vaccine (0.3%), then there is a 50% chance of observing at least 1 SAE among 250 participants in the pPCV group.

For the Phase 2 safety comparisons, risk differences between the 2 vaccination groups that could be detected with an 80% probability are summarized in Table 10 for a variety of hypothetical true incidence rates. These calculations assume that there are 250 evaluable participants in both groups and are based on a 2-sided significance level of α=0.05. No multiplicity adjustments were made in these calculations.

Table 10 Differences in the Incidence of Adverse Event Rates Between the 2 Vaccination Groups in Phase 2 That Can be Detected With Approximately 80% Probability

Incidence of Adverse Event		Risk Difference
pPCV (%)	**PNEUMOVAX™23 (%)**	**Percentage Points**
3.6	0.1	3.5
7.6	2.0	5.6
12.3	5.0	7.3
19.2	10.0	9.2
25.5	15.0	10.5
31.4	20.0	11.4
42.5	30.0	12.5

The incidence rates for each vaccination group are hypothetical and do not represent actual adverse events in either group.

The incidences assume a 2-sided 5% alpha level with 250 participants in each group. No multiplicity adjustments were made.

The calculations are based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. 1990].

9.10 Subgroup Analyses

Subgroup analyses will be provided for Phase 2, where the geometric mean ratio between pPCV and PNEUMOVAX™23 as assessed by OPA GMTs and IgG GMCs will be summarized by age subgroup (ie, 50 to 64 years, 65 to 74 years, and ≥75 years).

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

9.11 Compliance (Medication Adherence)

Given that participants will receive a single dose of 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

In Phase 1, the extent of exposure will be summarized by the number and proportion of randomized participants administered pPCV-1, pPCV-2, or PNEUMOVAX™23.

In Phase 2, 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 Committees Structure

10.1.4.1 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate siDMC will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency (Section 9.7[Interim Analyses]) for evidence of adverse effects of study intervention and immunogenicity data, as described in the detailed monitoring guidelines. The siDMC will determine whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

10.1.7 Compliance with Law, Audit, and Debarment

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted 30 days after the last dose of study intervention.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 11 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology (Phase 1 only)	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry (Phase 1 only)	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Creatinine
	Alkaline phosphatase	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) • All study-required laboratory assessments will be performed by a central laboratory, with the exception of pregnancy tests.			

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

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, 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/toxicity

- 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.

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

Injection-Site AE Toxicity Grading Scale

Injection Site Reaction to Study Vaccine/Placebo[a]	Grade 1	Grade 2	Grade 3	Grade 4
Injection-site AEs occurring Days 1 through 5 following receipt of study vaccine/placebo				
Pain/Tenderness	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Erythema/Redness	Size measured as B	Size measured as C or D	Size measured as E→	Necrosis or exfoliative dermatitis or results in ER visit or hospitalization
Induration/Swelling	Size measured as B	Size measured as C or D	Size measured as E→	Necrosis or ER visit or hospitalization
Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Any injection-site reaction that begins ≥6 days after receipt of study vaccine/placebo				
Pain/tenderness Erythema/Redness Induration/Swelling Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization

AE = adverse event; ER = emergency room; eVRC = electronic Vaccine Report Card; SAE = serious adverse event; VRC = vaccination report card.

[a] Based upon information provided by the participant on the paper VRC/eVRC and verbally during VRC review. Erythema/Redness and Induration/Swelling are specific injection-site AEs with size designations of letters A through E→, based upon a graphic in the paper VRC/eVRC. Size A is not assigned a toxicity grade; however, injection-site AEs that measure size A should be reported as adverse experiences. If the participant has an ER visit or is hospitalized for any injection-site AE, that AE is to be assigned a toxicity grade of 4, regardless of the size measured.

Specific Systemic AE Toxicity Grading Scale

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

ER = emergency room

Other Systemic AE Toxicity Grading Scale

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

ER = emergency room; eVRC = electronic Vaccine Report Card; SAE = serious adverse event; VRC = vaccination report card.
[a] Based upon information provided by the patient on the paper VRC/eVRC and verbally during the eVRC review during the primary safety follow-up period. For SAEs reported beyond the primary safety follow-up period, grading will be based upon the initial report and/or follow-up of the event.
[b] AEs resulting in death will be assessed as Grade 4.

Vital Sign (Temperature) Toxicity Grading Scale

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

[a] Participant should be at rest for all vital sign requirements.
[b] Oral temperature; no recent hot or cold beverages or smoking.

Assessment of causality

- Did the 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 initialled 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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

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

10.5.2.1 Contraception Requirements in Phase 1

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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.

1. 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.

10.5.2.2 Contraception Requirements in Phase 2

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable

Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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.

2. 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.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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 participant' 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 gender, 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.

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ALT	Alanine Aminotransferase
APaT	All-Participants-as-Treated
AST	Aspartate Aminotransferase
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
eVRC	electronic Vaccination Report Card
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

Abbreviation	Expanded Term
PnECL	pneumococcal electrochemiluminescence
PnP	pneumococcal polysaccharide
PP	Per-protocol
pPCV	polyvalent pneumococcal conjugate vaccine
REML	restricted or residual maximum likelihood
RNA	ribonucleic acid
SAE	serious adverse event
SLAB	supplemental laboratory test
SoA	Schedule of Activities
siDMC	standing internal Data Monitoring Committee
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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