Official Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children with Sickle Cell Disease (PNEU–SICKLE)
NCT number:	NCT03731182
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Title Page

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Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children with Sickle Cell Disease (PNEU–SICKLE)

Protocol Number: 023-00

Compound Number: V114

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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Regulatory Agency Identifying Number(s):

IND	14115
EudraCT	2018-001152-35

Approval Date: 06-September-2018

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children with Sickle Cell Disease (PNEU–SICKLE)

Short Title: Safety and Immunogenicity of V114 in Children with Sickle Cell Disease

Acronym: PNEUmococcal Conjugate Vaccine Trials: V114-023 (PNEU–SICKLE)

Hypotheses, Objectives, and Endpoints:

There is no formal hypothesis testing in this study.

The following objectives and endpoints will be evaluated in participants from 5 years to 17 years of age (inclusive) with SCD:

Primary Objectives	Primary Endpoints
- Objective: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs)	- Solicited injection-site AEs from Day 1 through Day 14 postvaccination - Solicited systemic AEs from Day 1 through Day 14 postvaccination - Vaccine-related serious adverse events (SAEs) through completion of study participation
- Objective: To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination (Day 30) for each vaccination group.	- Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at Day 30
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination (Day 30) for each vaccination group.	- Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at Day 30
- Objective: To evaluate the anti-PnPs serotype-specific Geometric Mean Fold Rises (GMFRs) from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for each vaccination group.	- Anti-PnPs serotype-specific OPA and IgG responses for the 15 serotypes contained in V114 at Day 1 and Day 30

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal disease
Population	Children with sickle cell disease
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control without placebo
Study Blinding	Double-blind, with in-house blinding
Masking	Participant or Subject Care Provider Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 19 months from the time the first participant signs the informed consent/assent 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 100 participants will be randomized, with approximately 67 participants in the V114 intervention group and 33 participants in the Prevnar 13™ intervention group.

Intervention Groups and Duration:

Intervention Groups	See table below
Total Number	2 intervention groups
Duration of Participation	Each participant will participate in the study for approximately 6 months from the time the participant signs the Informed Consent Form (ICF) through the final contact.

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Vaccination Regimen	Use
V114	V114	Refer to IB	Single dose	IM	Single Dose at Visit 1 (Day 1)	Experimental
Prevnar 13™	Prevnar 13™	Refer to product labeling	Single dose	IM	Single Dose at Visit 1 (Day 1)	Experimental
IB = Investigator's Brochure; IM = intramuscular						

Study Governance Committees:

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

Study Accepts Healthy Volunteers: No

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

1.2 Schema

The key components of the study design are depicted in Figure 1.

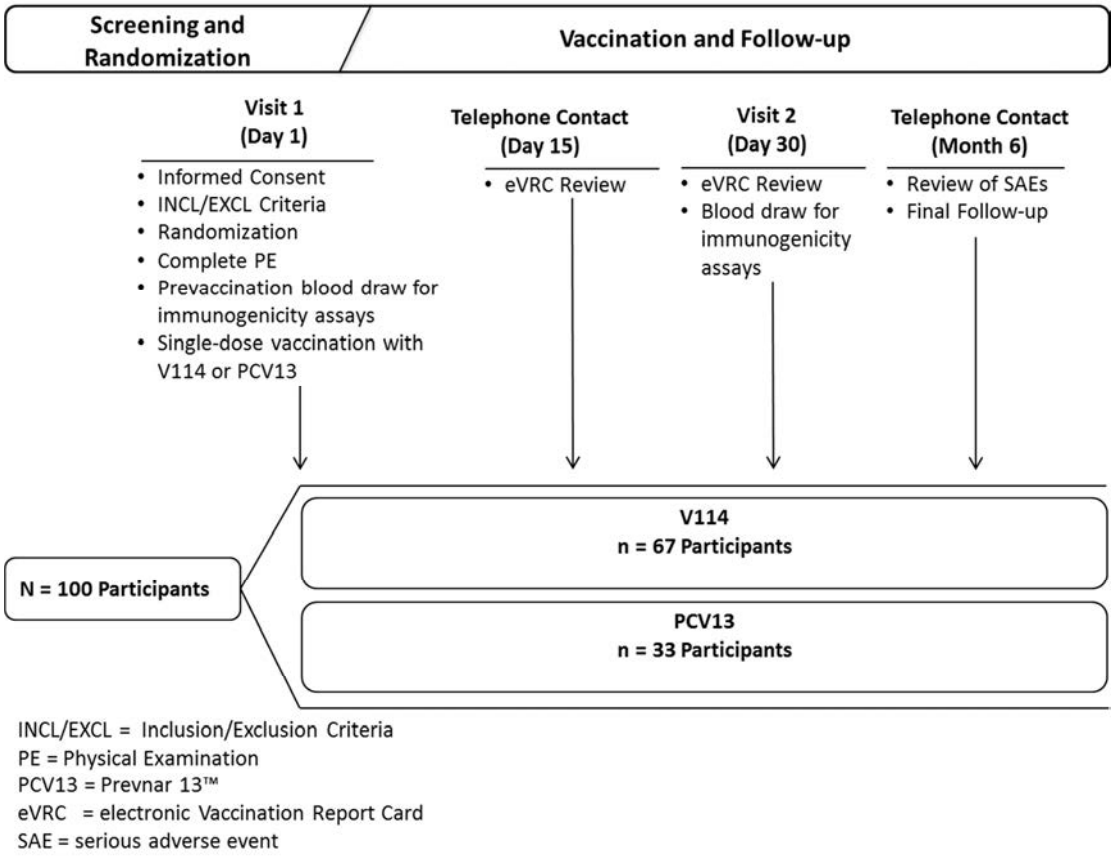

Figure 1 V114-023 Study Design

1.3 Schedule of Activities (SoA)

Visit Number:	**1**	**Telephone Contact**	**2**	**Telephone Contact**	**Comments**
Scheduled Time:	**Day 1**	**Day 15**	**Day 30**	**Month 6**	
Visit Window:		**Day 15 to Day 19 after Visit 1**	**Day 30 to Day 44 after Visit 1**	**Day 166 to Day 194 after Visit 1**	
Administrative and General Procedures					
Screening Procedures					
Informed Consent/Assent	X				Consent/assent must be obtained before any study procedures.
Informed Consent/Assent for Future Biomedical Research	X				Consent/assent for future biomedical research is optional and must be obtained before the collection of saliva DNA samples.
Assignment of Screening Number	X				
Participant Identification Card	X				
Inclusion/Exclusion Criteria	X				
Medical History	X				The participant's medical history for the 5 years prior to study entry will be reviewed.
Post-enrollment Procedures					
Assignment of Randomization Number	X				
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X		See Section 8.1.5.for details.
V114 or Prevnar 13™ Administration (Blinded)	X				At Visit 1 (Day 1), participants will receive either a single dose of V114 or a single dose of Prevnar 13™.
Provide eVRC	X				All participants will be provided an eVRC at Visit 1 (Day 1) to record AEs and body temperature measurements. Instructions for using the eVRC will be reviewed with the participant or participant's legally acceptable representative.
Review eVRC data with participant or participant's legally acceptable representative		X	X		
Collect eVRC from participant or participant's legally acceptable representative			X		
Complete the Telephone Contact Questionnaire				X	The Telephone Contact Questionnaire will be provided by the Sponsor.
Safety Procedures					
Complete Physical Examination	X				To be performed by the investigator or medically qualified designee before study vaccine is administered.

Visit Number:	**1**	**Telephone Contact**	**2**	**Telephone Contact**	**Comments**
Scheduled Time:	**Day 1**	**Day 15**	**Day 30**	**Month 6**	
Visit Window:		**Day 15 to Day 19 after Visit 1**	**Day 30 to Day 44 after Visit 1**	**Day 166 to Day 194 after Visit 1**	
Pregnancy Test – if applicable	X				A pregnancy test consistent with local requirements must be performed before administration of the study vaccine in women of child-bearing potential. Urine or serum tests can be used, and results must be negative before vaccination can occur.
Body Temperature Measurement	X				Each participant's body temperature must be taken before vaccination (see Section 8.3.3 for details on the method of temperature collection). Participants who have febrile illness occurring at or within 72 hours of Visit 1 must be rescheduled (see Section 5.2 for details).
30-minute Postvaccination Observation Period	X				To be performed by blinded study site personnel only.
AE Monitoring	X	X	X	X	Nonserious AEs are to be reported from Days 1 through 14 postvaccination. SAEs and deaths are to be reported throughout the duration of the participant's study participation.
Immunogenicity Procedures					
Serum for immunogenicity assays (including retention serum)	X		X		Blood samples must be collected before study vaccination when applicable.
Future Biomedical Research					
Saliva (DNA) for Future Biomedical Research	X				Collected from randomized participants who provided consent/assent for Future Biomedical Research (See Section 8.8).

AE = adverse event; DNA = deoxyribonucleic acid; eVRC = electronic Vaccination Report Card; SAE = serious adverse event.

2 INTRODUCTION

Merck Sharp & Dohme Corp. (MSD) is developing an investigational 15-valent pneumococcal conjugate vaccine (PCV) (referred to as V114) for prevention of pneumococcal disease caused by the serotypes contained in the vaccine. V114 contains the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F) present in the licensed vaccine Prevnar 13™ (pneumococcal 13-valent conjugate vaccine [diphtheria CRM_{197} protein], Wyeth Pharmaceuticals, a subsidiary of Pfizer, Inc., Philadelphia, PA), plus 2 additional serotypes (22F, 33F).

2.1 Study Rationale

Sickle cell disease (SCD) is a group of disorders caused by abnormal hemoglobin which can deform or "sickle" red blood cells and lead to end-organ damage. Children with SCD have an increased risk of invasive disease caused by encapsulated bacteria, such as *Streptococcus pneumoniae,* secondary to splenic dysfunction and abnormalities of innate immunity. Early interventions with vaccinations against encapsulated bacteria have significantly reduced the mortality of SCD in the United States and Europe [Quinn, C. T., et al 2010] [Telfer, P., et al 2007].

Immunization guidelines recommend that infants and children with SCD follow the same PCV schedule as healthy infants and children up to 5 years of age, including catch up vaccination. Children with SCD 2 to 18 years of age, without a history of immunization with the 13-valent Prevnar 13™ are recommended to receive catch up immunization with Prevnar 13™, regardless of previous immunization with other PCVs containing fewer pneumococcal polysaccharide (PnPs) serotypes. In addition, it is recommended that children with SCD receive 2 doses of the 23-valent PnPs vaccine, PNEUMOVAX™23; the first dose at 2 years of age and the second dose either at 5 years of age [National Heart, Lung and Blood Institute 2014] or at 7 years of age (5 years after first dose) [Centers for Disease Control and Prevention (CDC) 2013].

This clinical study is designed to describe the safety, tolerability, and immunogenicity of V114 compared with Prevnar 13™ in children with SCD 5 to 17 years of age (inclusive) who are either PCV naïve or have a history of previous PCV immunization. Because of widespread adherence to immunization guidelines for children with SCD, it is anticipated that a majority of participants will have been previously vaccinated with a PCV. Safety and immunogenicity data collected in this study will support recommendations for V114 catch-up vaccination in children who received a PCV containing fewer than 15 serotypes or who are PCV naïve. In addition, the data from this study will contribute to the overall safety database and immunogenicity profile of V114 in children.

2.2 Background

2.2.1 V114 and Pneumococcal Disease

Refer to the Investigator's Brochure (IB) for V114 for detailed background, including information on pneumococcal disease burden.

Streptococcus pneumoniae remains a significant cause of disease worldwide, with clinical manifestations including meningitis, sepsis, pneumonia, sinusitis and otitis media. Currently, many countries worldwide have incorporated licensed PCVs (eg, Prevnar 13™ and/or Synflorix™ (pneumococcal polysaccharide conjugate vaccine [adsorbed], GlaxoSmithKline Biologicals S.A, Rixensart, Belgium) into their infant immunization programs. Prevnar™ was first licensed in 2000 and later replaced by Prevnar 13™ in 2009 (European Union) and 2010 (United States). Synflorix™ was licensed in the European Union in 2009. Although Prevnar 13™ is indicated for children and adults, Synflorix™ is only indicated for children up to 5 years of age. Widespread use of PCVs have reduced the burden of pneumococcal disease caused by the serotypes contained in the vaccines in children who received the vaccines, as well as unvaccinated individuals through herd protection [Centers for Disease Control and Prevention 2008] [Ruckinger, S., et al 2009] [Farrell, D. J, et al 2007] [Pilishvili, Tamara, et al 2010] [Lexau, C. A., et al 2005] [Metlay, J. P., et al 2006] [Whitney, Cynthia G., et al 2003] [Moore, M. R., et al 2015] [Lepoutre, A., et al 2015] [Weiss, S., et al 2015] [Martinelli, D., et al 2014] [Guevara, M., et al 2016] [Waight, P. A., et al 2015] [Jokinen, J., et al 2015] [Palmu, A. A., et al 2015] [Wagenvoort, G. H., et al 2016]. Despite this, an increase in the burden of invasive pneumococcal disease (IPD) caused by serotypes not contained in currently available vaccines has been observed.

V114 contains all the pneumococcal serotypes contained in Prevnar 13™ plus 2 additional serotypes (22F, 33F). The selection of 22F and 33F was primarily based on the emergence of these 2 serotypes as important causes of IPD in the era of Prevnar™ and Prevnar 13™. Approximately 4 years after inclusion of Prevnar™ in the United States infant immunization schedule, serotypes 22F and 33F accounted for approximately 13% of IPD cases in children <5 years of age (incidence rate of IPD due to 22F and 33F combined of 3.1 cases per 100,000 person-years [PY]), in contrast to 1.3% of IPD cases in the pre-PCV7 era (incidence rate of 22F and 33F IPD of 1.2 cases per 100,000 PY) [Hicks, L. A., et al 2007]. By 2013, both 22F and 33F were among the leading serotypes causing IPD beyond those already included in Prevnar 13™, accounting for approximately 21% of all IPD in children <5 years of age in the United States [Moore, M. R., et al 2015].

The additional serotypes contained in V114 will provide broader coverage against the leading serotypes associated with pneumococcal disease worldwide. V114 is designed to meet continuing medical and public health needs for PCVs globally, as well as address the emergence of pneumococcal disease caused by serotypes not contained in currently licensed PCVs.

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Information on Other Study-related Therapy

Refer to approved labeling for detailed background information on Prevnar 13™.

Prevnar 13™ is a pneumococcal conjugate vaccine that contains the 7 pneumococcal serotypes included in Prevnar™ (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A). In many countries, Prevnar 13™ is given as a part of routine immunization schedules for all infants and children 2 to 59 months of age. Children with SCD 2 to 18 years of age, without a history of immunization with Prevnar 13™ are recommended to receive catch up immunization with Prevnar 13™, regardless of previous immunization with other PCVs containing fewer PnPs serotypes. [Centers for Disease Control and Prevention (CDC) 2013].

Prevnar™ and Prevnar 13™ are also known as Prevenar™ and Prevenar 13™ in many countries outside of the United States; these vaccines will be referred to as Prevnar™ and Prevnar 13™ throughout this document.

2.3 Benefit/Risk Assessment

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

This study will evaluate the safety and immunogenicity of V114 in a pediatric SCD population who are either PCV naïve or have received previous PCV immunization. For those children previously vaccinated with a PCV, an additional PCV dose will likely increase pneumococcal antibody titers against serotypes contained in the previous vaccine, but is not anticipated to be associated with safety or tolerability issues. This is supported by a previous study in which 2 doses of Prevnar 13™ were administered 6 months apart in children with SCD with no change in the safety profile with the second dose [De Montalembert, M., et al 2015]. Furthermore, safety and tolerability issues were not identified following the widespread practice of catch up Prevnar 13™ vaccination in children previously vaccinated with Prevnar™.

Prevnar 13™ is the current standard of care for PCVs in many countries worldwide and is the active comparator in this study. Approximately 33% of participants will receive Prevnar 13™ in this study. Based on available data, V114 is expected to provide comparable immune responses and a comparable safety profile to Prevnar 13™ for the shared pneumococcal serotypes while providing additional coverage for the 2 serotypes unique to V114 (22F, 33F). However, it is unknown if the investigational V114 will have the same benefit/risk profile as Prevnar 13™.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There is no formal hypothesis testing in this study.

The following objectives and endpoints will be evaluated in participants from 5 years to 17 years of age (inclusive) with SCD:

Objectives	Endpoints
Primary	
• **Objective:** To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs)	• Solicited injection-site AEs from Day 1 through Day 14 postvaccination • Solicited systemic AEs from Day 1 through Day 14 postvaccination • Vaccine-related serious adverse events (SAEs) through completion of study participation
• **Objective:** To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination (Day 30) for each vaccination group.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at Day 30
Secondary	
• **Objective:** To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination (Day 30) for each vaccination group.	• Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at Day 30
• **Objective:** To evaluate the anti-PnPs serotype-specific Geometric Mean Fold Rises (GMFRs) from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for each vaccination group.	• Anti-PnPs serotype-specific OPA and IgG responses for the 15 serotypes contained in V114 at Day 1 and Day 30

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active comparator-controlled, parallel-group, multi-site, double-blind (with in-house blinding), study of V114 in participants 5 to 17 years of age (inclusive) with SCD. Approximately 100 participants will be randomly assigned in a 2:1 ratio to receive either V114 (67 participants) or Prevnar 13™ (33 participants) on Visit 1 (Day 1).

Participants will be followed for local and systemic AEs through Day 14 following vaccination. Information for serious adverse events (SAEs) and deaths, regardless of whether the events are considered to be vaccine-related by the investigator, will be collected from the time consent/assent is signed through completion of participation in the study. An external Data Monitoring Committee (DMC) will conduct a periodic review of safety and tolerability data for this study, as well as all studies in the pediatric V114 Phase 3 program. A description of the structure, function, and guidelines for decision-making by the DMC, along with the timing and content of the safety reviews will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1.

To obtain baseline pneumococcal antibody titers, blood samples for immunogenicity assays will be drawn immediately before V114 or Prevnar 13™ vaccination at Visit 1 (Day 1). An additional blood draw for immunogenicity testing (including OPA and electrochemiluminescence [ECL] testing to measure V114 or Prevnar 13™-induced pneumococcal-specific immune responses) will occur at Visit 2 (Day 30).

After completion of immunogenicity testing, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. For randomized study participants who provided consent/assent for future biomedical research, leftover sera from the study may be used for 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 clinical study is designed to describe the safety, tolerability, and immunogenicity of V114 compared with Prevnar 13™ in children with SCD 5 to 17 years of age (inclusive) who are either PCV naïve or have a history of previous PCV immunization. The primary and secondary immunogenicity endpoints (IgG and OPA) measure anti-pneumococcal serotype-specific antibody responses, which are known to be associated with protection from IPD. Injection-site reactions and systemic symptoms following vaccination will be solicited for 14 days. Participants will be followed for 6 months following immunization for reports of SAEs or death. The duration of the safety follow-up period is consistent with previous studies evaluating the immunogenicity and safety of PCVs in children with SCD. The immunogenicity and safety objectives are descriptive and do not test formal hypotheses.

V114 has the potential to offer additional protection against IPD caused by 2 PnPs serotypes not contained in Prevnar 13™ in addition to boosting immune responses to serotypes shared with Prevnar 13™. Safety and immunogenicity data collected in this study will support recommendations for V114 catch-up vaccination in children with SCD who received a PCV containing fewer than 15 serotypes or who are PCV-naïve.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

Sera from participants will be used to measure vaccine-induced, serotype-specific IgG and OPA responses for all 15 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) included in V114 using the pneumococcal electrochemiluminescence (PnECL) assay and multiplexed opsonophagocytic assay (MOPA). Anti-PnPs serotype-specific IgG responses will be measured at baseline and at 30 days following the dose of V114 or Prevnar 13™.

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. It is noted that threshold values that correlate with protection in children with SCD have not been defined for either assay.

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

4.2.1.2 Safety Endpoints

The safety endpoints evaluated in this study were selected based on the product's safety profile demonstrated in previous studies, published data from marketed PCVs, and feedback received from regulatory agencies during product development. The electronic Vaccination Report Card (eVRC) used to record AEs during the postvaccination periods, as defined in Section 8.1.9, was structured as recommended in the final 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 8.3.4 and Section 9.4.2.

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

4.2.1.3 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [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 this future biomedical research substudy are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator

Placebo-controlled clinical studies for new PCVs are no longer acceptable given the proven clinical efficacy, public health impact, and widespread use of licensed PCVs worldwide. Prevnar 13™ is currently the most widely recommended vaccine for the prevention of pneumococcal disease in infants and children in many countries worldwide, includes the largest number of serotypes, and will be used as the active comparator in this study.

Refer to approved labeling for detailed background information on Prevnar 13™.

4.3 Justification for Dose

The dosing regimen of V114 is similar to that used in previous V114 adult and pediatric Phase 2 clinical studies in which 1 dose administered to adults resulted in a robust immune response and had an acceptable safety and tolerability profile.

The dose of Prevnar 13™ for use in this study is the approved dose.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent/assent form. 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, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or an unacceptably high number of discontinuations or withdrawals due to administrative reasons.

5 STUDY POPULATION

Male/Female participants with SCD between the ages of 5 and 17 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Have a documented diagnosis of SCD in their medical record.

Demographics

2. Be male or female, from 5 years to 17 years of age (inclusive), at the time of obtaining the informed consent/assent.

Female Participants

3. Not be pregnant (Appendix 5) or breastfeeding, and at least 1 of the following conditions applies:
   a. Not be a woman of childbearing potential (WOCBP) as defined in Appendix 5.
      OR

   b. A WOCBP must agree to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 6 weeks after the last dose of study intervention.

Informed Consent/Assent

4. Have a legally acceptable representative who understands the study procedures, alternate treatments available, and risks involved with the study and voluntarily agrees to participate by giving written informed consent/assent. The legally acceptable representative may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

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

Medical Conditions

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

2. Has a known hypersensitivity to any component of pneumococcal conjugate vaccine (PCV), or any diphtheria toxoid-containing vaccine.

3. Has a known or suspected impairment of immunological function.

4. Has a history of congenital or acquired immunodeficiency.

5. Has a documented human immunodeficiency virus (HIV) infection.

6. Has a history of autoimmune disease (including but not limited to systemic lupus erythematosus, antiphospholipid syndrome, Behcet's disease, autoimmune thyroid disease, polymyositis and dermatomyositis, scleroderma, or type 1 diabetes mellitus).

7. Has a known coagulation disorder contraindicating intramuscular vaccination.

8. *Has had a recent febrile illness (defined as oral or tympanic temperature ≥38.1°C [≥100.5°F]; axillary or temporal temperature ≥37.8°C [≥100.0°F]) or received antibiotic therapy for any acute illness occurring within 72 hours before receipt of study vaccine.

9. Has a history of malignancy ≤5 years prior to signing informed consent/assent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

10. Is a WOCBP who has a positive urine or serum pregnancy test before the first vaccination at Visit 1 (Day 1).

Prior/Concomitant Therapy

11. Has received any PCV or PnPs vaccine <3 years before Visit 1 (Day 1).

12. Is 5 years of age and has received <3 doses of PCV.

13. *Meets one or more of the following systemic corticosteroid exclusion criteria:

    a. Has received systemic corticosteroids (prednisone equivalent of ≥20 mg/day) for ≥14 consecutive days and has not completed treatment at least 30 days before study vaccination.

b. Has received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) within 14 days before study vaccination.

c. Is expected to require systemic corticosteroids within 30 days after study vaccination.

Note: Topical, ophthalmic, intra-articular or soft-tissue (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.

14. 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.

Note: Hydroxyurea is permitted.

15. *Has received any non-live vaccine within the 14 days before receipt of the study vaccine or is scheduled to receive any non-live vaccine within 30 days following receipt of the study vaccine. **Exceptions**: Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of the study vaccine or at least 15 days after receipt of the study vaccine. PNEUMOVAX™23 may be administered after the blood draw at Visit 2 (Day 30).

16. *Has received any live vaccine within 30 days before receipt of the study vaccine or is scheduled to receive any live vaccine within 30 days following receipt of the study vaccine.

17. Has received immunoglobulin within 6 months before receipt of study vaccine.

Prior/Concurrent Clinical Study Experience

18. Has participated in another clinical study of an investigational product within 2 months before the beginning or anytime during the duration of the current clinical study. Participants enrolled in observational studies may be included; these will be reviewed on a case-by-case basis for approval by the Sponsor.

Other Exclusions

19. Has a recent history (within the last year) of more than 3 inpatient hospitalizations.

20. Is, at the time of signing informed consent/assent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence as assessed by the study investigator.

21. Has a history or current evidence of any condition, therapy, lab 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 in the opinion of the Investigator.

22. 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, Visit 1 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/assent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (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 (V114 and Prevnar 13™) 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.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
V114	Experimental	V114	Biological/ Vaccine	Sterile Suspension	Refer to IB	0.5 mL	IM	Single Dose at Visit 1 (Day 1)	Experimental	IMP	Central
Prevnar 13™	Active Comparator	Prevnar 13™	Biological/ Vaccine	Sterile Suspension	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.

Definitions of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) are 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 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 where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

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 authorized site staff.

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 2:1 ratio to V114 or Prevnar 13™, respectively.

6.3.2 Stratification

No stratification will be used in this study.

6.3.3 Blinding

A double-blinding technique will be used. V114 and Prevnar 13™ will be prepared and/or dispensed by an unblinded pharmacist or unblinded qualified study site personnel. The participant and the investigator who is involved in the clinical evaluation of the participants will remain blinded to the group assignments.

Because V114 and Prevnar 13™ differ in appearance, a member of the study site staff will be unblinded for the purposes of receiving, maintaining, preparing, and administering these study vaccines. Procedures for handling, preparing, and administering the unblinded vaccines are located in the Investigator Trial File Binder.

In order 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

Interruptions from the protocol-specified plan for V114 or Prevnar 13™ vaccination indicated in Section 1.3 require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (see Section 5.2 for details). 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 a medical condition requires the use of a prohibitive steroid regimen, immunoglobulin, blood, or blood products during a participant's participation in this study, one of the

individuals listed on the Sponsor Contact Information page must be notified as soon as possible. Any concurrent medication or medical treatment must be recorded on the appropriate electronic Case Report Form (eCRF). It is important to record the use of any analgesic or antipyretic use that occurs on the day of vaccination on the eVRC and appropriate eCRF.

During influenza season, it is anticipated that participants may be given an influenza vaccine. Influenza vaccine should be administered either 7 days prior to or 15 days after the administration of the study vaccine. In addition, PNEUMOVAX™23 may be administered after the blood draw at Visit 2 (Day 30) outside of the study.

Documentation of which arm was used for the administration of V114 or Prevnar 13™ should be recorded on the appropriate eCRF. This information should also be recorded on the eVRC to inform the parent or legally acceptable representative of the appropriate limb to monitor for AEs related to the V114 or Prevnar 13™.

No other investigational compound or device may be administered at any time during this study without prior approval by the Sponsor.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

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

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.13). 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 or participant's legally acceptable representative withdraws consent from the study.

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from 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 or trained 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, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Table 2 shows the approximate blood volumes drawn by study visit and by sample type. The maximum amount of blood collected from each participant for study procedures at each study visit will not exceed 10 mL and the total amount of blood for the entire study collected during planned study visits will not exceed 20 mL.

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

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

Study Visit	**Visit 1 (Day 1)**	**Visit 2 (Day 30)**
Blood parameter	Approximate Blood Volume (mL)	
Serum for immunogenicity assays (including retention serum)	10 mL	10 mL
Expected total (mL)	10 mL	10 mL

N/A = not applicable

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative 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/assent is in place.

8.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

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

The initial informed consent/assent form, any subsequent revised written informed consent/assent form, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative'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. The assent, as applicable will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent/assent to the participant, answer all of his/her questions, and obtain written informed consent/assent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent/assent 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. The investigator should consult with the Sponsor's Clinical Director for any questions about participant eligibility.

If the participant meets any of the exclusion criteria with an asterisk (*), Visit 1 (Day 1) may be rescheduled for a time when these criteria are not met.

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/assent. At the time of intervention allocation/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 before vaccination at Visit 1. The participant's medical history for the 5 years prior to Visit 1 will be obtained to ensure that the participant satisfies the inclusion and exclusion criteria of the study.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior vaccinations and medications taken by the participant within 30 days before the first dose of study vaccine at Visit 1.

8.1.5.2 Concomitant Medications

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

If a medical condition requires the use of a prohibitive steroid regimen, immunoglobulin, blood, or blood products during a participant's participation in this study, one of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible. Any concurrent medication or medical treatment must be recorded on the appropriate eCRF.

It is important to record the use of any analgesic or antipyretic use that occurs on the day of vaccination on the eVRC and appropriate eCRF. Concomitant medications taken after Visit 1 and nonstudy vaccines received since Visit 1 will be recorded with the eVRC as specified in Section 8.3.4.

Other vaccinations administered during the study should be recorded on the appropriate eCRF. Injectable vaccines should not be administered in the same limb as V114 or Prevnar 13™. Documentation of which limb was used for the administration of V114 or Prevnar 13™ should be recorded on the eVRC (Section 8.3.4) and appropriate eCRF.

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.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.12.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Unblinded study personnel not otherwise involved in the conduct of the study will prepare and administer the study vaccine. 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 Prevnar 13™ as specified in the product labels.

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.

If the V114 is provided as a syringe: Prior to administration of study vaccine, the unblinded pharmacist should shake vigorously to obtain a homogenous white suspension. If white-colored insoluble particle appears, the unblinded pharmacist should use rapid, horizontal hand-shaking for 5 to 10 seconds while holding the syringe in between the thumb and index finger until complete resuspension. This action should be repeated, as necessary. If appearance is otherwise, the vaccine should not be administered.

If V114 is provided as a vial: Prior to administration of study vaccine, the unblinded pharmacist should use rapid, horizontal hand-shaking for up to 5 seconds while holding the vial in between the thumb and index finger to obtain a homogenous white suspension. This action should be repeated, as necessary. If appearance is otherwise, the vaccine should not be administered.

The vaccine should not be used if the vaccine cannot be resuspended.

Study vaccine will be administered as a single 0.5-mL intramuscular injection in the deltoid region of the participant's arm. Prevnar 13™ will be supplied as a pre-filled syringe. 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 vaccines, which includes all safety follow-up procedures. All safety and immunogenicity assessments will be conducted by blinded personnel, and the participant and/or participant's parent/guardian will be blinded to the study vaccine received by the participant. Vaccination information, such as Component Identification Number and time of vaccination, must be recorded on the appropriate eCRF as per the Data Entry Guidelines.

8.1.8.1 Timing of Dose Administration

V114 or Prevnar 13™ will be administered as indicated in Section 1.3. All participants will be observed for 30 minutes postvaccination 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).

Participants must be afebrile for at least 72 hours prior to vaccination.

Blood samples must be collected and pregnancy tests (in WOCBP) must be administered before study vaccination.

8.1.9 Electronic Vaccination Report Card

The eVRC was developed to be administered electronically via a hand-held device. This item was 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 or participant's legally acceptable representative in the use of the eVRC as indicated in Section 1.3.

Body temperatures, injection-site reactions, vaccine-specific complaints, other complaints or illnesses, and concomitant medications or vaccinations will be recorded on the eVRC as described in Section 1.3 and Section 8.3.4. The investigator or delegate will review the data captured on the eVRC with the participant or participant's legally acceptable representative as indicated in Section 1.3.

For the AEs outlined above, the investigator will use the information provided by the participant or participant's legally acceptable representative both on the eVRC, and verbally at the time of eVRC review, to apply the appropriate assessment of intensity as described in Appendix 3.

8.1.10 Telephone Contact Guide for Day 15 Postdose

Site personnel will contact study participants on Day 15 postdose to review eVRC data with the participant or participant's legally acceptable representative. The Day 15 Postdose Telephone Contact Guide will be provided by the Sponsor. This guide is designed to assist site personnel to collect any updates or edits to data previously entered on the eVRC from the participant or participant's legally acceptable representative. Any differences between eVRC data and the clinical database must be clearly explained in the participant's source documentation with an indication of where the information was obtained (eg, from the Day 15 Postdose Telephone Contact with the participant or participant's legally acceptable representative).

8.1.11 Telephone Contact Questionnaire

Site personnel will contact study participants or the participant's legally acceptable representative approximately 6 months after administration 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 discontinue study intervention prior to completion of the protocol-specified vaccinations should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit (Visit 2) 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

A Participant's consent for Future Biomedical Research may be withdrawn by the participant or the participant's legally acceptable representative (as appropriate). A participant's consent may be withdrawn at any time by contacting the principal 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 drug 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 treatment assignment, the

investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (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 that is part of the study design has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

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

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. 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.

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 is 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 for serotypes included in V114 and Prevnar 13™. These endpoints will be tested for all blood draws. 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 GMTs. 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.

Measurement of 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* for the serotypes included in the study vaccines.

8.2.1 Multiplex Opsonophagocytic Assay

The MOPA, developed and published by Professor Moon Nahm (Director of the United States World Health Organization pneumococcal serology reference laboratory and National Institutes of Health pneumococcal reference laboratories), is a multiplexed OPA assay capable of measuring 4 serotypes at a time, against a total of 16 serotypes of pneumococci [Burton, Robert L. and Nahm, Moon H. 2006]. The OPA 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. The Sponsor has developed and optimized the MOPA in a high throughput micro-colony platform. The MOPA assay for all 15 V114 serotypes has undergone validation. The validation study evaluated various performance parameters of the assay including precision, relative accuracy/dilutional linearity, and specificity. The validation results were evaluated against pre-specified acceptance criteria for each of the parameters.

8.2.2 Pneumococcal Electrochemiluminescence

The Sponsor has developed and optimized a multiplex, ECL-based detection method for the quantitation of IgG serotype-specific antibodies to the 15 PnPs serotypes contained in V114. 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 15 serotypes included in V114 is performed using an assay format consisting of 2 groups of 7 and 8 serotypes each. The PnECL v2.0 assay for all 15 serotypes has undergone validation. The validation study evaluated various performance parameters of the assay including precision, ruggedness, relative accuracy, dilutional linearity, selectivity, and specificity. The validation results were evaluated against pre-specified acceptance criteria for each of the parameters.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected 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 with V114 or Prevnar 13™ as indicated in Section 1.3.

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

8.3.2 Pregnancy Test

A pregnancy test consistent with local requirements (sensitive to at least 25 IU beta human chorionic gonadotropin [β-hCG]) must be performed before vaccination in WOCBP as described in Section 1.3. Urine or serum tests can be used, and results must be negative before vaccination can occur.

8.3.3 Body Temperature Measurement

Pre-vaccination body temperature will be taken by study staff as indicated in Section 1.3. Participants who have febrile illness (oral temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring at or within 72 hours of Visit 1 must be rescheduled. Oral is the preferred method of obtaining participant's temperature. Axillary (underarm) is an acceptable method but temperature needs to be confirmed by oral measurement if fever is detected. If an axillary temperature is reported to be ≥37.8°C (≥100.0°F), an oral temperature must be taken. In this case, both axillary and oral temperatures must be recorded on the eVRC. Temperature readings should be taken at approximately the same time each day. Use of temporal or tympanic thermometers to collect temperature for this study is prohibited.

The participant or the participant's legally acceptable representative will be asked to record a body temperature reading on the eVRC from Day 1 through Day 7 postvaccination. Temperature measurement must be recorded in the eVRC if fever is suspected during Day 8 through Day 14 postvaccination.

8.3.4 Safety Assessments and Use of the eVRC

All participants will be observed for 30 minutes after each vaccination for any immediate reactions. If any immediate AEs are observed during this period, the time at which the event occurred within this timeframe, as well as the event itself, any concomitant medications that were administered, and resolution of the event, must be recorded on the appropriate eCRF.

The participant or the participant's legally acceptable representative will use the eVRC (Section 8.1.9) to document the following information:

- Body temperatures measured Day 1 (day of vaccination) through Day 7 postvaccination; Day 8 through Day 14 postvaccination if fever is suspected
- Solicited injection-site AEs (redness, swelling, tenderness, and hard lump) Day 1 through Day 14 postvaccination

- Solicited systemic AEs (muscle pain, joint pain, headache, tiredness, and hives or welts) Day 1 through Day 14 postvaccination
- Any other injection-site or systemic AEs Day 1 through Day 14 postvaccination
- The arm that was used for the administration of V114 or Prevnar 13™ (**Note**: the study will report injection-site AEs from V114 or Prevnar 13™; the location of V114 or Prevnar 13™ administration can be used by the participant or participant's legally acceptable representative to monitor the appropriate limb for injection-site AEs related to V114 or Prevnar 13™)
- Use of any analgesic or antipyretic on the day of vaccination
- Concomitant medications and nonstudy vaccinations Day 1 to Day 14 postvaccination

8.3.5 Clinical 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.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and Section 1.3.
- 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 (AEs), Serious Adverse Events (SAEs), 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 allocation/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 AEs, SAEs, and other reportable safety events must be reported by the investigator from the day of allocation/randomization to the first vaccination and from the day of each vaccination through 14 days postvaccination. SAEs must also be reported throughout the duration of the individual's participation in the study, regardless of whether or not related to the Sponsor's product.

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

1. A death that occurs prior to the participant completing the study.

OR

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

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

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

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

Type of Event	**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	There are no ECIs for this study.		Not required	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 AE and/or SAE 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, 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 wth 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 suspected unexpected serious adverse reactions (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 (ECIs)

There are no events of clinical interest for this study.

8.5 Treatment of Overdose

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

No specific information is available on the treatment of overdose.

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

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 electronic data collection (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant's legally acceptable representative signs the future biomedical research consent and the participant assents if applicable, the following specimens will be obtained as part of future biomedical research:

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

8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

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.

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. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental Statistical Analysis Plan and referenced in the referenced in the Clinical Study Report for the study. Post hoc exploratory analyses will be clearly identified in the Clinical Study Report.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children with Sickle Cell Disease (PNEU-SICKLE).
Intervention Assignment	Participants will be randomly assigned in a 2:1 ratio to V114 or Prevnar 13™, respectively.
Analysis Populations	**Immunogenicity**: Per-Protocol (PP) **Safety**: All Participants as Treated (APaT)

Primary Endpoint(s)	**Immunogenicity**: Anti-PnPs Serotype-specific IgG GMCs at 30 days postvaccination (Day 30) **Safety**: • Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 following V114 or Prevnar 13™ • Proportion of participants with solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, tiredness/fatigue, and hives or welts/urticarial) from Day 1 through Day 14 following V114 or Prevnar 13™ • Proportion of participants with vaccine-related SAEs from Day 1 through completion of study participation following V114 or Prevnar 13™
Key Secondary Endpoints	**Immunogenicity**: • Anti-PnPs serotype-specific OPA GMTs for the 15 serotypes contained in V114 at 30 days postvaccination (Day 30) • Anti-PnPs serotype-specific GMFR from prevaccination (Day 1) to 30 days postvaccination for both OPA and IgG responses
Statistical Methods for Key Immunogenicity Analyses	Immunogenicity analyses will be conducted for each of the 15 pneumococcal serotypes contained in V114 separately. To address the primary immunogenicity objective, evaluation of the IgG GMCs at 30 days postvaccination with V114 or Prevnar 13™ will include descriptive summaries. The point estimates will be calculated by exponentiating the estimates of the mean of the natural log values and the within-group CIs will be derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution. A similar statistical approach will be used to evaluate the OPA GMTs at 30 days postvaccination with V114 or Prevnar 13™ (Day 30).
Statistical Methods for Key Safety Analyses	The analysis strategy for safety parameters following vaccination is described in Section 9.6.2. Safety parameters will be summarized via descriptive statistics. In addition, for select safety parameters, 95% within-group CIs will be provided.
Interim Analyses	To support the periodic review of safety and tolerability data across the V114 Phase 3 program, an external unblinded statistician will provide unblinded interim safety summaries to an independent DMC for their review. There are no plans to conduct an interim analysis of unblinded immunogenicity data in this study. However, unblinded immunogenicity data will be made available to the DMC upon request to enable a benefit-risk assessment.
Multiplicity	No multiplicity adjustment is planned.

Sample Size and Power	**Immunogenicity**: The planned sample size is 100 participants. Participants are to be randomly assigned in 2:1 ratio to V114 or Prevnar 13™, respectively (resulting in approximately 67 participants in the V114 group and 33 participants in the Prevnar 13™ group). It is assumed that approximately 54 participants in the V114 group and 26 in the Prevnar 13™ group will be evaluable for the PP immunogenicity analyses at Day 30 (80% evaluability rate). There are no hypotheses to be evaluated for primary objectives. Section 9.9.1 provides information about the expected variability of IgG GMCs given the sample size. **Safety**: Section 9.9.2 provides information about the ability of this study to estimate the incidence of AEs within the V114 group.

9.2 Responsibility for Analyses/In-house Blinding

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

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

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

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

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

9.4.1 Immunogenicity Endpoints

A description of immunogenicity assessments is presented in Section 8.2.

Immune responses will be measured for each of the following serotypes contained in V114: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F.

The primary immunogenicity analysis endpoints are the anti-PnPs serotype-specific IgG GMCs at 30 days postvaccination with V114 or Prevnar 13™.

The secondary immunogenicity analysis endpoints include:

- Anti-PnPs serotype-specific OPA GMTs at 30 days postvaccination
- Anti-PnPs serotype-specific GMFR from prevaccination (Day 1) to 30 days postvaccination for both OPA and IgG responses

9.4.2 Safety Endpoints

A description of safety measures is presented in Section 8.3 and Section 8.4. The analysis of safety results is described in Section 9.6.2.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements following V114 or Prevnar 13™.

The safety analysis endpoints include:

- Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 postvaccination with V114 or Prevnar 13™
- Proportion of participants with solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, and tiredness/fatigue, and hives or welts/urticaria) from Day 1 through Day 14 postvaccination with V114 or Prevnar 13™
- Proportions of participants with the broad AE categories consisting of any AE, a vaccine-related AE, a SAE, an AE which is both vaccine-related and serious, and discontinuation due to an AE and the proportion of participants who died
- Proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 7 postvaccination with V114 or Prevnar 13™

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

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

- Failure to receive any study vaccine at Visit 1 (Day 1)
- Failure to receive correct clinical material as per randomization schedule (ie, participants who were cross-treated)

- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination

Additional potential deviations that may result in the exclusion of a participant from the PP population for specific immunogenicity analyses (depending on the time point) include:

- Receipt of a prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of a blood sample outside of the pre-specified window (as described in Section 1.3)

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

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

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least 1 dose of study vaccination. Participants will be included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. This will be the group to which they are randomized except for participants who take incorrect study vaccination; such participants will be included in the treatment group corresponding to the study vaccination actually received.

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

9.6 Statistical Methods

Statistical testing and inference for immunogenicity and safety analyses are described in Section 9.6.1 and Section 9.6.2, respectively. Section 9.6.3 describes how demographic and baseline characteristics will be summarized.

9.6.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the primary and secondary immunogenicity objectives. Methods related to exploratory objectives will be further described in the supplemental statistical analysis plan.

Immunogenicity analyses will be conducted for each of the 15 pneumococcal serotypes contained in V114 separately. To address the primary immunogenicity objective, evaluation

of the serotype-specific IgG GMCs at 30 days postvaccination will include descriptive summaries and within-group 95% confidence intervals (CIs) to be calculated for each vaccination group. Point estimates for the IgG GMCs will be calculated by exponentiating the estimates of the mean of the natural log values. The within-group CIs will be derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

A similar statistical approach will be used to evaluate serotype-specific OPA GMTs at 30 days postvaccination for each vaccination group. Point estimates of serotype-specific GMFR and its associated 95% CI will be calculated based on the t-distribution of natural log-transformed fold rise.

Reverse cumulative distribution curves for OPA titers and IgG concentrations will be graphically displayed by serotype at Day 30.

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

Table 4 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
Anti-PnPs IgG GMCs at Day 30	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints				
Anti-PnPs OPA GMTs at Day 30	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
GMFR from Day 1 to Day 30 for both OPA and IgG responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

[†] P = primary approach; S = supportive approach.

CI = confidence interval; FAS = Full Analysis Set; GMC = Geometric Mean Concentration; GMFR = Geometric Mean Fold Rise; GMT = Geometric Mean Titer; IgG = immunoglobulin G; OPA = opsonophagocytic activity; PnPs = pneumococcal polysaccharide; PP = Per-Protocol.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis strategy for safety parameters following each vaccination is summarized in Table 5. The proportion of participants with solicited injection-site AEs (redness/erythema, swelling, tenderness/pain, and hard lump/induration Day 1 to Day 14 postvaccination) and solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, tiredness/fatigue, and hives or welts/urticarial from Day 1 to Day 14 postvaccination) will be provided along with the corresponding within-group 95% CIs (based on the exact binomial method proposed by Clopper and Pearson [Collett, D. 1999]. In addition, the broad AE categories consisting of the proportion of participants with any AE, a vaccine-related AE, an SAE, an AE which is both vaccine-related and serious, discontinuation due to an AE, and the proportion of participants who died will be summarized in the same manner. The proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points (from Day 1 through Day 7) will also be provided along with the corresponding within-group 95% CIs. Point estimates by vaccination group will be provided for all other safety parameters (specific AE terms and system organ class terms).

The analysis of safety parameters will be evaluated following administration of V114 or Prevnar 13™ (Day 30). Descriptive summaries of AEs following administration of V114 or Prevnar 13™ will include non-serious AEs within 14 days of vaccination and SAEs occurring Day 1 through completion of study participation (end of the study).

Table 5 Analysis Strategy for Safety Parameters Following Each Vaccination

Safety Endpoint	95% CI for Within-Group Comparison	Descriptive Statistics
Injection-site redness/erythema (Days 1 to 14)†	X	X
Injection-site swelling (Days 1 to 14)†	X	X
Injection-site tenderness/pain (Days 1 to 14)†	X	X
Injection-site hard lump/induration (Days 1 to 14)	X	X
Muscle pain/myalgia (Days 1 to 14)†	X	X
Joint pain/arthralgia (Days 1 to 14)†	X	X
Headache (Days 1 to 14)†	X	X
Tiredness/fatigue (Days 1 to 14)†	X	X
Hives or welts/urticaria (Days 1 to 14)	X	X
Any AE‡	X	X
Any vaccine-related AE‡	X	X
Any SAE‡	X	X
Any vaccine-related SAE‡	X	X
Discontinuation due to AE‡	X	X
Death‡	X	X
Maximum temperature measurements meeting the Brighton Collaboration cut points (Days 1 to 7)	X	X
Specific AEs by SOCs and PT		X

† Includes solicited events only.
‡ These endpoints are broad adverse event 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.
AE = adverse event; CI = confidence interval; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; X = results will be provided.

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

9.6.3 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

A periodic review of safety and tolerability data across the V114 Phase 3 pediatric program will be conducted by an independent, unblinded, external DMC. A description of the structure, function, and guidelines for decision-making by the DMC, along with the timing and content of the safety reviews will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1. There are no plans to conduct an interim analysis of unblinded immunogenicity data in this study. However, unblinded immunogenicity data will be made available to the DMC upon request to enable a benefit-risk assessment.

Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to intervention assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician performing interim analyses.

The DMC will serve as the primary reviewer of the results of the safety interim analyses and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor (see Appendix 1 for details on the Committees Structure for this study). If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this Executive Oversight Committee (EOC) of the Sponsor (and potentially other limited Sponsor personnel) may be unblinded to results at the intervention level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the external unblinded statistician. Additional logistical details will be provided in the DMC Charter.

Intervention-level results from the safety interim analysis will be provided by the external unblinded statistician to the DMC. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

9.8 Multiplicity

No adjustment will be made for multiplicity.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

This is a descriptive study**.** The planned sample size is 100 participants. Participants are to be randomly assigned in 2:1 ratio to V114 (67 participants) or Prevnar 13™ (33 participants). It is assumed that approximately 54 participants in the V114 group and 26 in the Prevnar 13™ group will be evaluable for PP immunogenicity analyses at Day 30 (based on an 80% evaluability rate).

The width of the within-group 95% CIs for the serotype-specific IgG GMCs depends on the sample size, variability of the natural log concentrations, and the magnitude of the IgG GMC. In Table 6, 95% CIs for various hypothetical IgG GMCs at 30 days postvaccination and various hypothetical standard deviation estimates for the natural log titers are displayed.

Table 6 Within-Group 95% CIs for Varying Hypothetical IgG GMCs and Varying Standard Deviations

Standard Deviation of Natural Log Titers[†]	Observed Serotype-specific IgG GMC[†]					
	1		5		10	
	V114	Prevnar 13™	V114	Prevnar 13™	V114	Prevnar 13™
1.0	(0.76, 1.31)	(0.67, 1.50)	(3.81, 6.57)	(3.34, 7.49)	(7.61, 13.14)	(6.68, 14.98)
1.5	(0.66, 1.51)	(0.55, 1.83)	(3.32, 7.53)	(2.73, 9.16)	(6.64, 15.06)	(5.46, 18.33)
2.0	(0.58, 1.73)	(0.45, 2.24)	(2.90, 8.63)	(2.23, 11.22)	(5.79, 17.26)	(4.46, 22.43)

[†] The estimates of the standard deviation and IgG GMC ratio are representative of those observed in a previous MSD study.
Based on 54 evaluable participants in the V114 group and 26 evaluable participants in the Prevnar 13™ group.
CI = confidence interval; GMC = Geometric Mean Concentration.

9.9.2 Sample Size and Power for Safety Analyses

The sample size was selected to achieve a reasonably sized safety database in this population exposed to V114. The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying percentage of participants with a SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 67 participants in the V114 group if the underlying incidence of a SAE is 2.4% (1 of every 42 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 67 participants in the V114 group if the underlying incidence of a SAE is 1.0% (1 of 97 every participants receiving the vaccine). If no SAEs are observed among the 67 participants in the V114 group, this study will provide 97.5% confidence that the

underlying percentage of participants with a SAE is <5.4 % (1 in every 19 participants) in the V114 group.

9.10 Subgroup Analyses

Subgroup analyses (eg, sex = female vs male) will be performed for the primary immunogenicity endpoint and selected safety endpoints (summary of AEs). Details of subgroup analyses will be documented in the supplemental Statistical Analysis Plan.

9.11 Compliance (Medication Adherence)

Given that participants will receive a single dose of V114 or Prevnar 13™, compliance will not be calculated. However, the number and proportion of randomized participants receiving each vaccination will be summarized (Section 9.12).

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V114 or Prevnar 13™.

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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. 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 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 general principles of 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-noncompliance 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 primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

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

III. Participant Protection

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

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

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 representative), 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 to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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 Scientific Advisory Committee

This study was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the external DMC regarding the study.

10.1.4.3 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (see Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

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

10.1.5 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 Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (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 Studies.

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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed according to local requirements.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Other Screening Tests	• Serum or urine β-hCG pregnancy test (as needed for WOCBP)

β-hCG = β human chorionic gonadotropin; WOCBP = woman/women of childbearing potential.

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, or are 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."

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.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

- Injection site redness or swelling from the day of vaccination through Day 5 postvaccination will be evaluated by maximum size.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This 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 electronic data collection (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 and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

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

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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 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

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use 1 of the contraception methods described in Table 8 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 8 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception[b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen only hormonal contraception[b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant[b] ● Intrauterine hormone-releasing system[b] ● Intrauterine device ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner 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.
● 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.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). b. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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 8.8 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 drugs/vaccines may interact with
- 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 the future biomedical research substudy

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 this substudy. 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 principal 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
AE	adverse event
APaT	all participants as treated
B-hCG	beta human chorionic gonadotropin
CI	confidence interval
CRF	case report form
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECL	electrochemiluminescence
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EOC	Executive Oversight Committee
eVRC	electronic Vaccination Report Card
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
FAS	full analysis set
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFRs	geometric mean fold rises
GMT	geometric mean titers
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IPD	invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
MSD	Merck Sharp & Dohme Corp.
MOPA	multiplexed opsonophagocytic assay
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate disease
PnECL	pneumococcal electrochemiluminescence
PnPs	pneumococcal polysaccharide
PP	per protocol
PY	person-years
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SCD	sickle cell disease
SoA	schedule of activities
WOCBP	woman/women of childbearing potential

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Supplemental Statistical Analysis Plan (sSAP)

Table of Contents

List of Tables

1. INTRODUCTION

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

2. SUMMARY OF CHANGES

2.1 Summary of Changes from Protocol SAP

A summary of changes is provided in the table below:

Section	Description of Change	Rationale
Section 3.4.2 Safety Endpoints	Added a paragraph to specify the timeframe associated with the reporting of AEs.	Revisions made for clarity.
Section 3.5.1 Immunogenicity Analysis Populations	Updated one sentence in this section from "The FAS population consists of all randomized participants who received the study vaccination and have at least 1 serology result" to "The FAS population consists of all randomized participants who received the study vaccination and have at least 1 serology result at the time point for the analysis."	Revisions made to clarify the criteria for inclusion in the FAS population.
Section 3.6.1 Statistical Methods for Immunogenicity Analyses	Added a paragraph and a table (Table 2) to explain how values below the LLOQ or above the ULOQ should be treated in various analyses.	Added to provide additional statistical analysis details/data derivations.
Section 3.6.2 Statistical Methods for Safety Analyses	Added a paragraph to explain the rationale for not including laboratory AEs in the summary tables.	Added to provide additional statistical analysis details/data derivations.
Section 3.6.2 Statistical Methods for Safety Analyses	Added a paragraph to describe an additional supportive analysis of the proportion of participants with solicited complaints using the data collected directly from participants via the VRC.	Added to provide additional statistical analysis details/data derivations.
Section 3.10 Subgroup Analyses	Added details of subgroup analyses.	Added to provide additional statistical analysis details/data derivations.
Throughout	Corrected minor typographical and grammatical errors.	Revisions made for accuracy.

2.2 Summary of Changes from Previous Versions of the sSAP

Previous Version	Current Version	Section	Description of Change	Rationale
None	30 Sep 2020	Not Applicable	Not Applicable	This is the first version of the sSAP.

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2 through 3.12.

Study Design Overview	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children with Sickle Cell Disease (PNEU-SICKLE).
Intervention Assignment	Participants will be randomly assigned in a 2:1 ratio to V114 or Prevnar 13™, respectively.
Analysis Populations	**Immunogenicity**: Per-Protocol (PP) **Safety**: All Participants as Treated (APaT)
Primary Endpoint(s)	**Immunogenicity**: Anti-PnPs Serotype-specific IgG GMCs at 30 days postvaccination (Day 30) **Safety**: • Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 following V114 or Prevnar 13™ • Proportion of participants with solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, tiredness/fatigue, and hives or welts/urticaria) from Day 1 through Day 14 following V114 or Prevnar 13™ • Proportion of participants with vaccine-related SAEs from Day 1 through completion of study participation following V114 or Prevnar 13™
Key Secondary Endpoint(s)	**Immunogenicity**: • Anti-PnPs serotype-specific OPA GMTs for the 15 serotypes contained in V114 at 30 days postvaccination (Day 30) • Anti-PnPs serotype-specific GMFR from prevaccination (Day 1) to 30 days postvaccination for both OPA and IgG responses
Statistical Methods for Key Immunogenicity Analyses	Immunogenicity analyses will be conducted for each of the 15 pneumococcal serotypes contained in V114 separately. To address the primary immunogenicity objective, evaluation of the IgG GMCs at 30 days postvaccination with V114 or Prevnar 13™ will include

	descriptive summaries. The point estimates will be calculated by exponentiating the estimates of the mean of the natural log values and the within-group CIs will be derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution. A similar statistical approach will be used to evaluate the OPA GMTs at 30 days postvaccination with V114 or Prevnar 13™ (Day 30).
Statistical Methods for Key Safety Analyses	The analysis strategy for safety parameters following vaccination is described in Section 3.6.2. Safety parameters will be summarized via descriptive statistics. In addition, for select safety parameters, 95% within-group CIs will be provided.
Interim Analyses	To support the periodic review of safety and tolerability data across the V114 Phase 3 program, an external unblinded statistician will provide unblinded interim safety summaries to an independent DMC for their review. There are no plans to conduct an interim analysis of unblinded immunogenicity data in this study. However, unblinded immunogenicity data will be made available to the DMC upon request to enable a benefit-risk assessment.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	**Immunogenicity**: The planned sample size is 100 participants. Participants are to be randomly assigned in 2:1 ratio to V114 or Prevnar 13™, respectively (resulting in approximately 67 participants in the V114 group and 33 participants in the Prevnar 13™ group). It is assumed that approximately 54 participants in the V114 group and 26 in the Prevnar 13™ group will be evaluable for the PP immunogenicity analyses at Day 30 (80% evaluability rate). There are no hypotheses to be evaluated for primary objectives. Section 3.9.1 provides information about the expected variability of IgG GMCs given the sample size. **Safety**: Section 3.9.2 provides information about the ability of this study to estimate the incidence of AEs within the V114 group.

3.2 Responsibility for Analyses/In-House Blinding

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

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

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

Blinding issues related to the planned interim analyses are described in Section 3.7.

3.3 HYPOTHESES/ESTIMATION

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

3.4 ANALYSIS ENDPOINTS

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

3.4.1 Immunogenicity Endpoints

A description of immunogenicity assessments is contained in Section 8.2 of the protocol.

Immune responses will be measured for each of the following serotypes contained in V114: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F.

The primary immunogenicity analysis endpoints are the anti-PnPs serotype-specific IgG GMCs at 30 days postvaccination with V114 or Prevnar 13™.

The secondary immunogenicity analysis endpoints include:

- Anti-PnPs serotype-specific OPA GMTs at 30 days postvaccination
- Anti-PnPs serotype-specific GMFR from prevaccination (Day 1) to 30 days postvaccination for both OPA and IgG responses

3.4.2 Safety Endpoints

A description of safety measures is presented in Sections 8.3 and 8.4 of the protocol. The analysis of safety results is described in Section 3.6.2.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements following V114 or Prevnar 13™.

The safety analysis endpoints include:

- Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 postvaccination with V114 or Prevnar 13™
- Proportion of participants with solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, and tiredness/fatigue, and hives or welts/urticaria) from Day 1 through Day 14 postvaccination with V114 or Prevnar 13™
- Proportions of participants with the broad AE categories consisting of any AE, a vaccine-related AE, a SAE, an AE which is both vaccine-related and serious, discontinuation due to an AE, and the proportion of participants who died

- Proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 7 postvaccination with V114 or Prevnar 13™

The timeframe associated with the reporting of AEs is consistent with the collection. Nonserious adverse events (NSAEs) are reported from Day 1 through Day 14 following vaccination. SAEs are reported from Day 1 through completion of study participation.

3.5 ANALYSIS POPULATIONS

3.5.1 Immunogenicity Analysis Populations

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

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

Additional potential deviations that may result in the exclusion of a participant from the PP population for specific immunogenicity analyses (depending on the time point for analysis) include:

- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of blood sample outside of the pre-specified window (as described in Section 1.3 of the protocol)

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

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

3.5.2 Safety Analysis Populations

Safety analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least 1 dose of study

vaccination. Participants will be included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. This will be the group to which they are randomized except for participants who take incorrect study vaccination; such participants will be included in the vaccination group corresponding to the study vaccination actually received.

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

3.6 STATISTICAL METHODS

Statistical testing and inference for immunogenicity and safety analyses are described in Section 3.6.1 and Section 3.6.2, respectively. Section 3.6.3 describes how demographic and baseline characteristics will be summarized.

3.6.1 Statistical Methods for Immunogenicity Analyses

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

Immunogenicity analyses will be conducted for each of the 15 pneumococcal serotypes contained in V114 separately. To address the primary immunogenicity objective, evaluation of the serotype-specific IgG GMCs at 30 days postvaccination will include descriptive summaries and within-group 95% confidence intervals (CIs) to be calculated for each vaccination group. Point estimates for the IgG GMCs will be calculated by exponentiating the estimates of the mean of the natural log values. The within-group CIs will be derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

A similar statistical approach will be used to evaluate serotype-specific OPA GMTs at 30 days postvaccination for each vaccination group. Point estimates of serotype-specific GMFR and its associated 95% CI will be calculated based on the t-distribution of natural log-transformed fold rise.

Reverse cumulative distribution curves for OPA titers and IgG concentrations will be graphically displayed by serotype at Day 30.

A detailed analysis strategy for immunogenicity endpoints is listed in Table 1.

Table 1 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
Anti-PnPs IgG GMCs at Day 30	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints				
Anti-PnPs OPA GMTs at Day 30	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
GMFR from Day 1 to Day 30 for both OPA and IgG responses	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

† P = primary approach; S = supportive approach.

CI = confidence interval; FAS = Full Analysis Set; GMC = Geometric Mean Concentration; GMFR = Geometric Mean Fold Rise; GMT = Geometric Mean Titer; IgG = immunoglobulin G; OPA = opsonophagocytic activity; PnPs = pneumococcal polysaccharide; PP = Per-Protocol.

The detectable ranges for OPA and IgG responses differ across serotypes. The limits of quantitation define the range of responses over which the assay provides precise and accurate measurements. Table 2 gives the limits of quantitation defined for each serotype for OPA and IgG responses. For responses smaller than the lower limit of quantitation (LLOQ), half of the LLOQ is used for analysis when calculating the OPA GMTs and IgG GMCs. The value of the LLOQ is used for analysis when calculating the GMFR for OPA and IgG responses. For OPA and IgG responses that are larger than the upper limit of quantitation (ULOQ), a value equal to ULOQ + 1 is used for analysis.

3.6.2 Statistical Methods for Safety Analyses

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

The analysis strategy for safety parameters following each vaccination is summarized in Table 3. The proportion of participants with solicited injection-site AEs (redness/erythema, swelling, tenderness/pain, and hard lump/induration Day 1 to Day 14 postvaccination) and solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, tiredness/fatigue, and hives or welts/urticaria from Day 1 to Day 14 postvaccination) will be provided along with the corresponding within-group 95% CIs (based on the exact binomial method proposed by Clopper and Pearson [Collett, D. 1999]. In addition, the broad AE categories consisting of the proportion of participants with any AE, a vaccine-related AE, an SAE, an AE which is both vaccine-related and serious, discontinuation due to an AE, and the proportion of participants who died will be summarized in the same manner. The proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points (from Day 1 through Day 7) will also be provided along with the

corresponding within-group 95% CIs. Point estimates by vaccination group will be provided for all other safety parameters (specific AE terms and system organ class terms).

The analysis of safety parameters will be evaluated following administration of V114 or Prevnar 13™ (Day 30). Descriptive summaries of AEs following administration of V114 or Prevnar 13™ will include non-serious AEs within 14 days of vaccination and SAEs occurring Day 1 through completion of study participation (end of the study).

Table 3 Analysis Strategy for Safety Parameters

Safety Endpoint	95% CI for Within-Group Comparison	Descriptive Statistics
Injection-site redness/erythema (Days 1 to 14)†	X	X
Injection-site swelling (Days 1 to 14)†	X	X
Injection-site tenderness/pain (Days 1 to 14)†	X	X
Injection-site hard lump/induration (Days 1 to 14)	X	X
Muscle pain/myalgia (Days 1 to 14)†	X	X
Joint pain/arthralgia (Days 1 to 14)†	X	X
Headache (Days 1 to 14)†	X	X
Tiredness/fatigue (Days 1 to 14)†	X	X
Hives or welts/urticaria (Days 1 to 14)	X	X
Any AE‡	X	X
Any vaccine-related AE‡	X	X
Any SAE‡	X	X
Any vaccine-related SAE‡	X	X
Discontinuation due to AE‡	X	X
Death‡	X	X
Maximum temperature measurements meeting the Brighton Collaboration cut points (Days 1 to 7)	X	X
Specific AEs by SOCs and PT		X

† Includes solicited events only.
‡ These endpoints are broad adverse event 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.
AE = adverse event; CI = confidence interval; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; X = results will be provided.

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

Additionally, laboratory AEs will not be reported in summary tables as laboratory testing is not performed as part of the study and, as such, AEs would only be reported spontaneously. A listing of laboratory AEs will be provided.

A supportive analysis summarizing the proportion of participants reporting each of the solicited complaints on the VRC will be conducted in support of the primary safety analyses

that are based on solicited AEs. This supportive analysis will use the methodology specified in Table 3 for solicited AEs. The analysis will be conducted on the subset of the APaT population who entered solicited complaints data on the VRC.

3.6.3 Demographic and Baseline Characteristics

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

3.7 INTERIM ANALYSES

A periodic review of safety and tolerability data across the V114 Phase 3 pediatric program will be conducted by an independent, unblinded, external DMC. A description of the structure, function, and guidelines for decision-making by the DMC, along with the timing and content of the safety reviews will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1 of the protocol. There are no plans to conduct an interim analysis of unblinded immunogenicity data in this study. However, unblinded immunogenicity data from this study and other ongoing V114 clinical studies will be made available to the DMC upon request to enable a benefit-risk assessment.

Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to intervention assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician performing interim analyses.

The DMC will serve as the primary reviewer of the results of the safety interim analyses and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor (see Appendix 1 of the protocol for details on the Committees Structure for this study). If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this Executive Oversight Committee (EOC) of the Sponsor (and potentially other limited Sponsor personnel) may be unblinded to results at the intervention level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the external unblinded statistician. Additional logistical details will be provided in the DMC Charter.

Intervention-level results from the safety interim analysis will be provided by the external unblinded statistician to the DMC. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

3.8 MULTIPLICITY

No adjustment will be made for multiplicity.

3.9 SAMPLE SIZE AND POWER CALCULATIONS

3.9.1 Sample Size and Power for Immunogenicity Analyses

This is a descriptive study. The planned sample size is 100 participants. Participants are to be randomly assigned in 2:1 ratio to V114 (67 participants) or Prevnar 13™ (33 participants). It is assumed that approximately 54 participants in the V114 group and 26 in the Prevnar 13™ group will be evaluable for PP immunogenicity analyses at Day 30 (based on an 80% evaluability rate).

The width of the within-group 95% CIs for the serotype-specific IgG GMCs depends on the sample size, variability of the natural log concentrations, and the magnitude of the IgG GMC. In Table 4, 95% CIs for various hypothetical IgG GMCs at 30 days postvaccination and various hypothetical standard deviation estimates for the natural log titers are displayed.

Table 4 Within-Group 95% CIs for Varying Hypothetical IgG GMCs and Varying Standard Deviations

Standard Deviation of Natural Log Titers[†]	Observed Serotype-specific IgG GMC[†]					
	1		5		10	
	V114	Prevnar 13™	V114	Prevnar 13™	V114	Prevnar 13™
1.0	(0.76, 1.31)	(0.67, 1.50)	(3.81, 6.57)	(3.34, 7.49)	(7.61, 13.14)	(6.68, 14.98)
1.5	(0.66, 1.51)	(0.55, 1.83)	(3.32, 7.53)	(2.73, 9.16)	(6.64, 15.06)	(5.46, 18.33)
2.0	(0.58, 1.73)	(0.45, 2.24)	(2.90, 8.63)	(2.23, 11.22)	(5.79, 17.26)	(4.46, 22.43)

[†] The estimates of the standard deviation and IgG GMC ratio are representative of those observed in a previous MSD study.
Based on 54 evaluable participants in the V114 group and 26 evaluable participants in the Prevnar 13™ group.
CI = confidence interval; GMC = Geometric Mean Concentration.

3.9.2 Sample Size and Power for Safety Analyses

The sample size was selected to achieve a reasonably sized safety database in this population exposed to V114. The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying percentage of participants with a SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 67 participants in the V114 group if the underlying incidence of a SAE is 2.4% (1 of every 42 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 67 participants in the V114 group if the underlying incidence of a SAE is 1.0% (1 of every 97 participants receiving the vaccine). If no SAEs are observed among the 67 participants in the V114 group, this study will provide 97.5% confidence that the

underlying percentage of participants with a SAE is <5.4 % (1 in every 19 participants) in the V114 group.

3.10 SUBGROUP ANALYSES

An overall summary of AEs and a summary of solicited AEs following vaccination will be provided for each subgroup (point estimates only) with more than 10 participants in each vaccination group.

To determine whether the intervention effect is consistent across various subgroups, the estimate of the within-group intervention effect (with a nominal 95% CI) will be summarized for the primary immunogenicity endpoint (IgG GMCs at 30 days postvaccination) for each subgroup with more than 10 participants in each vaccination group.

The following subgroups are planned for evaluation:

- Age category (5 to 9 years, 10 to 14 years, 15 to 17 years)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Multiple, Native Hawaiian or Other Pacific Islander, White
- Sex (Female, Male)

3.11 COMPLIANCE (MEDICATION ADHERENCE)

Given that participants will receive a single dose of V114 or Prevnar 13™, compliance will not be calculated. However, the number and proportion of randomized participants receiving each vaccination will be summarized (Section 3.12).

3.12 EXTENT OF EXPOSURE

The extent of exposure will be summarized by the number and proportion of randomized participants administered V114 or Prevnar 13™.

4. LIST OF REFERENCES

[Collett, D. 1999] Collett D. Statistical inference for binary data. In: Collett D, ed. Modelling Binary Data. New York: Chapman & Hall, 1999:17-42. 03NVVC