Official Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Active-comparator controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 3-dose Regimen of V114 in Healthy Infants (PNEU-PED-EU-2)
NCT number:	NCT04016714
Document Date:	14-Sep-2021

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 a 3-dose Regimen of V114 in Healthy Infants (PNEU-PED-EU-2)

Protocol Number: 026-03

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:

One Merck Drive

P.O. Box 100

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

Regulatory Agency Identifying Number(s):

IND	14115
EudraCT	2018-003788-70

Approval Date: 14 September 2021

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	14-SEP-2021	Amendment to expand the visit windows for Visit 2 (Dose 2 vaccination), Visit 3 (postdose 2 blood draw), Visit 4 (Dose 3 vaccination), and Visit 5 (postdose 3 blood draw) to allow inclusion of more participants in the immunogenicity analysis based on the per-protocol population. This change is being made in response to the COVID-19 global pandemic which impacted the ability of many participants to attend study visits within the prescribed visit windows due to local conditions and travel restrictions.
Amendment 2	12-SEP-2019	This country-specific amendment incorporates feedback received from the Norwegian Health Authority and study investigators in Denmark.
Amendment 1	25-JUL-2019	This country-specific amendment incorporates feedback received from the Swedish Health Agency.
Original Protocol	22-FEB-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

The COVID-19 global pandemic impacted the ability of many participants to attend study visits within the prescribed visit windows due to local conditions and travel restrictions. The primary purpose of this amendment is to expand the visit windows for Visit 2 (Dose 2 vaccination), Visit 3 (postdose 2 blood draw), Visit 4 (Dose 3 vaccination), and Visit 5 (postdose 3 blood draw) to allow inclusion of more participants in the immunogenicity analysis based on the per-protocol population.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Section 10.7.2.2 Schedule of Activities (For Sites in Norway and Denmark Only)	The visit window for Visit 2 (Dose 2 vaccination) and Visit 4 (Dose 3 vaccination) was expanded by 14 days. The visit windows for Visit 3 (postdose 2 blood draw) and Visit 5 (postdose 3 blood draw) were expanded by 18 days.	The expansion of the visit windows will allow inclusion of more participants in the immunogenicity analysis based on the per-protocol population. This change is being made in response to the COVID-19 global pandemic which impacted the ability of many participants to attend study visits within the prescribed visit windows due to local conditions and travel restrictions.
Section 9.5.1 Immunogenicity Analysis Populations	Text describing potential deviations that may result in the exclusion from the PP population immunogenicity analyses at a particular time point was revised to align with the changes to the visits windows for Visit 2 and Visit 4 (vaccination visits).	Revision to align with changes to the visit windows for vaccination visits.

Section # and Name	Description of Change	Brief Rationale
Section 10.8 Appendix 8: Abbreviations	Added COVID-19 to the List of Abbreviations.	Revision made for completeness.
Throughout	Editorial revisions	Changes are minor and have not been summarized individually.

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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 a 3-dose Regimen of V114 in Healthy Infants (PNEU-PED-EU-2)

Short Title: Safety, tolerability, and immunogenicity of V114 in healthy infants

Acronym: PNEUmococcal Conjugate Vaccine Trials: V114-026 (PNEU-PED-EU-2)

Hypotheses, Objectives, and Endpoints:

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

The following objectives and endpoints will be evaluated in healthy infants enrolled at approximately 3 months of age (from 70 to 111 days [inclusive]) administered V114 or Prevenar 13™. The statistical criteria for the primary hypotheses are provided in the table below and for the secondary hypotheses can be found in Section 9.9.1.

Primary Objectives	Primary Endpoints
- Objective: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	Following any vaccination with V114: - 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 compare the anti--pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype--specific IgG threshold value of ≥0.35 µg/mL) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevenar 13™. Hypothesis (H1): V114 is noninferior to Prevenar 13™ for the 13 shared serotypes between V114 and Prevenar 13™ based on response rates at 30 days following Dose 3.	- Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3)

(The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in responses rates [V114 minus Prevenar 13™] to be greater than -0.1). Hypothesis (H2): V114 is superior to Prevenar 13™ for the 2 serotypes unique to V114 based on the response rates at 30 days following Dose 3. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI for the difference in response rates [V114 minus Prevenar 13™] to be greater than 0.1).	
- Objective: To compare anti-PnPs serotype-specific IgG geometric mean concentrations (GMCs) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevenar 13™. Hypothesis (H3): V114 is noninferior to Prevenar 13™ for the 13 shared serotypes between V114 and Prevenar 13™ based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio [V114/ Prevenar 13™] to be greater than 0.5). Hypothesis (H4): V114 is superior to Prevenar 13™ for the 2 serotypes unique to V114 based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio [V114/ Prevenar 13™] to be greater than 2.0).	- Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3

Secondary Objectives	Secondary Endpoints
- Objective: To compare the antigen-specific response rate to each antigen included in Vaxelis™ at 30 days following Dose 3 for participants administered V114 concomitantly with Vaxelis™ versus participants administered Prevenar 13™ concomitantly with Vaxelis™. Hypothesis (H5): Vaxelis™ administered concomitantly with V114 is non-inferior to Vaxelis™ administered concomitantly with Prevenar 13™ at 30 days following Dose 3 for each antigen included in Vaxelis™.	Antibody responses to: - diphtheria toxoid - tetanus toxoid - pertussis toxin (PT) - pertussis filamentous hemagglutinin (FHA) - pertussis fimbriae 2/3 (FIM 2/3) - pertussis pertactin (PRN) - Haemophilus influenzae type b polyribosylribitol phosphate (Hib-PRP) - hepatitis B surface antigen (HBsAg) - poliovirus serotypes 1, 2, and 3 at 30 days PD3 of V114 or Prevenar 13™
- Objective: To evaluate the anti-PnPs serotype-specific- IgG response rates and GMCs at 30 days following Dose 2 by each vaccination group.	- Anti-PnP serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD2
- Objective (OPA Subset): To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) GMTs and response rate at 30 days following Dose 3 by each vaccination group.	- Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at 30 days PD3

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal disease
Population	Healthy infants
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 20 months from the time that written informed consent is provided for the first participant 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 1180 participants will be randomized, with approximately 590 in each intervention group.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Vaccine</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Vaccination Regimen</th><th>Use</th></tr>
<tr><td>V114</td><td>V114</td><td>Refer to IB</td><td>3 doses</td><td>IM</td><td>Single dose at Visits 1, 2, and 4 (~3, 5 and 12 months of age, respectively)</td><td>Experimental</td></tr>
<tr><td>Prevenar 13™</td><td>Prevenar 13™</td><td>Refer to product labeling</td><td>3 doses</td><td>IM</td><td>Single dose at Visits 1, 2, and 4 (~3, 5, and 12 months of age, respectively)</td><td>Experimental</td></tr>
<tr><td colspan="7">Admin = administration; IB = Investigator’s Brochure; IM = intramuscular.
Note: All participants will also receive other pediatric vaccines, including Vaxelis™, M-M-R™II, and VARIVAX™, as part of the study design (Table 1 and Table 2). Tradenames for licensed vaccines may vary depending on where clinical supplies are sourced by the Sponsor.</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>2 intervention groups</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 15 months, from the time the participant’s legally acceptable representative signs the Informed Consent Form (ICF) through the final contact.</td></tr>
</table>

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: Yes

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

1.2 Schema

The study design is depicted in Figure 1. The study design for participants enrolled at sites in Norway and Denmark is provided in Figure 2 (Appendix 7, Section 10.7.2.1).

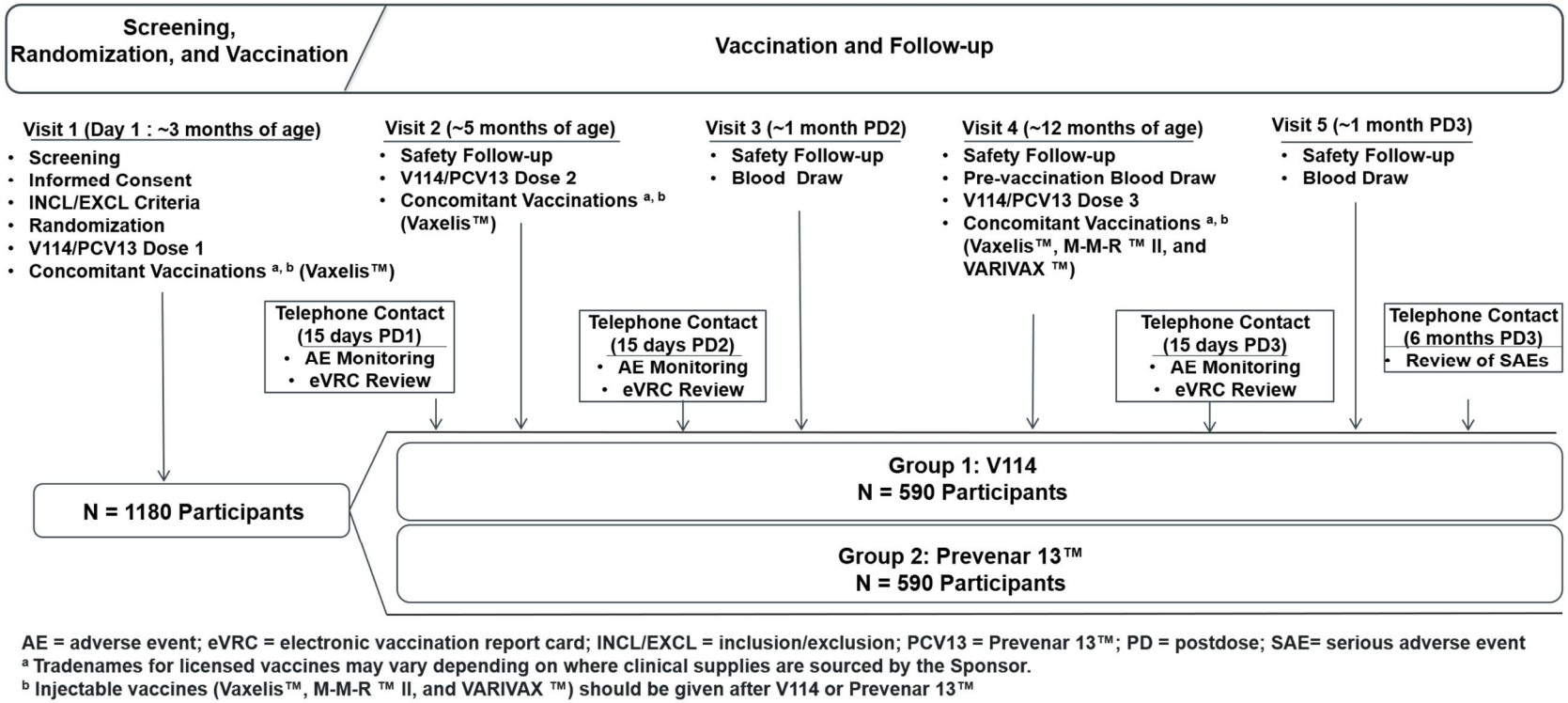


Figure 1 V114-026 Study Design

1.3 Schedule of Activities (SoA)

The schedule of activities for participants enrolled at sites in Norway and Denmark is provided in Appendix 7 (Section 10.7.2.2).

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Administrative and General Procedures										
Screening Procedures										
Informed Consent/Assent	X									Consent must be obtained before any study procedures.
Informed Consent/Assent for Future Biomedical Research	X									Participation in future biomedical research is optional and consent must be obtained before collection of buccal swab DNA samples.
Assignment of Screening Number	X									
Participant Identification Card	X									
Inclusion/Exclusion Criteria	X									Review of prior medications/vaccinations, a complete physical examination, and temperature measurement are required at Visit 1 to determine eligibility.
Medical History	X									

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Post-Randomization Procedures										
Assignment of Randomization Number	X									
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	X	X	X	X	X		
V114 or Prevenar 13™[b] Administration (Blinded)	X		X			X				Before vaccine administration, the investigator (or designee) must review medical history to ensure the participant has no new contraindication to the vaccine(s) scheduled to be given (see Section 8.1.8).

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Concomitant Vaccine Administration (Open-label)[b] • Vaxelis™	X		X			X				Before vaccine administration, the investigator (or designee) must review medical history to ensure the participant has no new contraindication to the vaccine(s) scheduled to be given. (see Section 8.1.8). See Section 6.5 for details on concomitant vaccines. Vaxelis™ should be given after V114 or Prevenar 13™.

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Concomitant Vaccine Administration (Open-label)[b] • M-M-R™II • VARIVAX™						X				Before vaccine administration, the investigator (or designee) must review medical history to ensure the participant has no new contraindication to the vaccine(s) scheduled to be given (see Section 8.1.8). M-M-R™II and VARIVAX™ should be given after V114 or Prevenar 13™ (see Section 6.5).
Provide eVRC	X									An eVRC will be provided at Visit 1 to record AEs, body temperature, concomitant medications, and nonstudy vaccinations. Instructions for using the eVRC will be reviewed with the participant's legally acceptable representative.

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Review eVRC data with participant's legally acceptable representative		X	X	X	X	X	X	X		See Section 8.1.9 for details.
Collect eVRC from participant's legally acceptable representative								X		
Complete the Telephone Contact Questionnaire									X	See Section 8.1.11 for details.
Safety Procedures										
Complete Physical Examination	X									To be performed by the investigator or medically qualified designee before vaccine is administered (see Section 8.3.1).
Targeted Physical Examination			X			X				To be performed by the investigator or medically qualified designee before vaccine is administered (see Section 8.3.1).

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Body Temperature Measurement	X		X			X				Each participant's body temperature must be taken before vaccination (see Section 8.3.2 for method). Participants who have febrile illness at or within 72 hours of vaccination must be rescheduled.
30-minute Postvaccination Observation Period	X		X			X				To be performed by blinded study site personnel only.
AE Monitoring	X	X	X	X	X	X	X	X	X	Nonserious AEs are to be reported from Days 1 through 14 following each vaccination with V114 or Prevenar 13™. SAEs and deaths are to be reported throughout the duration of an individual's study participation.
Immunogenicity Procedures										
Serum for Immunogenicity Assays (Including Retention Serum)					X	X		X		Blood samples must be collected before vaccination where applicable.

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Future Biomedical Research										
Collect Buccal Swabs for Future Biomedical Research	X									Buccal swab DNA samples for analysis should be obtained prior to vaccination at Visit 1, on randomized and FBR consented participants only, or at a later date as soon as the informed consent is obtained.

AE = adverse event; DNA = deoxyribonucleic acid; eVRC = electronic vaccination report card; FBR = Future Biomedical Research; SAE = serious adverse event; TC = telephone contact.

[a] For calculating the visit windows, the day of vaccination is considered Day 1. To calculate visit windows for subsequent vaccinations, confirm participant date of birth and ensure the age of the participant will fall within the appropriate age range for each study visit.

[b] Tradenames for licensed vaccines may vary depending on where clinical supplies are sourced by the Sponsor.

2 INTRODUCTION

Merck Sharp & Dohme Corp. (MSD) is developing an investigational 15-valent pneumococcal conjugate vaccine (PCV) (referred to as V114) for the prevention of pneumococcal disease caused by the serotypes in the vaccine. V114 contains the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) present in the licensed vaccine Prevenar 13™ (pneumococcal 13-valent conjugate vaccine [diphtheria CRM197 protein], Wyeth Pharmaceuticals, a subsidiary of Pfizer, Inc., Philadelphia, PA), plus 2 additional serotypes (22F, 33F).

2.1 Study Rationale

Routine PCV immunization of children is effective in preventing vaccine serotype--specific pneumococcal disease. Despite the availability of PCVs, pneumococcal disease remains a concern as non-vaccine serotypes have emerged in increasing frequency in invasive pneumococcal disease (IPD) isolates. Given the high morbidity and mortality of IPD worldwide, the evolving serotype distribution, and the value of multiple suppliers to strengthen global supply, there is a continued need to develop new PCVs with expanded serotype coverage. V114 includes an additional 2 key serotypes compared with Prevenar 13™ and will address an unmet medical and public health need for a PCV with expanded coverage. This clinical study, to be conducted in healthy infants approximately 3 months of age (70 to 111 days of age), is part of a Phase 3 pediatric clinical program to support an initial registration of V114 for use in healthy infants and children for the prevention of pneumococcal disease caused by the 13 pneumococcal serotypes contained in Prevenar 13™ and the 2 additional serotypes (22F and 33F) in V114.

The purpose of this clinical study is to evaluate the safety and immunogenicity of a 3-dose schedule (2-dose primary series followed by a toddler dose) of PCV as one of the currently recommended by the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunizations and practiced in many countries. Country--specific routine immunization regimens vary by schedule and number of doses. In this study, infants will be given 3 doses of the study vaccine at approximately 3, 5, and 12 months of age.

In most countries, it is recommended that PCVs are to be given at the same time as other recommended pediatric vaccines. The concomitant administration of V114 with recommended pediatric vaccines will be evaluated as part of the Phase 3 pediatric clinical program. This study will evaluate the concomitant administration of V114 and the pediatric vaccine, Vaxelis™. Other routine vaccines (M--M--R™II, and VARIVAX™) will also be provided in the study (Section 6.5). In addition to concomitant vaccines being provided in the study, other nonstudy pediatric vaccines may be permitted according to local, regional, and/or country guidelines.

Countries participating in this study must follow the vaccination schedule being evaluated in the study with respect to PCV and the concomitant vaccines.

2.2 Background

2.2.1 V114 and Pneumococcal Disease

Refer to the IB for detailed background information on V114 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, Prevenar 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 Prevenar 13™ in 2009 (European Union, EU) and Prevnar 13™ 2010 (United States, US). Synflorix™ was licensed in the EU in 2009. Although Prevenar 13™ is indicated for children and adults, Synflorix™ is only indicated for children up to 5 years of age. Widespread use of PCVs has 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 IPD caused by serotypes not contained in currently available vaccines has been observed.

V114 contains all the pneumococcal serotypes contained in Prevenar 13™ plus 2 additional serotypes (22F and 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 Prevenar™ and Prevenar 13™. Approximately 4 years after inclusion of Prevenar™ in the US 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), 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 person-years) [Hicks, L. A., et al 2007]. By 2013, both 22F and 33F were among the leading serotypes causing IPD beyond those already included in Prevenar 13™, accounting for approximately 21% of all IPD in children <5 years of age in the US [Moore, M. R., et al 2015]. Data from 2014 reported in the 2016 annual epidemiological report on IPD by the European Centre for Disease Prevention and Control showed that both serotypes 22F and 33F are among the most common serotypes causing IPD [European Centre for Disease Prevention and Control 2016]. In a systematic review and meta-analysis of serotype distribution of *S pneumoniae* causing invasive disease in children conducted across geographical regions, including Europe, serotypes 22F and 33F were identified among the overall predominant non-Prevenar 13™ serotype [Balsells, E., et al 2017].

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 Prevenar 13™ and other licensed pediatric vaccines administered concomitantly.

Prevenar 13™ contains the 7 pneumococcal serotypes included in Prevenar™ (4, 6B, 9V, 14, 18C, 19F, and 23F) plus 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A).

Prevenar™ and Prevenar 13™ are also known as Prevnar™ and Prevnar 13™ in the US; these vaccines will be referred to as Prevenar™ and Prevenar 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 effectiveness of an investigational medicine.

Approximately 50% of participants will receive 3 doses of Prevenar 13™, the standard of care, as the active comparator in this study. V114 is expected to provide comparable immune responses and a comparable safety profile to Prevenar 13™ for the shared pneumococcal serotypes while providing additional coverage for the 2 serotypes (22F and 33F) unique to V114. It is unknown if the investigational V114 will have the same benefit/risk profile as Prevenar 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 documents. See Appendix 7 for Country-specific requirements for Sweden.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives and endpoints will be evaluated in healthy infants enrolled at approximately 3 months of age (from 70 to 111 days [inclusive]) administered V114 or Prevenar 13™. The statistical criteria for the primary hypotheses are provided in the table below and for the secondary hypotheses can be found in Section 9.9.1.

Objectives	Endpoints
Primary	
• **Objective**: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	Following any vaccination with V114: • 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 compare the anti--pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype--specific IgG threshold value of ≥0.35 µg/mL) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevenar 13™. **Hypothesis (H1):** V114 is noninferior to Prevenar 13™ for the 13 shared serotypes between V114 and Prevenar 13™ based on response rates at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in responses rates [V114 minus Prevenar 13™] to be greater than -0.1). **Hypothesis (H2):** V114 is superior to Prevenar 13™ for the 2 serotypes unique to V114 based on the response rates at 30 days following Dose 3. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI for the difference in response rates [V114 minus Prevenar 13™] to be greater than 0.1).	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3)

Objectives	Endpoints
• **Objective**: To compare anti-PnPs serotype-specific IgG geometric mean concentrations (GMCs) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevenar 13™. **Hypothesis (H3):** V114 is noninferior to Prevenar 13™ for the 13 shared serotypes between V114 and Prevenar 13™ based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio [V114/ Prevenar 13™] to be greater than 0.5). **Hypothesis (H4):** V114 is superior to Prevenar 13™ for the 2 serotypes unique to V114 based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3. (The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio [V114/ Prevenar 13™] to be greater than 2.0).	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3

Objectives	Endpoints
Secondary	
• **Objective:** To compare the antigen-specific response rate to each antigen included in Vaxelis™ at 30 days following Dose 3 for participants administered V114 concomitantly with Vaxelis™ versus participants administered Prevenar 13™ concomitantly with Vaxelis™. **Hypothesis (H5):** Vaxelis™ administered concomitantly with V114 is non-inferior to Vaxelis™ administered concomitantly with Prevenar 13™ at 30 days following Dose 3 for each antigen included in Vaxelis™.	Antibody responses to: • diphtheria toxoid • tetanus toxoid • pertussis toxin (PT) • pertussis filamentous hemagglutinin (FHA) • pertussis fimbriae 2/3 (FIM 2/3) • pertussis pertactin (PRN) • *Haemophilus influenzae* type b polyribosylribitol phosphate (Hib-PRP) • hepatitis B surface antigen (HBsAg) • poliovirus serotypes 1, 2, and 3 at 30 days PD3 of V114 or Prevenar 13™
• **Objective:** To evaluate the anti-PnPs serotype-specific- IgG response rates and GMCs at 30 days following Dose 2 by each vaccination group.	• Anti-PnP serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD2
• **Objective (OPA Subset):** To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) GMTs and response rate at 30 days following Dose 3 by each vaccination group.	• Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at 30 days PD3
Tertiary/Exploratory	
• **Objective:** To evaluate the anti-PnPs serotype-specific IgG GMCs immediately prior to Dose 3 by each vaccination group.	• Anti-PnP serotype-specific IgG responses for the 15 serotypes contained in V114 immediately prior to Dose 3 (Predose 3)

Objectives	Endpoints
• **Objective:** To evaluate the antigen-specific response rate to each antigen included in Vaxelis™ at 30 days following Dose 2 for participants administered V114 concomitantly with Vaxelis™ versus participants administered Prevenar 13™ concomitantly with Vaxelis™.	Antibody responses to: • diphtheria toxoid • tetanus toxoid • pertussis toxin (PT) • pertussis filamentous hemagglutinin (FHA) • pertussis fimbriae 2/3 (FIM 2/3) • pertussis pertactin (PRN) • *Haemophilus influenzae* type b polyribosylribitol phosphate (Hib-PRP) • hepatitis B surface antigen (HBsAg) • poliovirus serotypes 1, 2, and 3 at 30 days PD2 of V114 or Prevenar 13™
• **Objective (OPA Subset):** To evaluate the anti-PnPs serotype-specific OPA GMTs and response rate at 30 days following Dose 2 and immediately prior to Dose 3 by each vaccination group.	• Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at 30 days PD2 and Predose 3

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, parallel-group, multi-site, double--blind (with in-house blinding) study of V114 in healthy infants enrolled at approximately 3 months of age (from 70 to 111 days [inclusive]). Approximately 1180 healthy infant participants will be randomly assigned, in a 1:1 ratio, to receive either V114 (590 participants) or Prevenar 13™ (590 participants).

A 0.5-mL intramuscular dose of V114 or Prevenar 13™ will be administered (blinded) to healthy infants at approximately 3, 5, and 12 months of age. All participants will also be administered concomitant pediatric vaccines (ie, Vaxelis™, M-M-R™II, and VARIVAX™) during the study (Section 1.3). These vaccines will be administered open label.

Participants will be followed for injection-site and systemic AEs through Day 14 following each vaccination with V114 or Prevenar 13™. Information for SAEs and deaths, regardless

of whether the events are considered vaccine related by the investigator, will be collected from the time consent 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 the V114 Phase 3 pediatric program. A description of the structure and function of the DMC, along with the timing and content of the safety reviews will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1.

Blood samples (approximately 5 mL) for immunogenicity assays will be drawn at 3 time points: (1) 30 days after the 2-dose primary series of V114 or Prevenar 13™ (PD2), (2) immediately before receipt of Dose 3 of V114 or Prevenar 13™ administered at Visit 4 (Predose 3), and (3) 30 days following the toddler dose of V114 or Prevenar 13™ (PD3).

After completion of immunogenicity testing to evaluate the study objectives and hypotheses, serum samples will be stored to conduct any additional study-related testing as required by regulatory agencies or the Sponsor. For randomized study participants who provided consent for Future Biomedical Research, leftover sera from the study may be used for other purposes such as the development and/or validation of pneumococcal assays after completion of all study-related immunogenicity testing.

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

4.2 Scientific Rationale for Study Design

This study will be conducted in healthy infants approximately 3 months of age (70 to 111 days of age) at enrollment. These infants are at increased risk for pneumococcal disease and its associated morbidity and mortality [Drijkoningen, J. J 2014]. The study will assess safety, tolerability, and immunogenicity of the 2+1 PCV vaccination schedule and concomitant use with other pediatric vaccines recommended in many countries worldwide. The immune response to Vaxelis™ when administered concomitantly with V114 will also be evaluated in this study.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

The immunogenicity endpoints are consistent with previous studies evaluating PCVs and the concomitantly administered pediatric vaccines in this study.

The pneumococcal electrochemiluminescence (PnECL) assay and the multiplexed opsonophagocytic assay (MOPA) will be used to measure vaccine-induced, anti-PnPs serotype-specific immune responses for all 15 serotypes included in V114. PnECL measures serotype-specific IgG concentrations (primary endpoint based on GMCs), and MOPA measures serotype-specific OPA titers (secondary endpoint based on GMTs). OPA GMTs represent functional antibodies capable of inhibiting growth of *S pneumoniae* in culture. Additional information on the immunogenicity assays can be found in Section 8.2.

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]. Since MOPA requires more serum than the PnECL assay, the PnECL will be used to test the primary immunogenicity hypotheses in this study.

The use of the serotype-specific IgG antibody level of ≥0.35 µg/mL has been recommended by a WHO expert panel as an acceptable threshold value for evaluating the clinical performance of PCVs following a routine childhood vaccination regimen [World Health Organization 2008] [World Health Organization 2005]. The response rate (ie, the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 µg/mL) is a primary endpoint in this study.

Anti-PnPs serotype-specific IgG and OPA responses will be measured at 3 time points:

- Approximately 30 days following Dose 2 to evaluate the immune response to the primary vaccination series (IgG GMCs, IgG response rates, OPA GMTs, and OPA response rates)
- Immediately prior to Dose 3 to evaluate the persistence of protective immunity (IgG GMCs, OPA GMTs, and OPA response rates)
- Approximately 30 days following Dose 3 to evaluate anamnestic antibody responses (IgG GMCs, IgG response rates, OPA GMTs, and OPA response rates)

Measurement at 30 days following Dose 3 was selected for the primary endpoint, as this time point is considered the completion of the PCV series, where immune memory is boosted.

Due to the larger serum requirements of the MOPA assay, functional antibody activity (as by OPA GMTs) will be assessed in the first 20% of all participants with sufficient serum volume at PD2 to evaluate OPA responses (OPA Subset). Additionally, evaluation of OPA responses will be conducted at Predose 3 and PD3 for all participants who had OPA performed at PD2 for whom there is sufficient volume.

In addition, sera from study participants will be used to measure the immune responses to the following antigens contained in the pediatric vaccines administered concomitantly with either V114 or Prevenar 13™:

- Diphtheria toxoid, tetanus toxoid, pertussis (PT, FHA, FIM 2/3, and PRN), Hib-PRP, HBsAg and poliovirus (serotypes 1, 2, and 3) at PD2 and PD3

The endpoints used to evaluate the immune responses to the concomitantly administered pediatric vaccines are consistent with established protective and acceptable antibody levels [Plotkin, S. A. 2010]. For pertussis, there are no benchmark antibody concentrations that are widely accepted as correlates of protection; therefore, the pertussis antigen endpoints are based on previously published standards that are also above assay lower limit of quantitation [Edwards, K. M. 2014].

Results from clinical studies with Prevenar 13™ indicate that Prevenar 13™ can be administered concomitantly with the pediatric vaccines being administered in this study [Bryant, K. A., et al 2013]. Interference between V114 and these vaccines is not anticipated.

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 guidance from regulatory agencies during product development. Data from this study will also contribute to the overall safety database of V114 to support initial licensure in infants. 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 (FDA) Guidance for Industry: Patient-Reported Outcome Measures [U.S. Food and Drug Administration 2009].

Details on the safety endpoints evaluated in this study can be found in Section 8.3.3 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

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. Prevenar 13™ is currently the most widely recommended vaccine for the prevention of pneumococcal disease in infants 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 Prevenar 13™.

4.3 Justification for Dose

The dose and dosing schedule of V114 is similar to that used in previous pediatric V114 clinical studies, which demonstrated safety and comparable immune responses to those of Prevenar 13™. Refer to the V114 IB for details on dosing schedule.

This study will support initial licensure of V114 in countries that use the approved 2+1 Prevenar 13™ dosing schedule for full-term infants (2 doses in infant primary series followed by 1 toddler dose). This schedule has also been recommended by WHO SAGE on Immunizations and implemented in many countries including those in the EU.

4.4 Beginning and End of Study Definition

The overall study begins when written informed consent is provided for the first participant. 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 the number of discontinuations for administrative reasons is too high.

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Healthy male and female infants approximately 3 months of age, from 70 to 111 days (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

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

1. Is healthy (based on review of medical history and physical examination) based on the clinical judgment of the investigator.

Demographics

2. Is male or female, approximately 3 months of age, from 70 days to 111 days inclusive, at the time of signing the informed consent.

Informed Consent

3. Has 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. The legally acceptable representative may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research. See Appendix 7 for Sweden-specific information regarding the informed consent process.

5.2 Exclusion Criteria

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

1. Was born prior to 37 weeks of gestation.

Medical Conditions

2. Has a history of IPD (positive blood culture, positive cerebrospinal fluid culture, or other sterile site) or known history of other culture positive pneumococcal disease.

3. Has a known hypersensitivity to any component of the PCV, any component of the licensed pediatric vaccines to be administered concomitantly in the study, or any diphtheria toxoid containing vaccine.

4. Has any contraindication to the concomitant study vaccines being administered in the study (concomitant vaccine contraindication details provided in the Investigator Trial File Binder).

5. *Had a recent febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring within 72 hours prior to receipt of study vaccine.

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

7. Has a history of congenital or acquired immunodeficiency.

8. Has, or his/her mother has, a documented human immunodeficiency virus (HIV) infection.

9. Has, or his/her mother has, a documented hepatitis B surface antigen – positive test.

10. Has known or history of functional or anatomic asplenia.

11. Has failure to thrive based on the clinical judgment of the investigator.

12. Has a bleeding disorder contraindicating intramuscular vaccination.

13. 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, type 1 diabetes mellitus, or other autoimmune disorders).

14. Has a known neurologic or cognitive behavioral disorder, including encephalitis/myelitis, acute disseminating encephalomyelitis, pervasive development disorder, and related disorders.

Prior/Concomitant Therapy

15. Has received a dose of any pneumococcal vaccine prior to study entry.

16. Has received >1 dose of monovalent hepatitis B vaccine or hepatitis B-based combination vaccine prior to study entry.

17. Has received a dose of any acellular pertussis- or whole cell pertussis-based combination vaccines, *Haemophilus influenzae* type b conjugate vaccine, poliovirus vaccine, or any other combination thereof, prior to study entry.

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

    a. Has received systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/day for persons weighing >10 kg) for ≥14 consecutive days and has not completed this course of treatment at least 30 days prior to the first dose of study vaccine at randomization.

    b. Has received or is expected to receive systemic corticosteroids within 14 days prior to any dose of study vaccine.

    c. Is expected to require systemic corticosteroids within 30 days after any study vaccination during conduct of the study.

    Note: Topical, ophthalmic, and inhaled steroids are permitted.

19. *Has received other licensed non-live vaccines within 14 days before receipt of the first dose of study vaccines.

20. *Has received a licensed live vaccine within 30 days before receipt of the first dose of study vaccines. **Exception**: Rotavirus vaccine may be administered according to local guidelines.

21. Has received a blood transfusion or blood products, including immunoglobulins.

Prior/Concurrent Clinical Study Experience

22. Has participated in another clinical study of an investigational product 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

23. Has any other reason that, in the opinion of the investigator, may interfere with the evaluation required by the study. Reasons may include, but are not limited to, being unable to keep appointments or planning to relocate during the study.

24. Is or has an immediate family member (eg, parent/legal guardian or sibling) 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 whose legally acceptable representative provides consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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, Prevenar 13™, and concomitant vaccines listed in Table 2) 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 Visits 1, 2, and 4	Experimental	IMP	Central
V114	Experimental	Vaxelis™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 4	Experimental	IMP	Central
V114	Experimental	M-M-R™II	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 4	Experimental	NIMP	Central
V114	Experimental	VARIVAX™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 4[a]	Experimental	NIMP	Central
Prevenar 13™	Active Comparator	Prevenar 13™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 4	Experimental	IMP	Central
Prevenar 13™	Active Comparator	Vaxelis™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 4	Experimental	IMP	Central
Prevenar 13™	Active Comparator	M-M-R™II	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visits 4	Experimental	NIMP	Central
Prevenar 13™	Active Comparator	VARIVAX™	Biological/ Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 4[a]	Experimental	NIMP	Central

Arm Name	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin.	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Admin. = administration; IB = Investigator's Brochure; IM = intramuscular; IMP =Investigational medicinal product; NIMP = non-investigational medicinal product; SC = subcutaneous. Definition of IMP and NIMP is based on guidance issued by the European Commission. Regional and/or country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed. [a] Participants enrolled at sites in Norway and Denmark will receive a second dose of VARIVAX™ at Visit 5 according to local vaccination requirements. The second dose of VARIVAX™ may be locally sourced by sites in Norway and Denmark. See Appendix 7 (Section 10.7.2) for country-specific information.											

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. Information on preparation and administration of study vaccines is provided in Section 6.3.3 and Section 8.1.8.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

Because V114 and Prevenar 13™ have a different appearance, a member of the study site staff will be unblinded for the purposes of receiving, maintaining, preparing, and administering these study vaccines. The pediatric vaccines being provided in the study (ie, Vaxelis™, M-M-R™II, and VARIVAX™) will also be prepared and administered by unblinded study site staff for consistency even though these vaccines are being provided open label in this study. Procedures for handling, preparing, and administering the unblinded vaccines are in the Investigator Trial File Binder.

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

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

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified plan for V114, Prevenar 13™, and all concomitant vaccinations, as 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 study (see Section 5.2 for details). Although there are restrictions on licensed vaccines in the exclusion criteria before administration of the first dose of study vaccines, other nonstudy pediatric vaccines (such as rotavirus and influenza vaccines) are permitted during the study according to local, regional, and/or country guidelines. 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's legally acceptable representative.

If a medical condition requires the use of a prohibited steroid regimen, immunoglobulin, blood, or blood products during a subject'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 medication that occurs on the day of vaccination on the eVRC and appropriate eCRF.

All participants will receive licensed pediatric vaccines according to the recommended schedule (Table 2). Countries participating in this study must follow the vaccination schedule being evaluated in the study with respect to PCV and the concomitant vaccines.

Administration of meningococcal vaccine is permitted; however, administration of a meningococcal vaccine with a CRM_{197} or other diphtheria toxoid carrier protein (details provided in the Investigator Trial File Binder) should be given after the final blood draw of the study (Visit 5). Meningococcal B vaccine must not be given within 14 days before or after receipt of V114 or Prevenar 13™, or within 30 days before any scheduled blood draw. During influenza season, it is possible that participants 6 months of age and older could receive an inactivated influenza vaccine. Influenza vaccine should be administered at least 7 days prior to or at least 15 days after the administration of V114 or Prevenar 13™.

If the participant is scheduled to receive any other nonstudy pediatric vaccine (except for rotavirus, meningococcal, and influenza vaccines), the investigator should discuss this with the Sponsor Clinical Director as soon as possible. All nonstudy vaccinations should be recorded on the appropriate eCRF.

Concomitant vaccines should be administered on the same day as V114 or Prevenar 13™. Other nonstudy pediatric vaccines should be administered according to the local recommended schedule. Participants enrolled at sites in Norway and Denmark will receive a second dose of VARIVAX™ at Visit 5 according to local vaccination requirements. See Appendix 7 (Section 10.7.2) for country-specific information. If given at a study visit, oral

vaccines should be administered prior to the study vaccine and other injectable vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines. Other injectable vaccines should be given after V114 or Prevenar 13™. To avoid any confounding results, concomitant injectable vaccines and other nonstudy pediatric vaccines should not be administered in the same limb as V114 or Prevenar 13™. Recommended injection-site locations for V114 or Prevenar 13™ and concomitant injectable vaccines being provided in the study are listed in Table 3. Injection -site AEs for the licensed, concomitantly administered vaccines will not be collected.

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

Table 2 Concomitant Vaccine Schedule

Vaccine Tradename [a, b] **(Generic Name)**	**Indication**	**Visit 1 (~3 months of age)**	**Visit 2 (~5 months of age)**	**Visit 4 (~12 months of age)**
Vaxelis™ (Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus type b conjugate vaccine (adsorbed))	Prevention of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive disease due to *Haemophilus influenzae* type b	X	X	X
M-M-R™II (Measles, Mumps, and Rubella Virus Vaccine Live)	Prevention of measles, mumps, and rubella			X
VARIVAX™ (Varicella Vaccine Live)	Prevention of varicella			X [c]

rDNA = ribosomal deoxyribonucleic acid.

[a] Tradenames for licensed vaccines may vary depending on where clinical supplies are sourced by the Sponsor.

[b] Injectable vaccines administered in the study should be given after V114 or Prevenar 13™.

[c] Participants enrolled at sites in Norway and Denmark will receive a second dose of VARIVAX™ at Visit 5 according to local vaccination requirements. See Appendix 7 (Section 10.7.2) for country-specific information.

Table 3 Recommended Injection-site Location for Study Interventions

Vaccine	**Recommended Injection Site**
V114 or Prevenar 13™	Right thigh
Vaxelis™	Left thigh
M-M-R™II	Deltoid right arm
VARIVAX™	Deltoid left arm

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified vaccination regimen will still continue to participate in the study as specified in Section 1.3, unless the consent is withdrawn for the participant (Section 7.2). A participant may discontinue from study intervention (including receipt of V114, Prevenar 13™, and concomitant vaccines provided in the study) but continue to participate in protocol-specified, AE-monitoring activities (see Section 8.12.3 for details).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.12 and Section 8.12.3.

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

- The participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

For participants who are discontinued from study intervention but continue to be monitored in the study, see Section 1.3 and Section 8.12.3 for those procedures to be completed at each specified visit.

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

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant'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's legally acceptable representative and reschedule the missed visit. If the participant's legally acceptable representative is contacted, the participant's legally acceptable representative should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant's legally acceptable representative at each missed visit (eg, telephone calls and/or a certified letter to the participant's legally acceptable representative 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 be obtained from the participant's legally

acceptable representative. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Approximately 5 ml of blood will be drawn at each of Visits 3, 4, and 5 for immunogenicity assays. The maximum amount of blood collected from each participant over the duration of the study will not exceed approximately15 mL.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

A copy of the signed and dated consent form should be given to the participant's legally acceptable representative before the individual's participation in the study.

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

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.

See Appendix 7 for Sweden-specific information regarding the informed consent process.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant's legally acceptable representative, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant's legally acceptable representative.

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 participation eligibility.

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

8.1.3 Participant Identification Card

The legally acceptable representative for each participant will be given a Participant Identification Card identifying the individual as a participant in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the legally acceptable representative for each participant with a Participant Identification Card immediately after written informed consent is provided. At the time of treatment 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. Note: birth weight (kg) and gestational age will be documented in the participant's medical history.

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. The receipt of hepatitis B vaccine at birth must be reviewed and documented in the participant's chart and recorded in the study database.

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 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 8.3.3.

The administration of pediatric vaccines listed in Table 2 will be recorded on the appropriate eCRF. To avoid any confounding results, concomitant injectable vaccines should not be administered in the same limb as V114 or Prevenar 13™. Documentation of which limb was used for the administration of V114 or Prevenar 13™ must be recorded on the eVRC (Section 8.3.3) and appropriate eCRF. Documentation of injection-site location for the concomitant injectable vaccines must be recorded on the 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

Before each vaccine administration, the investigator (or designee) must review medical history to ensure that the participant has no new contraindication to the vaccine(s) scheduled to be given. This information should be documented in the participant's chart.

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 Prevenar 13™ as specified in the product label.

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

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.

Prevenar 13™ will be supplied as a pre-filled syringe.

A 0.5-mL intramuscular dose of study vaccine will be administered to healthy infants at approximately 3, 5, and 12 months of age. The study vaccines are to be administered at the locations recommended in Table 3 (Section 6.5). Documentation of which limb was used for the administration of V114 or Prevenar 13™ should be recorded on the appropriate eCRF. This information should also be recorded on the eVRC to inform the participant's legally acceptable representative of the appropriate limb to monitor for AEs related to the V114 or Prevenar 13™.

If an abnormality (ie, rash) is observed at the site where the previous dose of the study vaccine was administered, it is permissible to use the anterolateral muscle of the other limb to administer the following dose of the study vaccine. 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 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 Prevenar 13™ will be administered as indicated in Section 1.3. All participants will be observed for at least 30 minutes following each vaccination for any immediate reactions. This observation must be performed by blinded site personnel for V114 and Prevenar 13 ™ (Section 1.3 and Section 6.3.3).

Participants must be afebrile for at least 72 hours prior to vaccination (Section 1.3 and Section 8.3.2).

Blood samples must be collected 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 FDA Guidance for Industry: Patient-Reported Outcome Measures [U.S. Food and Drug Administration 2009]. The investigator or delegate will train the 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 nonstudy vaccinations will be recorded on the eVRC as described in Section 1.3 and Section 8.3.3. The investigator or delegate will review the data captured on the eVRC with the 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'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 Day 15 Postdose Telephone Contact Guide

Site personnel will contact the participant's legally acceptable representative on Day 15 after each vaccination dose of V114 or Prevenar 13™ to review eVRC data. 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'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's legally acceptable representative).

8.1.11 Telephone Contact Questionnaire

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

8.1.12 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the protocol-specified vaccination regimen should be encouraged to continue to be followed for all remaining study visits as outlined in Section 1.3 and Section 8.12.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit (Visit 5) 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

Consent for future biomedical research may be withdrawn by the participant's legally acceptable representative. Consent may be withdrawn by the legally acceptable representative 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's legally acceptable representative of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.13 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity 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.

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

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

8.1.14 Calibration of Equipment

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

8.2 Immunogenicity Assessments

Two immunogenicity assays (PnECL and MOPA) will be used to measure vaccine-induced, anti-PnPs serotype-specific immune responses for all 15 serotypes included in V114.

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

8.2.1 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 (ELISA) 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 prespecified acceptance criteria for each of the parameters.

The WHO Expert Committee on Biological Standardization has recommended that in house assays used in immunogenicity studies designed to evaluate protection against IPD be bridged to the WHO reference assay to maintain the link between immune responses to vaccination and the clinical demonstration of protective efficacy against IPD conferred by the 7 conjugated polysaccharides in Prevenar™. In 2012 and 2014, the Sponsor formally bridged the original PnECL assay to the WHO IgG ELISA in order to determine the PnECL threshold values that correspond to 0.35 µg/mL in the WHO ELISA for each of the 7 Prevenar™ serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) and for each of the additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A) in Prevenar 13™.

A confirmatory study was performed to formally bridge the optimized PnECL assay (v2.0) to the WHO reference ELISA, and to assess the PnECL threshold values that correspond to 0.35 µg/mL measured using the WHO ELISA for each of the serotypes in V114, including the Prevenar 13™ serotypes and serotypes 22F and 33F, which were not previously assessed. The bridging of the optimized PnECL to the WHO ELISA is complete, and the data showed good concordance between the PnECL and WHO ELISA around the 0.35 µg/mL threshold value for all 15 serotypes. It is recommended that a single PnECL threshold value of 0.35 µg/mL be applied to each of the 15 serotypes.

8.2.2 Multiplex Opsonophagocytic Assay

The MOPA, developed and published by Professor Moon Nahm (Director of the US WHO Pneumococcal Serology Reference Laboratory and National Institutes of Health Pneumococcal Reference Laboratory), 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 prespecified acceptance criteria for each of the parameters.

8.2.3 Anti-Diphtheria Toxoid, Tetanus Toxoid, and Pertussis Antigen Serology Assay

The diphtheria, tetanus, and pertussis 6-valent IgG (DTP-6 IgG) assay measures total IgG antibodies specific to the following antigens: pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbriae types 2/3 (FIM 2/3), diphtheria toxoid, and tetanus toxoid.

Antigen-specific immunoglobulin serum antibodies bind directly to the epitopes on antigens covalently conjugated to 6 distinct Luminex microspheres. The measured fluorescent signal of the phycoerythrin-labeled detection antibody is directly proportional to the amount of antigen-specific IgG antibodies present in a serum sample. Samples are read on a Luminex 200 instrument, which identifies the specific Luminex microspheres by their distinct red and infrared fluorescent dye spectral properties. Quantitation of the human IgG antibodies to DTP-6 antigens, or titer, is determined by comparison of the resulting test fluorescence measurement to the reference standard serum which was calibrated to 06/140 for PT, FHA, and PRN, FDA Lot 3 for FIM2/3, to TE-3 for tetanus toxoid and to 00/496 for diphtheria toxoid.

8.2.4 *Haemophilis Influenzae* Type B ELISA

The *Haemophilis influenzae* type b (Hib) IgG ELISA for the in-vitro measurement of specific IgG antibodies against Hib capsular polysaccharide in human serum uses the Vacczyme™ Human Anti-Haemophilus influenzae type b Enzyme Immunoassay Kit purchased from The Binding Site (catalog # MK016), which was further validated for use in clinical trials. The kit contains microtiter wells pre-coated with Hib polysaccharide antigen conjugated to human serum albumin. Diluted serum is added to the microtiter wells and allowed to incubate. After incubation and washing to remove non-bound serum proteins, horseradish peroxidase (HRP)-conjugated rabbit anti-human IgG is added, which binds to any captured Hib-specific IgG molecules. After another wash step, tetramethylbenzidine substrate is added; the ensuing color development reaction is then stopped at a defined time point by the addition of a dilute acid solution. The OD is measured at 450 nm and is directly proportional to the amount of anti-Hib IgG present in the serum specimen. Levels of anti-Hib IgG are quantified by interpolation from a standard curve that has been calibrated to the FDA Lot 1983 reference serum.

8.2.5 Hepatitis B Enhanced Chemiluminescence (ECi) Assay

The purpose of the hepatitis B ECi assay is to detect total antibody to human plasma-derived HBsAg subtypes ad and ay after vaccination with HBsAg-containing vaccine(s). This is the primary assay used to evaluate the serological response to the vaccine(s). The assay is a solid phase sandwich enzyme-labeled immunoassay. Results for the assay are reported in mIU/mL.

This assay involves the reaction of anti-HBs in a test sample with HBsAg (ad and ay subtypes) coated onto the wells. An HRP-labeled HBsAg conjugate (ad and ay subtypes) then forms a complex with the bound anti-HBs, forming an "antigen sandwich". Unbound materials are removed by washing. A reagent that contains luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent will be added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent will increase the level and duration of the light produced. The amount of HRP conjugate bound and subsequent light produced is indicative of the concentration of anti-HBs present in the sample.

Three internally prepared control serum pools, consisting of a high-positive, low-positive, and negative control, will be used to monitor the performance of the assay. These pools will each be prepared from 4 individual human immune sera obtained from an external vendor. Additionally, there will be anti-HBs positive and negative manufacturer-supplied controls, which will be prepared from freeze-dried recalcified human plasma. The hepatitis B WHO International reference standard at 10 mIU/mL will also run as a control in every assay. The lower limit of quantification of the assay is 5 mIU/mL.

8.2.6 Micrometabolic Inhibition Test (MIT)-based Virus Neutralization Assay (polio MIT)

The Polio method quantifies neutralizing (functional) antibodies to poliovirus serotypes 1, 2, and 3 in serial dilutions of serum using a MIT-based virus neutralization assay (polio MIT). The polio MIT assay quantifies the level of neutralizing antibodies to poliovirus type 1, type 2, and type 3 in human sera. The process that was validated is an assay method involving challenging serial diluted sera with Poliovirus type 1, type 2, or type 3. Tissue culture cells are then added to the serum-virus mixture, incubated for 6 to 8 days, and the ability of the sera to neutralize the cytotoxic effects of a particular type of poliovirus is determined. Poliovirus exerts a profound shut down of normal cell function. Metabolism and CO_2 production are stopped in mammalian cells infected with virus; consequently, the pH remains at 7.4 or higher as indicated by the red color of the phenol red indicator in the cell culture medium. Control cells that are incubated with antibody that neutralizes the virus, metabolize and produce CO_2 in normal amounts, lowering the pH of the cell culture medium to <7.0 and changing the color of the pH indicator to yellow. Therefore, poliovirus neutralizing antibody titers correlate with the ability of the serum to neutralize viral infectivity, which prevents the metabolic effects of infection on mammalian cells. Results are determined by the inverse serum dilution where the change in pH occurs, ranging from a titer of 4.0 to 65,536.0.

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) at Visit 1 for all participants. A targeted physical examination will be performed at subsequent vaccination visits as indicated in Section 1.3. Any clinically significant abnormality will be recorded on the appropriate eCRF.

Complete and targeted physical examination procedures include obtaining vital signs (heart rate, respiratory rate, and rectal temperature), auscultation of the heart and lung, and examination of the abdomen. In addition, a complete physical examination will include an assessment of the head, eyes, ears, nose and throat, skin, lymph nodes, neurological system, and musculoskeletal system.

Findings related to the physical examinations should be documented in the participant's chart/source documentation.

8.3.2 Body Temperature Measurements

Pre-vaccination rectal temperatures will be taken by study staff as indicated in Section 1.3. Participants who have febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) within 72 hours of vaccination must be rescheduled.

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

Rectal is the preferred method of obtaining participant's temperature. Axillary (underarm) is an acceptable method but temperature needs to be confirmed by rectal measurement if fever is detected. If an axillary temperature is reported to be ≥37.8°C (≥100.0°F), a rectal temperature must be taken. In this case, both axillary and rectal 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.

8.3.3 Safety Assessment and use of the eVRC

All participants will be observed for at least 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 limb that was used for the administration of V114 or Prevenar 13™ will be recorded in the eVRC (Note: the study will report injection-site AEs from V114 or Prevenar 13™ only; the location of V114 or Prevenar 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 Prevenar 13™).

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

- Rectal temperatures measured Day 1 (day of vaccination) through Day 7 following each vaccination; Day 8 through Day 14 following each vaccination if fever is suspected.
- Solicited injection-site AEs (swelling, redness, pain or tenderness, and hard lump) Day 1 through Day 14 postvaccination.
- Solicited systemic AEs (irritability, drowsiness, appetite lost, and hives or welts) Day 1 through Day 14 postvaccination.
- Any other unsolicited injection-site or systemic AEs Day 1 through Day 14 postvaccination.
- Use of any analgesic or antipyretic on the day of vaccination.
- Concomitant medications and nonstudy vaccinations Day 1 to Day 14 postvaccination.

8.3.4 Clinical Safety Laboratory Assessments

There are no laboratory safety evaluations required by the protocol.

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:

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

OR

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

Table 4 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	Not applicable since participants are infants.			
Event of Clinical Interest	There are no ECIs for this study.			Not applicable
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events,

including 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

Information in this section is not applicable since participants are infants.

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

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Planned Genetic Analysis Sample Collection

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

8.10 Future Biomedical Research Sample Collection

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

- Buccal swab DNA for future research
- Leftover study serum at the central laboratory stored for future research after aliquoting samples for completion of immunogenicity testing

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 as outlined in Section 1.3.

8.12.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3.

If the participant develops a new clinical condition during the study that makes him/her ineligible for the study, the investigator should discuss with the Sponsor Clinical Director as soon as possible. The decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant's legally acceptable representative.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

A participant may discontinue from study intervention (including receipt of V114, Prevenar 13™, and concomitant vaccines provided in the study) but continue to participate in protocol-specified, AE-monitoring activities as outlined in Section 1.3, as long as the participant's legally acceptable representative does not withdraw consent. Blood draws for immunogenicity testing could occur if agreed to by the participant's legally acceptable representative at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Council for Harmonisation [ICH] Guideline E-9). Changes to exploratory or other non-confirmatory 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 Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan are summarized below; the comprehensive plan is provided in 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 a 3-dose Regimen of V114 in Healthy Infants (PNEU-PED-EU-2)
Treatment Assignment	Participants will be randomly assigned in a 1:1 ratio to V114 or Prevenar 13™, respectively.
Analysis Populations	**Immunogenicity:** Per-Protocol (PP) **Safety:** All Participants as Treated (APaT)
Primary Endpoint(s)	**Immunogenicity:** • Anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days PD3 • Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 **Safety:** • Proportion of participants with solicited injection--site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™ • Proportion of participants with solicited systemic AEs (irritability, drowsiness/somnolence, appetite lost/decreased appetite, and hives or welts/urticaria) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™ • Proportion of participants with vaccine-related SAEs from Day 1 through completion of study participation
Key Secondary Endpoints	• Antigen-specific responses for all antigens included in Vaxelis™ at 30 days PD3 of V114 or Prevenar 13™ for participants administered V114 concomitantly with Vaxelis™ versus participants administered Prevenar 13™ concomitantly with Vaxelis™ • Anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) and GMCs for the 15 serotypes contained in V114 at 30 days PD2
Statistical Methods for Key Immunogenicity	To address the primary immunogenicity non-inferiority/superiority objectives (H1 and H2), the comparison between groups will be made based on the proportion of anti-PnPs serotype-specific IgG ≥0.35 µg/mL for the 15 serotypes contained in V114 at 30 days PD3. The between-treatment difference (V114 minus Prevenar 13™) and its 95% CI will be calculated using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985]. To address the primary immunogenicity non-inferiority/superiority objectives (H3 and H4), the comparison between groups will be made based on serotype-specific IgG GMCs for the 15 serotypes contained in V114 at 30 days PD3. The estimation of the IgG GMC ratios and computation of the corresponding 95% CIs will be calculated using the t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody concentration as the response and a single term for vaccination group.

	To address the secondary objectives regarding the non-inferiority evaluation of concomitant antigens contained in Vaxelis™ at 30 days PD3, the comparison between groups will be made based on the proportion of participants achieving the antigen-specific antibody threshold value described in Section 9.9.1. The between-treatment difference (V114 minus Prevenar 13™) and the corresponding 95% CIs will be calculated using the M&N method [Miettinen, O. and Nurminen, M. 1985]. All hypothesis testing, including both non-inferiority and superiority, will be based on the lower bound of the 2-sided 95% CI to be greater than the prespecified margins listed in Section 9.9.1.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. p--values (Tier 1 endpoints) and 95% CIs (Tier 1 and Tier 2 endpoints) will be provided for between-vaccination group differences in the percentage of participants with events; these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	To support the periodic review of safety and tolerability data across the V114 Phase 3 pediatric program, an external unblinded statistician will provide unblinded interim safety summaries to an independent external 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	The study will be considered to have met its primary immunogenicity objective if non-inferiority is demonstrated with respect to IgG GMCs and response rates for the 13 shared serotypes and superiority is demonstrated respect to IgG GMCs and response rates for the 2 unique serotypes at 30 days PD3. All hypotheses will be tested individually for each serotype at a 1-sided 0.025- alpha level. This approach controls the 1-sided type---I error rate at 0.025, thus no multiplicity adjustment is required. The study will be considered to have met its secondary objective for a specific concomitant vaccine if non-inferiority is demonstrated for all the antigens included in that concomitant vaccine. No multiplicity adjustments will be made for the safety objective.
Sample Size and Power	The study will randomize participants in a 1:1 ratio to V114 or Prevenar 13™, respectively. The overall sample size will be approximately 1180 with 590 participants into each vaccination group. For primary objectives/hypotheses, the study has >95% power. The overall power for the secondary hypotheses regarding concomitant vaccine evaluation of Vaxelis™ is ~90%. Details are provided in Section 9.9.1.

9.2 Responsibility for Analyses/In-house Blinding

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

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

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

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Immunogenicity and safety analysis endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.4.1 Immunogenicity Endpoints

The primary immunogenicity analysis endpoints include:

- The proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3
- Anti-PnPs IgG GMCs at 30 days PD3

The secondary immunogenicity analysis endpoints include:

- Antigen-specific response rates at 30 days PD3 for all antigens included in Vaxelis™ when administered concomitantly with V114 or Prevenar 13™ (Table 5)
- Anti-PnPs serotype-specific IgG response rates (proportion of participants with IgG ≥0.35 µg/mL) and IgG GMCs at 30 days PD2
- Anti-PnPs serotype-specific OPA GMTs and response rates at 30 days PD3

The exploratory immunogenicity analysis endpoints include:

- Anti-PnPs serotype-specific IgG GMCs for the 15 serotypes contained in V114 Predose 3
- Antigen-specific response rates for all antigens included in Vaxelis™ at 30 days PD2 of V114 or Prevenar 13™
- Anti-PnPs serotype-specific OPA GMTs and response rates at 30 days PD2 and Predose 3

Detailed immunogenicity endpoints for concomitant vaccines are listed in Table 5.

Table 5 Summary of Endpoints for Concomitant Vaccine Antigens

Vaccine	Antigen	Endpoint	Time Point†
Vaxelis™	Diphtheria toxoid	% ≥0.1 IU/mL	PD3
	Tetanus toxoid	% ≥0.1 IU/mL	PD3
	Pertussis – PT	% ≥5 EU/mL	PD3
	Pertussis – FHA	% ≥5 EU/mL	PD3
	Pertussis – FIM 2/3	% ≥20 EU/mL	PD3
	Pertussis – PRN	% ≥5 EU/mL	PD3
	Hib-PRP	% ≥0.15 µg/mL	PD3
	HBsAg	% ≥10 mIU/mL	PD3
	Poliovirus 1	% with Nab ≥1:8 dilution	PD3
	Poliovirus 2	% with Nab ≥1:8 dilution	PD3
	Poliovirus 3	% with Nab ≥1:8 dilution	PD3

EU = endotoxin unit; FHA = filamentous hemagglutinin; FIM 2/3 = fimbriae types 2 and 3; HBsAg = hepatitis B surface antigen; IU = international unit; Nab = neutralizing antibodies; PD = postdose; PRN = pertactin; PRP = polyribosylribitol phosphate; PT = pertussis toxin.

† Same endpoints will be evaluated at PD2 as exploratory analyses.

9.4.2 Safety Endpoints

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

The safety analysis endpoints include:

- Proportion of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportion of participants with solicited systemic AEs (irritability, drowsiness/somnolence, hives or welts/urticaria, and appetite loss/decreased appetite) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportions of participants with the broad AE categories consisting of any AE and a vaccine-related AE from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportions of participants with an SAE, a vaccine-related SAE, and discontinuation due to an AE, and death from Day 1 through 6 months following the vaccination 3 with V114 or Prevenar 13™

- Participants body temperature measured Day 1 (day of vaccination) through Day 7 following any vaccination with V114 or Prevenar 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(s). Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive infant series vaccination (V114 or Prevenar 13™ Doses 1 and 2) as per randomization schedule

- Receipt of prohibited medication or prohibited vaccine prior to the first study vaccination

Additional potential deviations that may result in the exclusion from the PP population immunogenicity analyses at a particular time point include:

- Failure to receive Dose 3 of V114 or Prevenar 13™ according to the vaccination schedule required at the time point for the analysis

- Failure to receive Vaxelis™ according to the vaccination schedule required at the time point for the analysis

- Failure to receive the scheduled doses of V114 or Prevenar 13™ (at least 28 days between Doses 1 and 2 [5 months of age to 1 day prior to 6 months of age (+14 days)] [for PD2 and Predose 3 analysis], 12 months to 1 day prior to 13 months of age [+14 days] for Dose 3 [for PD3 analyses])

- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection

- Collection of blood sample at the time point for the analysis 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 FAS population will also be performed for the primary immunogenicity endpoints and the secondary endpoints for the evaluation of concomitant vaccines. The FAS population consists of all randomized participants who received all study vaccinations required at the time point for the analysis and have serology result. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the FAS population.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one 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. Safety parameters for cross-treated participants (ie, those who received vaccinations of both V114 and Prevenar 13™) will be summarized separately.

At least 1 temperature measurement obtained after study intervention is required for inclusion in the analysis 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. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level. Section 9.6.3 describes how demographic and baseline characteristics will be summarized.

9.6.1 Statistical Methods for Immunogenicity

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

Primary Endpoint

Primary Endpoints/Hypotheses (H1 and H2)

The primary endpoint, anti-PnPs serotype-specific IgG responses at or above the threshold value of 0.35 µg/mL for 13 shared serotypes contained in V114 and Prevenar 13™ at 30 days PD3 will be assessed via the following non-inferiority hypotheses:

H_0: p_1-p_2 $\leq$-0.1 versus
H_1: p_1-p_2 >-0.1,

and for the 2 unique serotypes contained in V114, the primary endpoint, anti--PnPs IgG responses will be assessed via the following superiority hypotheses:

H_0: p_1-p_2 $\leq$0.1 versus
H_1: p_1-p_2 >0.1,

where p_1 is the response rate for the V114 group and p_2 is the response rate for the Prevenar 13™ group. V114 is non-inferior to Prevenar 13^{TM} if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevenar 13™) is greater than -0.1 for the 13 shared serotypes, and superior to Prevenar 13^{TM} if the lower bound of the

2-sided 95% CI for the between-treatment differences (V114 minus Prevenar 13™) is greater than 0.1 for the 2 unique serotypes contained in V114. The Miettinen and Nurminen (M&N) method (1985), an unconditional, asymptotic method, will be used for this analysis [Miettinen, O. and Nurminen, M. 1985].

Primary Endpoints/Hypotheses (H3 and H4)

The primary endpoint, anti-PnPs serotype-specific IgG GMCs for 13 shared serotypes contained in V114 and Prevenar 13™ at 30 days PD3 will be assessed via the following non-inferiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 0.5$ versus
H_1: $GMC_1/GMC_2 > 0.5$,

and for the 2 unique serotypes contained in V114, the primary endpoint, anti--PnPs IgG GMCs will be assessed via the following superiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 2.0$ versus
H_1: $GMC_1/GMC_2 > 2.0$

where GMC_1 is the anti-PnPs serotype-specific IgG GMCs for V114 group and GMC_2 is the anti-PnPs serotype-specific IgG GMCs for the Prevenar 13™. For the 13 shared serotypes, V114 is non-inferior to Prevenar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevenar 13™) is greater than 0.5; for the 2 unique serotypes, V114 is superior to Prevenar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevenar 13™) is greater than 2.0. Estimation of the IgG GMC ratios and computation of the corresponding 95% CIs will be calculated using t--distribution with the variance estimate from a linear model utilizing the log-transformed antibody concentrations as the response and a single term for vaccination group.

Secondary Endpoints

Secondary Endpoint/Hypothesis (H5)

For this hypothesis (H5), the antigen-specific response rates for participants administered V114 concomitantly with Vaxelis™ will be compared with participants administered Prevenar 13™ concomitantly with Vaxelis™ at 30 days PD3 via the following non-inferiority hypotheses:

H_0: $p_1 - p_2 \leq \delta$ versus
H_1: $p_1 - p_2 > \delta$

where p_1 is the response rate for the V114 group, p_2 is the response rate for the Prevenar 13™ group, and δ is the prespecified non-inferiority margin and the values of δ are listed in Table 8. Vaxelis™ administered concomitantly with V114 is non-inferior to Vaxelis™ administered concomitantly with Prevenar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment difference between V114 vs Prevenar 13™ greater than δ.

The M&N method (1985) will be used for this analysis.

Other Secondary Endpoints/Exploratory Endpoints

Other secondary/exploratory objectives include the evaluation of anti--PnPs serotype--specific IgG GMCs at 30 days PD2 and Predose 3, anti-PnPs serotype-specific IgG response rates at 30 days PD2, and anti--PnPs serotype-specific OPA GMTs and response rates at 30 days PD2, Predose 3, and 30 days PD3. The evaluations of these objectives will be performed within each vaccination group separately. Descriptive statistics with point estimates and within--group 95% CIs will be provided. For the continuous endpoints, the point estimates will be calculated by exponentiating the estimates of the mean of the natural log values and the within--group CIs will be derived by exponentiating the bounds of CIs of the mean of the natural log values based on the 1-sample t-distribution. For the dichotomous endpoints, the within--group CIs will be calculated based on the exact method proposed by Clopper and Pearson [CLOPPER, C. J. and PEARSON, E. S. 1934].

Reverse Cumulative Distribution Curves for IgG concentrations at 30 days PD3 will be graphically displayed by serotype.

A detailed analysis strategy for immunogenicity endpoints is listed in Table 6.

Table 6 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint (H1 – H2)				
Anti-PnPs serotype-specific IgG response rates at 30 days PD3	P	Miettinen and Nurminen (estimate, 95% CI, p--value)	PP	Missing data will not be imputed
	S		FAS	
Primary Endpoint (H3 – H4)				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD3	P	t-distribution with the variance estimate from a linear model‡ (estimate, 95% CI, p--value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoint (H5)				
Antigen-specific response rates for all antigens included in Vaxelis™ at 30 days PD3 of V114 or Prevenar 13™	P	Miettinen and Nurminen (estimate, 95% CI, p--value)	PP	Missing data will not be imputed
	S		FAS	
	S		FAS	

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Other Secondary Endpoints				
Anti-PnPs serotype-specific IgG response rates and GMCs for the 15 serotypes contained in V114 at 30 days PD2	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific OPA GMTs and response rates at 30 days PD3	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

CI = confidence interval; FAS = Full Analysis Set; GMC = geometric mean concentration; GMT = geometric mean titer; H = hypothesis; IgG = Immunoglobulin G; OPA = opsonophagocytic activity; PD = postdose; PnPs = pneumococcal polysaccharide; PP = Per-Protocol.

† P = Primary approach; S = Supportive approach.

‡ Estimation of the IgG GMC ratios and computation of the corresponding 95% CIs will be calculated using t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody titers as the response and a single term for vaccination group.

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. Additional summaries on key safety parameters will also be provided following each vaccination.

The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) are either pre-specified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs to be provided for between-treatment differences in the proportion of participants with events; these analyses will be performed using the Miettinen and Nurminen (M&N) method (1985), an unconditional, asymptotic method. However, these p-values and CIs should be regarded as helpful descriptive measures to be used in review, not formal methods for assessing the statistical significance of the between-treatment differences in AEs. For this protocol, solicited injection-site AEs (redness/erythema, swelling, hard lump/induration, and tenderness/pain) from Day 1 through Day 14 postvaccination and solicited systemic AEs (irritability, drowsiness, hives or welts, and appetite loss) from Day 1 through Day 14 postvaccination are considered Tier 1 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (also via the M&N method [1985]) [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 4 participants in any treatment group show the event. The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a vaccine-related AE, an SAE, a vaccine-related SAE, discontinuation due to an AE, and death will be considered Tier 2 endpoints. The proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points (Days 1 to 7) will also be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Between-Group Comparison	Descriptive Statistics
Tier 1	Injection-site redness/erythema (Days 1 to 14)	X	X	X
	Injection-site swelling (Days 1 to 14)	X	X	X
	Injection-site tenderness/pain (Days 1 to 14)	X	X	X
	Injection-site hard lump/induration (Days 1 to 14)	X	X	X
	Irritability (Days 1 to 14)	X	X	X
	Drowsiness/somnolence (Days 1 to 14)	X	X	X
	Hives or welts/urticaria (Days 1 to 14)	X	X	X
	Appetite loss/decreased appetite (Days 1 to 14)	X	X	X

Safety Tier	Safety Endpoint†	p-Value	95% CI for Between-Group Comparison	Descriptive Statistics
Tier 2	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 SOC and PT‡ (incidence ≥4 participants in one of the vaccination groups)		X	X
Tier 3	Specific AEs by SOC and PT‡ (incidence <4 participants in all of the vaccination groups)			X

AE = adverse event; CI = confidence interval; PT = preferred term; SAE = serious adverse event; SOC = system organ class; X = results will be provided

† These endpoints are broad AE categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least one AE.

‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.

9.6.3 Summaries of Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed using summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, gender, birth weight, and gestational age), baseline characteristics, and 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 and function of the DMC, along with the timing and content of the safety review will be outlined in the DMC charter. Information regarding the composition of the DMC is provided in Appendix 1. 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.

The DMC will serve as the primary reviewer of the results of ongoing safety reviews 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 to act on these recommendations. The extent to which individuals are unblinded with respect to ongoing safety reviews will be documented by the external unblinded statistician. Additional logistical details will be provided in the DMC charter.

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

9.8 Multiplicity

The study will be considered to have met its primary immunogenicity objective if non-inferiority is demonstrated with respect to IgG GMCs and response rates for the 13 shared serotypes and superiority is demonstrated respect to IgG GMCs and response rates for the 2 unique serotypes at 30 days PD3. All hypotheses will be tested individually for each serotype at a 1-sided 0.025 alpha level. This approach controls the 1-sided type--I error rate at 0.025, thus no multiplicity adjustment is required. The study will be considered to have met its secondary objective for a specific concomitant vaccine if non-inferiority is demonstrated for all the antigens included in that concomitant vaccine.

No multiplicity adjustments will be made for the safety comparisons.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

The study will randomize participants in a 1:1 ratio to the 2 vaccination groups. The overall sample size will be approximately 1180 with 590 participants into each vaccination group. The sample size was chosen to ensure sufficient power for the multiple endpoints across both primary and secondary hypotheses. It is assumed that approximately 472 participants per vaccination group will be evaluable for PP immunogenicity analyses at 30 days PD2 (based on an 80% evaluability rate), and approximately 443 participants per vaccination group will be evaluable for PP immunogenicity analyses at 30 days PD3 (based on a 75% evaluability rate).

With this study sample size and the assumptions listed below, the overall power for the primary hypotheses is >95% for demonstrating non-inferiority of V114 to Prevenar 13™ for the 13 shared serotypes and superiority for the 2 unique serotypes for V114 formulations. The overall power for the secondary hypotheses for concomitant antigens evaluation is ~90%. The power for individual hypothesis components is provided below.

For the primary immunogenicity endpoint/hypothesis (H1), the study has >95% power at a 1--sided 2.5% alpha level to demonstrate V114 is non-inferior to Prevenar 13™ at 30 days PD3 for anti-PnPs serotype-specific IgG responses at or above the threshold value of 0.35 µg/mL for the 13 shared serotypes between V114 and Prevenar 13™ based on the following assumptions: (1) an approximately 75% evaluability rate at PD3 as observed in previous Phase 2 V114 pediatric studies; (2) a non-inferiority margin of --0.1 for the difference (V114-Prevenar 13™); and (3) underlying serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL at 30 days PD3 of V114 or Prevenar 13™) are 95% at 30 days PD3.

For the primary immunogenicity endpoint/hypothesis (H2), the study has >95% power at a 1--sided 2.5% alpha level to demonstrate V114 is superior to Prevenar 13™ at 30 days PD3 for anti-PnPs serotype-specific IgG responses at or above the threshold value of 0.35 µg/mL for the 2 unique serotypes contained in V114 based on the following assumptions: (1) an approximately 75% evaluability rate at 30 days PD3 as observed in previous V114 pediatric Phase 2 studies; (2) a superiority margin of 0.1 for the difference (V114-Prevenar 13™); and (3) underlying serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL at 30 days PD3 of V114 or Prevenar 13™) are 95% in V114 group and 2% in Prevenar 13™ group at 30 days PD3.

For the primary immunogenicity endpoint/hypothesis (H3), the study has >95% power at a 1--sided 2.5% alpha level to demonstrate V114 is non-inferior to Prevenar 13™ at 30 days PD3 for anti-PnPs serotype-specific IgG GMCs at 30 days PD3 based on the following assumptions: (1) an approximately 75% evaluability rate at 30 days PD3 as observed in previous V114 pediatric Phase 2 studies; (2) a non-inferiority margin of 0.5 (V114/Prevenar 13™); (3) SD of anti-PnPs serotype-specific IgG GMCs in log scale is 1.1 as those observed in previous MSD studies, and (4) the true GMC ratio (V114/Prevenar 13™) for anti--PnPs serotype-specific IgG GMCs is 1.0.

For the primary immunogenicity endpoint/hypothesis (H4), the study has >95% power at a 1-sided 2.5% alpha level to demonstrate V114 is superiority to Prevenar 13™ at 30 days PD3 for anti-PnPs serotype-specific IgG GMCs for the 2 unique serotypes contained in V114 based on the following assumptions: (1) an approximately 75% evaluability rate at PD3 as observed in previous Phase 2 V114 pediatric studies; (2) a superiority margin of 2.0 (V114/Prevenar 13™); and (3) SD of anti-PnPs serotype-specific IgG GMCs in log scale is 1.1 as those observed in previous MSD studies, and (4) the true GMC ratio (V114/Prevenar 13™) for anti-PnPs serotype-specific IgG GMCs is 10.0.

The study is considered to have met its primary objective if V114 is non-inferior to Prevenar 13™ for the 13 shared serotypes and superior to Prevenar 13™ for the 2 unique serotypes contained in V114.

For the secondary immunogenicity endpoint/hypothesis (H5), the power is ~90.9% the non-inferiority hypotheses when Vaxelis™ administered concomitantly with V114 or Prevenar 13™, respectively. This is based on the assumptions of approximately 75% evaluability rate at PD3 for Vaxelis™. The assumed response rates, GMT, and non-inferiority margins are listed in Table 8.

Table 8 Summary of Endpoints and Power for Concomitant Vaccine Antigens

	Antigen	Endpoint	Time point	Assumed Response Rate or Standard Deviation	NI Margin	Power
Vaxelis™	Diphtheria toxoid	% ≥0.1 IU/mL	PD3	95%	-10%	90.9%
	Tetanus toxoid	% ≥0.1 IU/mL	PD3	97%	-5%	
	Pertussis – PT	% ≥5 EU/mL	PD3	90%	-10%	
	Pertussis – FHA	% ≥5 EU/mL	PD3	90%	-10%	
	Pertussis – FIM 2/3	% ≥20 EU/mL	PD3	90%	-10%	
	Pertussis – PRN	% ≥5 EU/mL	PD3	90%	-10%	
	Hib-PRP	% ≥0.15 µg/mL	PD3	90%	-10%	
	HBsAg	% ≥10 mIU/mL	PD3	95%	-10%	
	Poliovirus 1	% with Nab ≥1:8 dilution	PD3	97%	-5%	
	Poliovirus 2	% with Nab ≥1:8 dilution	PD3	97%	-5%	
	Poliovirus 3	% with Nab ≥1:8 dilution	PD3	97%	-5%	

EU = endotoxin unit; FHA = filamentous hemagglutinin; FIM 2/3 = fimbriae types 2 and 3; HBsAg = hepatitis B surface antigen; Hib= *Haemophilus influenzae* type b; IU = international unit; Nab = neutralizing antibodies; NI = non-inferiority; PD = postdose; PRN = pertactin; PRP = polyribosylribitol phosphate; PT = pertussis toxin; SD = standard deviation (in log scale).

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying incidence of participants with an SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least one SAE among 590 participants in each of the V114 group and Prevenar 13™ group if the underlying incidence of an SAE is 0.27% (1 of every 368 participants receiving the vaccine). There is a 50% chance of observing at least one SAE among 590 participants in each of the V114 group and Prevenar 13™ group if the underlying incidence of an SAE is 0.12% (1 of every 861 participants receiving the vaccine). If no SAEs are observed among 590 participants in each of the V114 group and Prevenar 13™ group, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.62% (1 in every 160 participants).

Table 9 summarizes the percentage point differences between the 2 vaccination groups that could be detected with 80% probability for a variety of hypothetical underlying incidences of an adverse event. These calculations assume 590 participants in each group and are based on a 2-sided 5% alpha level. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. 1990]; no multiplicity adjustments were made.

Table 9 Differences in Incidence of Adverse Event Rates Between the 2 Vaccination Groups That Can be Detected With an ~80% Probability (Assuming 2-sided 5% Alpha Level With 590 Participants in Each Group)

Incidence of Adverse Event		**Risk Difference**
V114 (%) N=590	**Prevenar 13™ (%) N=590**	**Percentage Points**
1.6	0.1	1.5
5.0	2	3.0
9.2	5	4.2
15.4	10	5.4
21.3	15	6.3
26.9	20	6.9
37.7	30	7.7
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. Based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. 1990].		

9.10 Subgroup Analyses

Subgroup analyses based on sex (female vs male) and race will be performed for 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)

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 Prevenar 13™, and Vaxelis™ at each vaccination schedule.

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 (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

Not applicable.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

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:

- **Results in death**
- **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.
- **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.
- **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.

- **Is a congenital anomaly/birth defect**

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

- **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, swelling, or hard lump from the day of vaccination through Day 14 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

Not applicable.

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 8.10 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.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific request from Swedish Health Authority

10.7.1.1 Benefit/Risk Assessment

Prior to the evaluation of V114 in humans, preclinical animal studies were conducted in rats, mice, rabbits, and non-human primates, and study results showed that the vaccine was immunogenic and displayed an acceptable safety profile. V114 contains similar components as the licensed vaccines Prevenar™ and Prevenar 13™ which comprise a subset of respectively 7 and 13 of the 15 PnPs conjugated to the CRM_{197} carrier protein found in V114, as well as Aluminum Phosphate Adjuvant (APA). The safety profiles for Prevenar™ and Prevenar 13™ can be found in the respective product labeling. Two different formulations of V114 were studied in 8 Phase 1 and Phase 2 clinical studies involving 4140 subjects comprising of 2960 children (90 toddlers, 12 to 18 months of age and 2870 infants, 6 to 12 weeks of age) who received a 4-dose regimen of study vaccine given at 2, 4, 6, and 12 to 15 months of age and 1810 adults (180 young adults 18 to 49 years of age and 1630 adults ≥50 years of age) who received a single dose of the study vaccine. A total of 2685 subjects (1950 children and 735 adults) received at least 1 dose of V114.

Both nonadjuvanted V114 and APA-adjuvanted V114 were evaluated in early Phase 1 (single dose in toddlers and young adults 18-49 years of age) and Phase 2 (4-dose regimen in infants) clinical studies. The 2 vaccines displayed acceptable safety profiles comparable to Prevenar™ and Prevenar 13™. In 1 adult Phase 2 clinical study comparing the safety and immunogenicity of V114 to Prevenar 13™ and PNEUMOVAX™23, the safety profile of V114 was also shown to be comparable to PNEUMOVAX™23. Following vaccination with V114, the most frequently reported AEs were those solicited in the clinical study and included injection-site pain/tenderness (72% in infants and 60% in adults), redness (59% in infants and 14% in adults), and swelling (49% in infants and 20% in adults). Most frequently reported systemic AEs were those solicited in the studies; muscle pain (29%), fatigue (25%), headache (17%), and joint pain (17%) were commonly reported among adults while irritability (86%), drowsiness (72%), decreased appetite (57%) were commonly reported in infants following any vaccination. Vaccine-induced immune responses were directed to all 15 serotypes included in V114 and recipients of the adjuvanted V114 vaccine generally tended to exhibit higher serotype-specific IgG GMCs and OPA GMTs for the majority of the serotypes included in V114, justifying the inclusion of APA in the vaccine formulation to provide optimal antibody responses. Although the antibody responses measured in adults vaccinated with V114 were comparable to those measured in recipients of Prevenar 13™ for most shared serotypes, antibody responses measured in infants vaccinated with V114 were generally lower than those vaccinated with Prevenar 13™ for some shared serotypes at 1 month PD3. The results from study V114-003 indicated a need for formulation optimization of the candidate vaccine, particularly the need for determining the optimal amount of polysaccharide for each serotype and optimal concentration of aluminum adjuvant needed in V114 to elicit optimal serotype-specific IgG and OPA responses in infants.

The Sponsor conducted additional clinical studies to optimize the vaccine formulation and assess its tolerability, safety, and immunogenicity profiles. As part of the formulation

optimization, 2 formulations of V114 (Formulation A and Formulation B) were tested clinically in several Phase 1/2 clinical studies involving a small number (20 to 50 subjects per arm) of young adults (18 to 49 years of age) and infants (V114-004 and V114-005), as well as larger number (125 to 230 subjects per arm) of pneumococcal vaccine-naïve adults 50 years of age and older (V114-006) and adults 65 years of age or older with prior history (at least 1 year prior to study entry) of vaccination with PNEUMOVAX™23 (V114-007). Both V114 formulations displayed an acceptable safety profile and induced comparable levels of antibodies to Prevenar 13™ for the shared serotypes. V114 also induced higher antibodies to serotypes 22F and 33F, which are not included in Prevenar 13™ and have emerged recently as important causes of pneumococcal disease in both children and adults. Results from these studies identified a formulation (Formulation B) with improved clinical performance in both infants and older adults. A pediatric Phase 2 study (V114-008) involving 1050 infants (350 per arm) is ongoing to confirm the performance of Formulation B observed in V114-005. Following vaccination with V114 Formulation B, the most frequently reported AEs were those solicited in the clinical study and included injection-site pain/tenderness (64% in infants and 60% in adults), redness (38% in infants and 11% in adults), and swelling (20% in infants and 16% in adults). Most frequently reported systemic AEs were those solicited in the studies; muscle pain (18%), fatigue (17%), headache (12%), and joint pain (7%) were commonly reported among adults, while irritability (82%), drowsiness (60%), decreased appetite (32%) were commonly reported in infants following any vaccination.

Previous studies comparing the safety and immunogenicity of the investigational V114 to Prevenar 13™ and/or PNEUMOVAX™23 did not show a difference in the frequency and severity of AEs reported following vaccination [Ermlich, S. J., et al 2018]. The comparable safety and immunogenicity profiles of V114 to Prevenar 13™ and PNEUMOVAX™23 in previous clinical studies involving healthy children and adults indicate that V114 will likely display comparable safety and immunogenicity profiles to these licensed in the current study. Although V114 induces antibody responses to 2 more serotypes (22F and 33F) than Prevenar 13™, it cannot be guaranteed that participants in V114 clinical studies will directly benefit from intervention during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational vaccine.

In conclusion, the investigational V114 vaccine has comparable safety and immunogenicity profiles to Prevenar 13™ and PNEUMOVAX™23, 2 licensed pneumococcal vaccines that were clinically evaluated in a number of clinical studies and currently recommended for the prevention against pneumococcal disease. The satisfactory clinical performance and general tolerability of V114 in healthy children and adults to date supports the clinical evaluation of the investigational vaccine in the current study. Given the accepted benefit of vaccinating with Prevenar 13™ and PNEUMOVAX™23 by professional societies and national immunization institutions/agencies, the benefit/risk for vaccinating with V114 in the current study is favorable. The safety profile of the investigational V114 vaccine is closely monitored on a continuing basis by an external DMC.

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

The following statement will replace the Participant Protection Section III, Part A of Appendix 1, Code of Conduct for Clinical Trials:

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents must be submitted to and approved by the applicable Competent Authority and IRB/IEC before the study is initiated in accordance with EU Directive 2001/20/EC, Article 10 (a) and/or local requirements.

Any amendments to the protocol will require IRB/IEC and Competent Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants [2001/20/EC, Article 10 (b)].

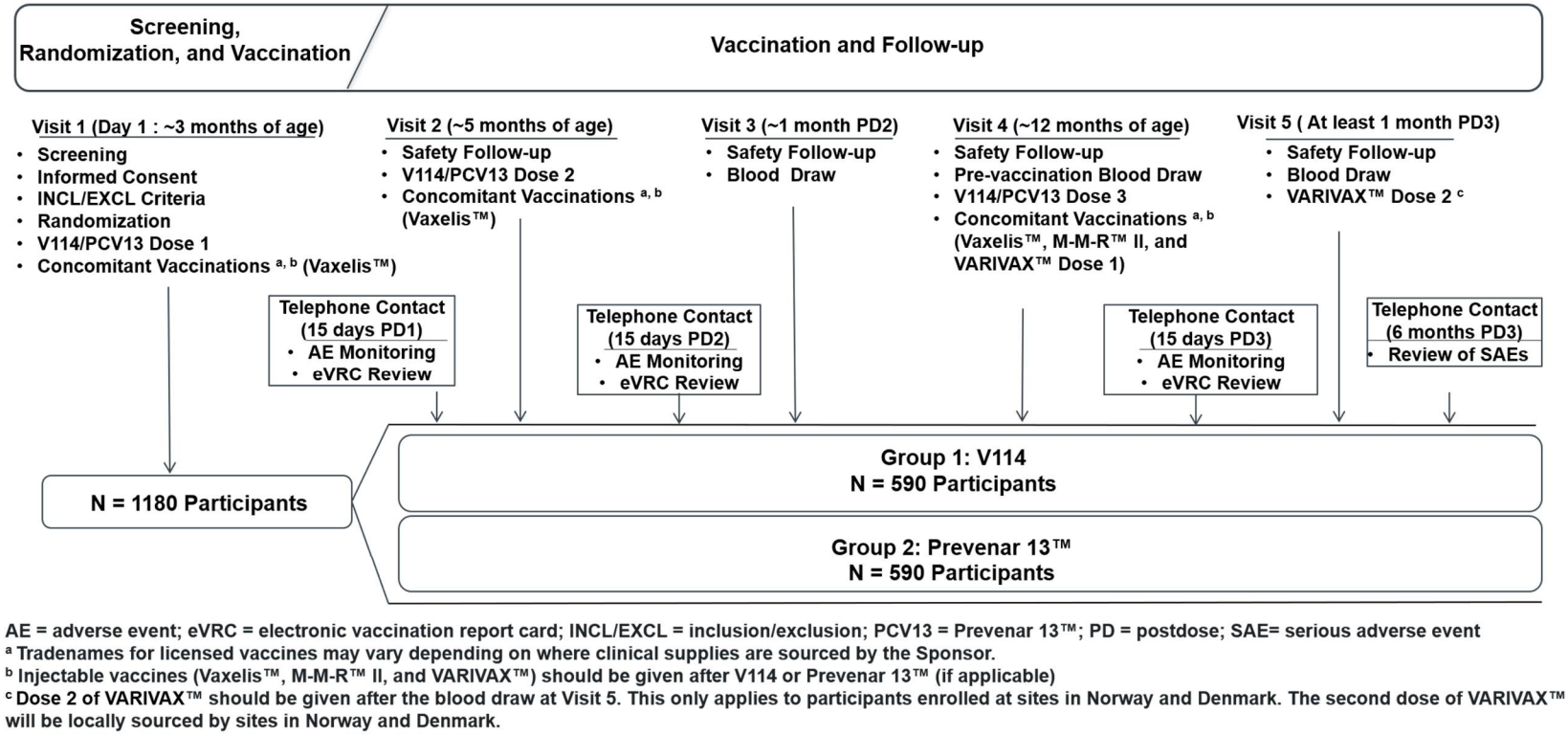
10.7.1.3 Informed Consent

According to Swedish law, Medical Products law (2015:315) 7 chapter 3 §, informed consent for minors should be obtained from both legally acceptable representatives or guardians (when there are 2 guardians).

10.7.2 Country-specific information for Norway and Denmark

10.7.2.1 Study Design

The study design for study sites in Norway and Denmark is shown in Figure 2.



AE = adverse event; eVRC = electronic vaccination report card; INCL/EXCL = inclusion/exclusion; PCV13 = Prevenar 13™; PD = postdose; SAE= serious adverse event
[a] Tradenames for licensed vaccines may vary depending on where clinical supplies are sourced by the Sponsor.
[b] Injectable vaccines (Vaxelis™, M-M-R™ II, and VARIVAX™) should be given after V114 or Prevenar 13™ (if applicable)
[c] Dose 2 of VARIVAX™ should be given after the blood draw at Visit 5. This only applies to participants enrolled at sites in Norway and Denmark. The second dose of VARIVAX™ will be locally sourced by sites in Norway and Denmark.

Figure 2 V114-026-02 Study Design (For Sites in Norway and Denmark Only)

10.7.2.2 Schedule of Activities (For Sites in Norway and Denmark Only)

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**At least 1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Administrative and General Procedures										
Screening Procedures										
Informed Consent/Assent	X									Consent must be obtained before any study procedures.
Informed Consent/Assent for Future Biomedical Research	X									Participation in future biomedical research is optional and consent must be obtained before collection of buccal swab DNA samples.
Assignment of Screening Number	X									
Participant Identification Card	X									
Inclusion/Exclusion Criteria	X									Review of prior medications/vaccinations, a complete physical examination, and temperature measurement are required at Visit 1 to determine eligibility.
Medical History	X									

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**At least 1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Post-Randomization Procedures										
Assignment of Randomization Number	X									
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	X	X	X	X	X	X		
V114 or Prevenar 13™[b] Administration (Blinded)	X		X			X				Before vaccine administration, the investigator (or designee) must review medical history to ensure the participant has no new contraindication to the vaccine(s) scheduled to be given (see Section 8.1.8).

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**At least 1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Concomitant Vaccine Administration (Open-label)[b] • Vaxelis™	X		X			X				Before vaccine administration, the investigator (or designee) must review medical history to ensure the participant has no new contraindication to the vaccine(s) scheduled to be given. (see Section 8.1.8). See Section 6.5 for details on concomitant vaccines. Vaxelis™ should be given after V114 or Prevenar 13™.

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**At least 1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Concomitant Vaccine Administration (Open-label)[b] • M-M-R™II						X				Before vaccine administration, the investigator (or designee) must review medical history to ensure the participant has no new contraindication to the vaccine(s) scheduled to be given (see Section 8.1.8). M-M-R™II and VARIVAX™ should be given after V114 or Prevenar 13™ (see Section 6.5). The second dose of VARIVAX™ at Visit 5 should be given after the blood draw.
Concomitant Vaccine Administration (Open-label)[b] • VARIVAX™						X		X		

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**At least 1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Provide eVRC	X									An eVRC will be provided at Visit 1 to record AEs, body temperature, concomitant medications, and nonstudy vaccinations. Instructions for using the eVRC will be reviewed with the participant's legally acceptable representative.
Review eVRC data with participant's legally acceptable representative		X	X	X	X	X	X	X		See Section 8.1.9 for details.
Collect eVRC from participant's legally acceptable representative								X		
Complete the Telephone Contact Questionnaire									X	See Section 8.1.11 for details.
Safety Procedures										
Complete Physical Examination	X									To be performed by the investigator or medically qualified designee before vaccine is administered (see Section 8.3.1).

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**At least 1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Targeted Physical Examination			X			X		X		To be performed by the investigator or medically qualified designee before vaccine is administered (see Section 8.3.1).
Body Temperature Measurement	X		X			X		X		Each participant's body temperature must be taken before vaccination (see Section 8.3.2 for method). Participants who have febrile illness at or within 72 hours of vaccination must be rescheduled.
30-minute Postvaccination Observation Period	X		X			X				To be performed by blinded study site personnel only.
AE Monitoring	X	X	X	X	X	X	X	X	X	Nonserious AEs are to be reported from Days 1 through 14 following each vaccination with V114 or Prevenar 13™. SAEs and deaths are to be reported throughout the duration of an individual's study participation.

Study Period	**Intervention**								**Follow-up**	
Visit Number	**1**	**TC**	**2**	**TC**	**3**	**4**	**TC**	**5**	**TC**	**Comments**
Scheduled Time	**Age: ~3 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~5 months (Dose 2)**	**Day 15 after Dose 2**	**~1 month after Dose 2**	**Age: ~12 months (Dose 3)**	**Day 15 after Dose 3**	**At least 1 month after Dose 3**	**~6 months after Dose 3**	Months of age is calculated according to the participant's birth date.
Visit Window[a]	**≥70 days of age to ≤111 days of age**	**Day 15 to Day 19 Postdose 1**	**5 months of age to 1 day prior to 6 months of age (+14 days)**	**Day 15 to Day 19 Postdose 2**	**Day 28 to Day 60 Postdose 2**	**12 months of age to 1 day prior to 13 months of age (+14 days)**	**Day 15 to Day 19 Postdose 3**	**Day 28 to Day 60 Postdose 3**	**Day 166 to Day 194 Postdose 3**	
Immunogenicity Procedures										
Serum for Immunogenicity Assays (Including Retention Serum)					X	X		X		Blood samples must be collected before vaccination where applicable.
Future Biomedical Research										
Collect Buccal Swabs for Future Biomedical Research	X									Buccal swab DNA samples for analysis should be obtained prior to vaccination at Visit 1, on randomized and FBR consented participants only, or at a later date as soon as the informed consent is obtained.

AE = adverse event; DNA = deoxyribonucleic acid; eVRC = electronic vaccination report card; FBR = Future Biomedical Research; SAE = serious adverse event; TC = telephone contact.

[a] For calculating the visit windows, the day of vaccination is considered Day 1. To calculate visit windows for subsequent vaccinations, confirm participant date of birth and ensure the age of the participant will fall within the appropriate age range for each study visit.

[b] Tradenames for licensed vaccines may vary depending on where clinical supplies are sourced by the Sponsor.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
APaT	All Participants as Treated
CI	confidence interval
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CRF	case report form
CSR	clinical study report
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECi	enhanced chemiluminescence
ECI	event of clinical interest
ECL	electrochemiluminescence
eCRF	electronic case report form
EDC	electronic data collection
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EU	European Union
eVRC	electronic vaccination report card
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FHA	filamentous hemagglutinin
FIM 2/3	fimbriae types 2/3
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
H	hypothesis
HBsAg	hepatitis B surface antigen
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HRP	horseradish peroxidase
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IPD	invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
M&N	Miettinen and Nurminen
MIT	micrometabolic inhibition test
MOPA	multiplexed opsonophagocytic activity
MSD	Merck Sharp & Dohme
OD	optical density
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
PD	postdose
PnECL	pneumococcal electrochemiluminescence
PnPs	pneumococcal polysaccharide

Abbreviation	Expanded Term
PP	Per-Protocol
PRN	pertactin
PRP	polyribosylribitol phosphate
PT	pertussis toxin
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAGE	Strategic Advisory Group of Experts
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
US	United States
WHO	World Health Organization

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