Official Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 4-dose Regimen of V114 in Healthy Infants (PNEU-PED)
NCT number:	NCT03893448
Document Date:	16-MAR-2021

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 4-dose Regimen of V114 in Healthy Infants (PNEU-PED)

Protocol Number: 029-02

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	2018-004109-21

Approval Date: 16 March 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
V114-029-02	16-MAR-2021	Amendment to expand the visit windows for Visit 3 (Dose 3 vaccination), Visit 4 (postdose 3 blood draw) and Visit 6 (postdose 4 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. This amendment also includes the addition of 3 secondary hypotheses relating to the demonstration of superiority for serotype 3 immune responses.
V114-029-01	28-FEB-2020	Amendment to incorporate changes to the statistical analyses for the evaluation of the 2 unique V114 serotypes compared with Prevnar 13™
V114-029-00	30-JAN-2019	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

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 3 (Dose 3 vaccination), Visit 4 (postdose 3 blood draw), and Visit 6 (postdose 4 blood draw) to allow inclusion of more participants in the immunogenicity analysis based on the per-protocol population. This amendment also includes the addition of 3 secondary hypotheses relating to the demonstration of superiority for serotype 3 immune responses.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	The visit window for Visit 3 (Dose 3 vaccination) was expanded by 14 days. The visit windows for Visit 4 (postdose 3 blood draw) and Visit 6 (postdose 4 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 # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3 Hypotheses, Objectives, and Endpoints Section 9.1 Statistical Analysis Plan Summary Section 9.4.1 Immunogenicity Endpoints Section 9.6.1 Statistical Methods for Immunogenicity Section 9.8 Multiplicity Section 9.9.1 Sample Size and Power for Immunogenicity Analyses	• Added a secondary objective to demonstrate superiority for serotype 3 based on the proportion of participants with anti-PnPs serotype 3 IgG ≥0.35 µg/mL at 30 days PD3. • Added secondary objectives to demonstrate superiority for serotype 3 based on the IgG GMCs at 30 days PD3 and at 30 days PD4. • Updated statistical methods corresponding to the changes made in endpoints.	Routine vaccination with Prevnar 13™ has not demonstrated a substantial impact on the incidence of serotype 3 invasive pneumococcal disease. To further assess vaccine-induced immune responses against serotype 3 in an infant population, an assessment of superiority for serotype 3 is being included.
Section 1.1 Synopsis Section 3 Hypotheses, Objectives, and Endpoints	Removed reference to the statistical criteria for success for secondary objectives #6 through #9.	Revisions align with secondary objectives #1 through #5.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Estimated Duration of Study Section 1.1 Synopsis, Duration of Participation Section 4.4 Beginning and End of Study Definition Section 8.1.1.1 General Informed Consent Section 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research Section 8.1.3 Participant Identification Card Section 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information Section 8.10 Future Biomedical Research Sample Collection Section 10.1.8 Data Quality Assurance	• Text related to informed consent with updated to "documented" informed consent instead of solely "written" informed consent to reflect legal language updates. • Study-related visits were changed to study-related "contacts" to include both in-person visits and other types of contacts with study participants.	The protocol template was updated to align with current informed consent procedures.

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.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

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 4-dose Regimen of V114 in Healthy Infants (PNEU-PED)

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

Acronym: PNEUmococcal Conjugate Vaccine Trials: V114-029 (PNEU-PED)

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 2 months of age (from 42 to 90 days [inclusive]) administered V114 or Prevnar 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 1: 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 2: To compare the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype-specific IgG threshold value of $\geq$0.35 µg/mL) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13™. Hypothesis (H1): V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes between V114 and Prevnar 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 the response rates [V114 minus Prevnar 13™] to be greater than -0.1.) Hypothesis (H2): V114 is non-inferior to Prevnar 13™ for the 2 unique V114 serotypes based on the response rate of the 2 unique V114 serotypes compared with the lowest response rate of any of the shared serotypes in Prevnar 13™, excluding serotype 3, 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 the response rates [V114 minus Prevnar 13™] to be greater than -0.1.)	
- Objective 3: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13™. Hypothesis (H3): V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes between V114 and Prevnar 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/ Prevnar 13™) to be greater than 0.5.) Hypothesis (H4): V114 is non-inferior to Prevnar 13™ for the 2 unique V114 serotypes based on the anti-PnPs serotype-specific IgG GMCs of the 2 unique V114 serotypes compared with the lowest IgG GMC of any of the shared serotypes in Prevnar 13™, excluding serotype 3, at 30 days following Dose 3.	- Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3

(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/ Prevnar 13™) to be greater than 0.5.)	
- Objective 4: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13™. Hypothesis (H5): V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes between V114 and Prevnar 13™ based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4. (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/ Prevnar 13™) to be greater than 0.5.) Hypothesis (H6): V114 is non-inferior to Prevnar 13™ for the 2 unique V114 serotypes based on anti-PnPs serotype-specific IgG GMCs of the 2 unique V114 serotypes compared with the lowest IgG GMC of any of the shared serotypes in Prevnar 13™, excluding serotype 3, at 30 days following Dose 4. (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/ Prevnar 13™) to be greater than 0.5.)	- Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4)

Secondary Objectives	Secondary Endpoints
- Objective 1: To compare the antigen-specific response rate to each antigen and the antigen-specific GMCs for the pertussis antigens included in Pentacel™ at 30 days following Dose 3 for participants administered V114 concomitantly with Pentacel™ versus participants administered Prevnar 13™ concomitantly with Pentacel™. Hypothesis (H7): Pentacel™ administered concomitantly with V114 is non-inferior to Pentacel™ administered concomitantly with Prevnar 13™ at 30 days following Dose 3 for each antigen included in Pentacel™.	Antibody responses to: - diphtheria toxoid - tetanus toxoid - pertussis toxin (PT) - pertussis filamentous hemagglutinin (FHA) - pertussis fimbrae types 2/3 (FIM 2/3) - pertussis pertactin (PRN) - poliovirus serotypes 1, 2 and 3 - Haemophilus influenzae type b polyribosylribitol phosphate (Hib-PRP) at 30 days PD3 of V114 or Prevnar 13™
- Objective 2: To compare the response rate to anti-hepatitis A antigen at 30 days following Dose 4 for participants administered V114 concomitantly with VAQTA™ versus participants administered Prevnar 13™ concomitantly with VAQTA™. Hypothesis (H8): VAQTA™ administered concomitantly with V114 is non-inferior to VAQTA™ administered concomitantly with Prevnar 13™ at 30 days following Dose 4.	- Antibody responses to hepatitis A antigen at 30 days PD4 of V114 or Prevnar 13™
- Objective 3: To compare the response rate to each antigen included in M-M-R™II at 30 days following Dose 4 for participants administered V114 concomitantly with M-M-R™II versus participants administered Prevnar 13™ concomitantly with M-M-R™II. Hypothesis (H9): M-M-R™II administered concomitantly with V114 is non-inferior to M-M-R™II administered concomitantly with Prevnar 13™ at 30 days following Dose 4 for each antigen included in M-M-R™II.	- Antibody responses to measles, mumps, and rubella virus at 30 days PD4 of V114 or Prevnar 13™

- Objective 4: To compare the response rate to anti-varicella antigen at 30 days following Dose 4 for participants administered V114 concomitantly with VARIVAX™ versus participants administered Prevnar 13™ concomitantly with VARIVAX™. Hypothesis (H10): VARIVAX™ administered concomitantly with V114 is non-inferior to VARIVAX™ administered concomitantly with Prevnar 13™ at 30 days following Dose 4.	- Antibody responses to varicella-zoster virus (VZV) at 30 days PD4 of V114 or Prevnar 13™
- Objective 5: To compare the response rate to anti-PRP antigen at 30 days following Dose 4 for participants administered V114 concomitantly with HIBERIX™ versus participants administered Prevnar 13™ concomitantly with HIBERIX™. Hypothesis (H11): HIBERIX™ administered concomitantly with V114 is non-inferior to HIBERIX™ administered concomitantly with Prevnar 13™ at 30 days following Dose 4.	- Antibody responses to PRP at 30 days PD4 of V114 or Prevnar 13™
- Objective 6: To compare the anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13™. Hypothesis (H12): V114 is superior to Prevnar 13™ for the 2 unique V114 serotypes based on the response rates at 30 days following Dose 3. Hypothesis (H13): V114 is superior to Prevnar 13™ for the 2 unique V114 serotypes based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3.	- Anti-PnPs serotype-specific IgG responses for the 2 unique serotypes contained in V114 at 30 days PD3

- Objective 7: To compare the anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13™. Hypothesis (H14): V114 is superior to Prevnar 13™ for the 2 unique V114 serotypes based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4.	- Anti-PnPs serotype-specific IgG responses for the 2 unique serotypes contained in V114 at 30 days PD4
- Objective 8: To compare the anti-PnPs serotype 3 IgG responses at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13™. Hypothesis (H15): V114 is superior to Prevnar 13™ for serotype 3 based on the response rates at 30 days following Dose 3. Hypothesis (H16): V114 is superior to Prevnar 13™ for serotype 3 based on anti-PnPs IgG GMCs at 30 days following Dose 3.	- Anti-PnPs serotype 3 IgG responses at 30 days PD3
- Objective 9: To compare the anti-PnPs serotype 3 IgG GMCs at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13™. Hypothesis (H17): V114 is superior to Prevnar 13™ for serotype 3 based on anti-PnPs IgG GMCs at 30 days following Dose 4.	- Anti-PnPs serotype 3 IgG responses at 30 days PD4
- Objective 10 (OPA Subset): To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) and response rates 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 26 months from the time that documented informed consent is provided for the first participant until the last participant's last study-related contact. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 1720 participants will be randomized, with approximately 860 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 Fre-quency</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>4 doses</td><td>IM</td><td>Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively)</td><td>Experi mental</td></tr>
<tr><td>Prevnar 13™</td><td>Prevnar 13™</td><td>Refer to product labeling</td><td>4 doses</td><td>IM</td><td>Single dose at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age, respectively)</td><td>Experi mental</td></tr>
<tr><td colspan="7">ACIP=Advisory committee on Immunization Practices; Admin.=administration; IB=Investigator’s Brochure; IM=intramuscular.
Note: All participants will also receive other pediatric vaccines, including RotaTeq™, Pentacel™, RECOMBIVAX HB™, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ , as part of the study design according to the ACIP-recommended schedule (Table 1 and Table 2). Tradenames for licensed vaccines may vary depending on where clinical supplies are sourced by 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 16 to 20 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.	

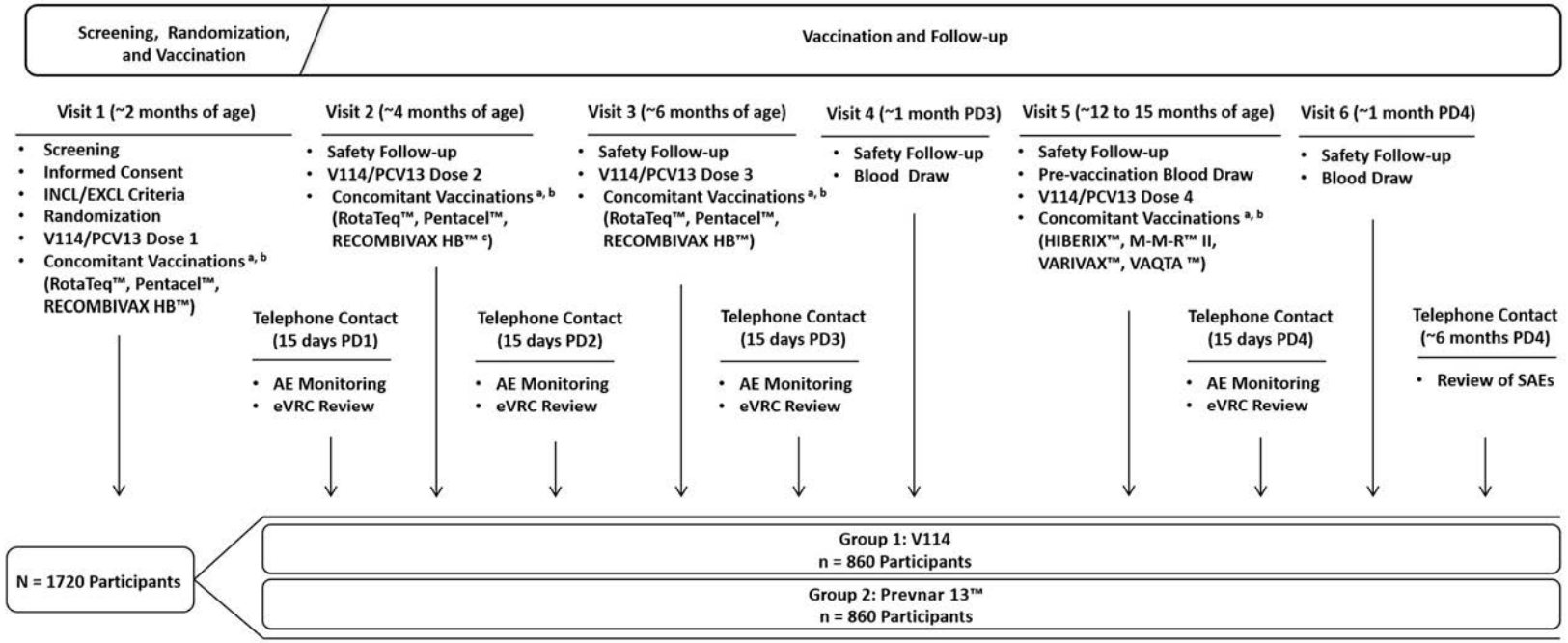
Study Accepts Healthy Volunteers: Yes

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

1.2 Schema

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

Figure 1 V114-029 Study Design



AE = adverse event; eVRC = electronic Vaccination Report Card; INCL/EXCL = Inclusion/Exclusion Criteria; PCV13 = Prevnar 13™; PD = postdose; SAE = serious adverse event

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

[b] RotaTeq™ is administered orally and should be given before V114 or Prevnar 13™ and other concomitant vaccines. Injectable vaccines (Pentacel ™, RECOMBIVAX HB™, HIBERIX™, M-M-R™ II, VARIVAX™, VAQTA ™) should be given after V114 or Prevnar 13™.

[c] For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ will be administered at ~2 and 6 months of age and not at ~4 months of age.

1.3 Schedule of Activities (SoA)

Study Period	Intervention										Follow-up	Comments
Visit Number:	**1**	**TC**	**2**	**TC**	**3**	**TC**	**4**	**5**	**TC**	**6**	**TC**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~4 months (Dose 2)**	**Day 15 after Dose 2**	**Age: ~6 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**Day 15 after Dose 4**	**~1 month after Dose 4**	**~6 months after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window[a]:	**≥42 days of age to ≤90 days of age**	**Day 15 to Day 19 Post dose1**	**4 months of age to 1 day prior to 5 months of age**	**Day 15 to Day 19 Post dose2**	**6 months of age to 1 day prior to 7 months of age (+14 days)**	**Day 15 to Day 19 Post dose 3**	**Day 28 to Day 60 Post dose 3**	**12 months of age to 1 day prior to 16 months of age**	**Day 15 to Day 19 Post dose 4**	**Day 28 to Day 60 Post dose 4**	**Day 166 to Day 194 Post dose 4**	
Administrative and General Procedures												
Screening Procedures												
Informed Consent	X											Consent must be obtained before any study procedures.
Informed Consent for Future Biomedical Research	X											Participation in future biomedical research is optional and consent must be obtained before 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											
Post-Randomization Procedures												
Assignment of Randomization Number	X											

Study Period	Intervention										Follow-up	Comments
Visit Number:	**1**	**TC**	**2**	**TC**	**3**	**TC**	**4**	**5**	**TC**	**6**	**TC**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~4 months (Dose 2)**	**Day 15 after Dose 2**	**Age: ~6 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**Day 15 after Dose 4**	**~1 month after Dose 4**	**~6 months after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window[a]:	**≥42 days of age to ≤90 days of age**	**Day 15 to Day 19 Post dose1**	**4 months of age to 1 day prior to 5 months of age**	**Day 15 to Day 19 Post dose2**	**6 months of age to 1 day prior to 7 months of age (+14 days)**	**Day 15 to Day 19 Post dose 3**	**Day 28 to Day 60 Post dose 3**	**12 months of age to 1 day prior to 16 months of age**	**Day 15 to Day 19 Post dose 4**	**Day 28 to Day 60 Post dose 4**	**Day 166 to Day 194 Post dose 4**	
Prior/Concomitant Medication and Non-Study Vaccination Review	X	X	X	X	X	X	X	X	X	X		
V114 or Prevnar 13™ [b] Administration (Blinded)	X		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 (Section 8.1.8).

Study Period	Intervention										Follow-up	Comments
Visit Number:	**1**	**TC**	**2**	**TC**	**3**	**TC**	**4**	**5**	**TC**	**6**	**TC**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~4 months (Dose 2)**	**Day 15 after Dose 2**	**Age: ~6 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**Day 15 after Dose 4**	**~1 month after Dose 4**	**~6 months after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window[a]:	**≥42 days of age to ≤90 days of age**	**Day 15 to Day 19 Post dose1**	**4 months of age to 1 day prior to 5 months of age**	**Day 15 to Day 19 Post dose2**	**6 months of age to 1 day prior to 7 months of age (+14 days)**	**Day 15 to Day 19 Post dose 3**	**Day 28 to Day 60 Post dose 3**	**12 months of age to 1 day prior to 16 months of age**	**Day 15 to Day 19 Post dose 4**	**Day 28 to Day 60 Post dose 4**	**Day 166 to Day 194 Post dose 4**	
Concomitant Vaccine Administration (Open-label)[b] • RotaTeq™ • Pentacel™ • RECOMBIVAX HB™	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). RotaTeq™ is administered orally and should be given before V114 or Prevnar 13™ and other concomitant vaccines. Injectable vaccines should be given after V114 or Prevnar 13™. *For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ will be administered at ~2 and 6 months of age. See Section 6.5 for details on concomitant vaccines.

Study Period	Intervention										Follow-up	Comments
Visit Number:	**1**	**TC**	**2**	**TC**	**3**	**TC**	**4**	**5**	**TC**	**6**	**TC**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~4 months (Dose 2)**	**Day 15 after Dose 2**	**Age: ~6 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**Day 15 after Dose 4**	**~1 month after Dose 4**	**~6 months after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window[a]:	**≥42 days of age to ≤90 days of age**	**Day 15 to Day 19 Post dose1**	**4 months of age to 1 day prior to 5 months of age**	**Day 15 to Day 19 Post dose2**	**6 months of age to 1 day prior to 7 months of age (+14 days)**	**Day 15 to Day 19 Post dose 3**	**Day 28 to Day 60 Post dose 3**	**12 months of age to 1 day prior to 16 months of age**	**Day 15 to Day 19 Post dose 4**	**Day 28 to Day 60 Post dose 4**	**Day 166 to Day 194 Post dose 4**	
Concomitant Vaccine Administration (Open-label)[b] • VAQTA™ • M-M-R™II • VARIVAX™ • HIBERIX™								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 (Section 8.1.8). These vaccines should be given after V114 or Prevnar 13™ (Section 6.5).
Provide eVRC	X											An eVRC will be provided at Visit 1 to record AEs, body temperature, concomitant medications, and non-study 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	X	X		See Section 8.1.10 for details.
Collect eVRC from participant's legally acceptable representative										X		

Study Period	Intervention										Follow-up	Comments
Visit Number:	**1**	**TC**	**2**	**TC**	**3**	**TC**	**4**	**5**	**TC**	**6**	**TC**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~4 months (Dose 2)**	**Day 15 after Dose 2**	**Age: ~6 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**Day 15 after Dose 4**	**~1 month after Dose 4**	**~6 months after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window[a]:	**≥42 days of age to ≤90 days of age**	**Day 15 to Day 19 Post dose1**	**4 months of age to 1 day prior to 5 months of age**	**Day 15 to Day 19 Post dose2**	**6 months of age to 1 day prior to 7 months of age (+14 days)**	**Day 15 to Day 19 Post dose 3**	**Day 28 to Day 60 Post dose 3**	**12 months of age to 1 day prior to 16 months of age**	**Day 15 to Day 19 Post dose 4**	**Day 28 to Day 60 Post dose 4**	**Day 166 to Day 194 Post dose 4**	
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			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			X				To be performed by blinded study site personnel only.

Study Period	Intervention										Follow-up	Comments
Visit Number:	**1**	**TC**	**2**	**TC**	**3**	**TC**	**4**	**5**	**TC**	**6**	**TC**	
Scheduled Time:	**Age: ~2 months (Dose 1)**	**Day 15 after Dose 1**	**Age: ~4 months (Dose 2)**	**Day 15 after Dose 2**	**Age: ~6 months (Dose 3)**	**Day 15 after Dose 3**	**~1 month after Dose 3**	**Age: ~12 to 15 months (Dose 4)**	**Day 15 after Dose 4**	**~1 month after Dose 4**	**~6 months after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window[a]:	**≥42 days of age to ≤90 days of age**	**Day 15 to Day 19 Post dose1**	**4 months of age to 1 day prior to 5 months of age**	**Day 15 to Day 19 Post dose2**	**6 months of age to 1 day prior to 7 months of age (+14 days)**	**Day 15 to Day 19 Post dose 3**	**Day 28 to Day 60 Post dose 3**	**12 months of age to 1 day prior to 16 months of age**	**Day 15 to Day 19 Post dose 4**	**Day 28 to Day 60 Post dose 4**	**Day 166 to Day 194 Post dose 4**	
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	Nonserious AEs are to be reported from Days 1 through 14 following each vaccination. 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.
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 Prevnar 13™ (pneumococcal 13-valent conjugate vaccine [diphtheria CRM_{197} protein], Wyeth Pharmaceuticals, a subsidiary of Pfizer, Inc., Philadelphia, PA), plus 2 additional serotypes (22F, 33F).

2.1 Study Rationale

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 Prevnar 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 2 months of age (42 to 90 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 Prevnar 13™ and the 2 additional unique serotypes (22F and 33F) in V114.

The purpose of this clinical study is to evaluate the safety and immunogenicity of a 4-dose schedule (3-dose primary series followed by a toddler dose) of V114 compared with Prevnar 13™. The 3+1 PCV immunization schedule is currently recommended by the United States Advisory Committee on Immunization Practices (ACIP) [Centers for Disease Control and Prevention 2010]. Country-specific routine immunization regimens vary by schedule and number of doses. In this study, infants will be given study vaccine at 2, 4, 6, and 12 to 15 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 most 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 vaccines, Pentacel™, VAQTA™, HIBERIX™, M-M-R™II, and VARIVAX™. Other routine vaccines (RotaTeq™ and RECOMBIVAX HB™) will also be provided in the study (Section 6.5).

2.2 Background

2.2.1 V114 and Pneumococcal Disease

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

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

V114 contains all the pneumococcal serotypes contained in Prevnar 13™ plus 2 additional serotypes (22F, 33F). The selection of 22F and 33F was primarily based on the emergence of these 2 serotypes as important causes of IPD in the era of Prevnar™ and Prevnar 13™. Approximately 4 years after inclusion of Prevnar™ in the United States infant immunization schedule, serotypes 22F and 33F accounted for approximately 13% of IPD cases in children <5 years of age (incidence rate of IPD due to 22F and 33F combined of 3.1 cases per 100,000 person-years), 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 Prevnar 13™, accounting for approximately 21% of all IPD in children <5 years of age in the United States [Moore, M. R., et al 2015].

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

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Information on Other Study-related Therapy

Refer to approved labeling for detailed background information on Prevnar 13™ and other licensed pediatric vaccines administered concomitantly.

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

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

2.3 Benefit/Risk Assessment

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

Approximately 50% of participants will receive 4 doses of Prevnar 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 Prevnar 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 Prevnar 13™.

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

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 2 months of age (from 42 to 90 days [inclusive]) administered V114 or Prevnar 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 1**: 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 2**: 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 Prevnar 13™. **Hypothesis (H1):** V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes between V114 and Prevnar 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 the response rates [V114 minus Prevnar 13™] to be greater than -0.1.) **Hypothesis (H2):** V114 is non-inferior to Prevnar 13™ for the 2 unique V114 serotypes based on the response rate of the 2 unique V114 serotypes compared with the lowest response rate of any of the shared serotypes in Prevnar 13™, excluding serotype 3, 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 the response rates [V114 minus Prevnar 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 3**: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13™. **Hypothesis (H3):** V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes between V114 and Prevnar 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/ Prevnar 13™) to be greater than 0.5.) **Hypothesis (H4):** V114 is non-inferior to Prevnar 13™ for the 2 unique V114 serotypes based on the anti-PnPs serotype-specific IgG GMCs of the 2 unique V114 serotypes compared with the lowest IgG GMC of any of the shared serotypes in Prevnar 13™, excluding serotype 3, 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/ Prevnar 13™) to be greater than 0.5.)	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3

Objectives	Endpoints
• **Objective 4**: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13™. **Hypothesis (H5):** V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes between V114 and Prevnar 13™ based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4. (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/ Prevnar 13™) to be greater than 0.5.) **Hypothesis (H6):** V114 is non-inferior to Prevnar 13™ for the 2 unique V114 serotypes based on anti-PnPs serotype-specific IgG GMCs of the 2 unique V114 serotypes compared with the lowest IgG GMC of any of the shared serotypes in Prevnar 13™, excluding serotype 3, at 30 days following Dose 4. (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/ Prevnar 13™) to be greater than 0.5.)	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4)

Objectives	Endpoints
Secondary	
• **Objective 1**: To compare the antigen-specific response rate to each antigen and the antigen-specific GMCs for the pertussis antigens included in Pentacel™ at 30 days following Dose 3 for participants administered V114 concomitantly with Pentacel™ versus participants administered Prevnar 13™ concomitantly with Pentacel™. **Hypothesis (H7):** Pentacel™ administered concomitantly with V114 is non-inferior to Pentacel™ administered concomitantly with Prevnar 13™ at 30 days following Dose 3 for each antigen included in Pentacel™.	Antibody responses to: • diphtheria toxoid • tetanus toxoid • pertussis toxin (PT) • pertussis filamentous hemagglutinin (FHA) • pertussis fimbrae types 2/3 (FIM 2/3) • pertussis pertactin (PRN) • poliovirus serotypes 1, 2, and 3 • *Haemophilus influenzae* type b polyribosylribitol phosphate (Hib-PRP) at 30 days PD3 of V114 or Prevnar 13™
• **Objective 2:** To compare the response rate to anti-hepatitis A antigen at 30 days following Dose 4 for participants administered V114 concomitantly with VAQTA™ versus participants administered Prevnar 13™ concomitantly with VAQTA™. **Hypothesis (H8)**: VAQTA™ administered concomitantly with V114 is non-inferior to VAQTA™ administered concomitantly with Prevnar 13™ at 30 days following Dose 4.	• Antibody responses to hepatitis A antigen at 30 days PD4 of V114 or Prevnar 13™
• **Objective 3:** To compare the response rate to each antigen included in M-M-R™II at 30 days following Dose 4 for participants administered V114 concomitantly with M-M-R™II versus participants administered Prevnar 13™ concomitantly with M-M-R™II. **Hypothesis (H9)**: M-M-R™II administered concomitantly with V114 is non-inferior to M-M-R™II administered concomitantly with Prevnar 13™ at 30 days following Dose 4 for each antigen included in M-M-R™II.	• Antibody responses to measles, mumps, and rubella virus at 30 days PD4 of V114 or Prevnar 13™

Objectives	Endpoints
• **Objective 4:** To compare the response rate to anti-varicella antigen at 30 days following Dose 4 for participants administered V114 concomitantly with VARIVAX™ versus participants administered Prevnar 13™ concomitantly with VARIVAX™. **Hypothesis (H10)**: VARIVAX™ administered concomitantly with V114 is non-inferior to VARIVAX™ administered concomitantly with Prevnar 13™ at 30 days following Dose 4.	• Antibody responses to varicella-zoster virus (VZV) at 30 days PD4 of V114 or Prevnar 13™
• **Objective 5:** To compare the response rate to anti-PRP antigen at 30 days following Dose 4 for participants administered V114 concomitantly with HIBERIX™ versus participants administered Prevnar 13™ concomitantly with HIBERIX™. **Hypothesis (H11)**: HIBERIX™ administered concomitantly with V114 is non-inferior to HIBERIX™ administered concomitantly with Prevnar 13™ at 30 days following Dose 4.	• Antibody responses to PRP at 30 days PD4 of V114 or Prevnar 13™
• **Objective 6**: To compare the anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13™. **Hypothesis (H12):** V114 is superior to Prevnar 13™ for the 2 unique V114 serotypes based on the response rates at 30 days following Dose 3. **Hypothesis (H13):** V114 is superior to Prevnar 13™ for the 2 unique V114 serotypes based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3.	• Anti-PnPs serotype-specific IgG responses for the 2 unique serotypes contained in V114 at 30 days PD3

Objectives	Endpoints
• **Objective 7**: To compare the anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13™. **Hypothesis (H14):** V114 is superior to Prevnar 13™ for the 2 unique V114 serotypes based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4.	• Anti-PnPs serotype-specific IgG responses for the 2 unique serotypes contained in V114 at 30 days PD4
• **Objective 8:** To compare the anti-PnPs serotype 3 IgG responses at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13™. **Hypothesis (H15):** V114 is superior to Prevnar 13™ for serotype 3 based on the response rates at 30 days following Dose 3. **Hypothesis (H16):** V114 is superior to Prevnar 13™ for serotype 3 based on anti-PnPs IgG GMCs at 30 days following Dose 3.	• Anti-PnPs serotype 3 IgG responses at 30 days PD3
• **Objective 9:** To compare the anti-PnPs serotype 3 IgG GMCs at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13™. **Hypothesis (H17):** V114 is superior to Prevnar 13™ for serotype 3 based on anti-PnPs IgG GMCs at 30 days following Dose 4.	• Anti-PnPs serotype 3 IgG responses at 30 days PD4
• **Objective 10 (OPA Subset):** To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) and response rates 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

Objectives	Endpoints
Tertiary/Exploratory	
• **Objective 1:** To evaluate the anti-PnPs serotype-specific IgG GMCs immediately prior to Dose 4 by each vaccination group.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 immediately prior to Dose 4 (Predose 4)
• **Objective 2 (OPA Subset):** To evaluate the anti-PnPs serotype-specific OPA GMTs and response rates immediately prior to Dose 4 and 30 days following Dose 4 by each vaccination group.	• Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 Predose 4 and at 30 days PD4
• **Objective 3**: To evaluate the response rate to anti-PRP antigens with an alternative threshold value by each vaccination group a. for participants administered Pentacel™ concomitantly with V114 and participants administered Pentacel™ concomitantly with Prevnar 13™ at 30 days following Dose 3 b. for participants administered HIBERIX™ concomitantly with V114 and participants administered HIBERIX™ concomitantly with Prevnar 13™ at 30 days following Dose 4	• Antibody responses to PRP at 30 days PD3 and 30 days PD4 of V114 or Prevnar 13™

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active comparator-controlled, parallel-group, multi-site, double-blind (with in-house blinding) study of V114 in healthy infants enrolled at approximately 2 months of age (from 42 to 90 days [inclusive]). Approximately 1720 individuals will be randomly assigned, in 1:1 ratio, to receive either V114 (860 participants) or Prevnar 13™ (860 participants).

A 0.5 mL intramuscular dose of V114 or Prevnar 13™ will be administered (blinded) to healthy infants at approximately 2, 4, 6, and 12 to 15 months of age. All participants will also receive pediatric vaccines as part of the study design according to the ACIP-recommended schedule (Section 1.3 and Table 2). These vaccines will be administered open label and include RotaTeq™, Pentacel™, RECOMBIVAX HB™, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™.

Participants will be followed for injection-site and systemic AEs through Day 14 following each vaccination with V114 or Prevnar 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 for immunogenicity assays will be collected at 3 timepoints: (1) 30 days after the completion of the 3-dose primary series (PD3), (2) immediately before receipt of Dose 4 (Predose 4), and (3) 30 days after Dose 4 (PD4).

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 2 months of age (42 to 90 days of age). These infants are at increased risk for pneumococcal disease and its associated morbidity and mortality [Drijkoningen, J. J 2014]. The enrollment of infants in this study is intended to assess safety, tolerability, and immunogenicity in a population that is representative of children receiving commercially available PCVs and the recommended concomitant pediatric vaccines in the U.S. and non-U.S. countries.

The safety and immunogenicity endpoints are consistent with previous studies evaluating PCVs and immunogenicity of the concomitantly administered, pediatric vaccines when PCVs are given concomitantly.

Data from this study will contribute to the overall safety database and immunogenicity profile of V114 to support initial licensure of a 3+1 schedule in infants.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

The immunogenicity endpoints are consistent with previous studies evaluating PCVs (for the 13 shared serotypes between V114 and Prevnar 13™) and the concomitantly administered pediatric vaccines in this study.

The 2 unique V114 serotypes will be evaluated for non-inferiority to the immune response of the lowest of any of the shared serotypes in Prevnar 13™, excluding serotype 3, in alignment with the guidelines for the assessment of immune responses to PCVs from the World Health Organization [World Health Organization 2013]. For these comparisons, Prevnar 13™ serotype 3 immune responses will be excluded as the immunological profile of serotype 3 is not consistent with the performance of other Prevnar 13™ vaccine serotypes.

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 GMCs (primary endpoint), and MOPA measures serotype-specific OPA GMTs (secondary endpoint). 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.

MOPA requires a large volume of serum, which is difficult to obtain from infants. The PnECL assay requires less serum, and 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]. For these reasons, 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 World Health Organization (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 3 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 4 to evaluate the persistence of protective immunity (IgG GMCs, OPA GMTs, and OPA response rates)
- Approximately 30 days following Dose 4 to evaluate anamnestic antibody responses (IgG GMCs, OPA GMTs, and OPA response rates)

Due to the larger serum requirements of the MOPA, functional antibody activity (as measured by OPA GMTs) will be assessed in the first 20% of all participants with sufficient serum volume at PD3 to evaluate OPA responses (OPA Subset). Additionally, evaluation of OPA responses will be conducted at Predose 4 and PD4 for 50% of the participants who had OPA performed at PD3, 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 Prevnar 13™:

- Diphtheria toxoid, tetanus toxoid, pertussis (PT, FHA, FIM2/3, PRN), poliovirus (serotypes 1, 2, and 3), and PRP-Hib at PD3

- Hepatitis A, measles virus, mumps virus, rubella virus, VZV, and PRP-Hib at PD4

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] [Bernstein, H. H., et al 2007]. 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] [Schmitt, H. J., et al 1996] [Vesikari, T., et al 2017].

Results from clinical studies with Prevnar 13™ indicate that Prevnar 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. 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 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 (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from

appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator

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

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

4.3 Justification for Dose

The 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 Prevnar 13™. Refer to V114 IB for details on dosing schedule.

To support initial licensure in countries that use the 3+1 Prevnar 13™ dosing schedule (3 doses in the infant primary series followed by 1 toddler dose), this study will use the currently approved dose and United States ACIP-recommended 3+1 dosing schedule of Prevnar 13™.

4.4 Beginning and End of Study Definition

The overall study begins when documented informed consent is provided for the first participant. The overall study ends when the last participant completes the last study-related contact, 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.

5 STUDY POPULATION

Healthy male and female infants approximately 2 months of age, from 42 to 90 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 a review of medical history and physical examination) based on the clinical judgement of the investigator.

Demographics

2. Is male or female, approximately 2 months of age, from 42 days to 90 days inclusive, at the time of obtaining 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.

5.2 Exclusion Criteria

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

Medical Conditions

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

2. 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.

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

4. *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.

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

6. Has a history of congenital or acquired immunodeficiency.

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

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

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

10. Has failure to thrive based on the clinical judgement of the investigator.

11. Has a bleeding disorder contraindicating intramuscular vaccination.

12. 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).

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

Prior/Concomitant Therapy

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

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

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

17. *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/d 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.

18. *Has received other licensed non-live vaccines within 14 days before receipt of study vaccines or is scheduled to receive any licensed non-live vaccine within 30 days following receipt of study vaccines. **Exception**: Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of study vaccines or at least 15 days after receipt of study vaccines.

19. *Has received a licensed live vaccine within 30 days before receipt of study vaccines or is scheduled to receive any live vaccine within 30 days following receipt of study vaccines.

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

Prior/Concurrent Clinical Study Experience

21. 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

22. 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.

23. 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, Prevnar 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 intervention(s) to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength (s)	Dosage Level(s)	Route of Admin.	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
V114	Experimental	V114	Biological /Vaccine	Sterile Suspension	Refer to IB	0.5 mL	IM	Single dose at Visits 1, 2, 3, and 5	Experimental	IMP	Central
V114	Experimental	RotaTeq™	Biological /Vaccine	Sterile Solution	Refer to product labeling	2 mL	Oral	Single dose at Visits 1, 2, and 3	Background Treatment	NIMP	Central or Local
V114	Experimental	Pentacel™	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3	Experimental	IMP	Central or Local
V114	Experimental	RECOMBIVAX HB™*	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3	Background Treatment	NIMP	Central or Local
V114	Experimental	VAQTA™	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visit 5	Experimental	IMP	Central or Local
V114	Experimental	M-M-R™II	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 5	Experimental	IMP	Central or Local
V114	Experimental	VARIVAX™	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 5	Experimental	IMP	Central or Local
V114	Experimental	HIBERIX™	Biological /Vaccine	Sterile Solution	Refer to product labeling	0.5 mL	IM	Single dose at Visit 5	Experimental	IMP	Central or Local

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
Prevnar 13™	Active Comparator	Prevnar 13™	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, 3, and 5	Experimental	IMP	Central
Prevnar 13™	Active Comparator	RotaTeq™	Biological /Vaccine	Sterile Solution	Refer to product labeling	2 mL	Oral	Single dose at Visits 1, 2, and 3	Background Treatment	NIMP	Central or Local
Prevnar 13™	Active Comparator	Pentacel™	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3	Experimental	IMP	Central or Local
Prevnar 13™	Active Comparator	RECOMBIVAX HB™*	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visits 1, 2, and 3	Background Treatment	NIMP	Central or Local
Prevnar 13™	Active Comparator	VAQTA™	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	IM	Single dose at Visit 5	Experimental	IMP	Central or Local
Prevnar 13™	Active Comparator	M-M-R™II	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 5	Experimental	IMP	Central or Local
Prevnar 13™	Active Comparator	VARIVAX™	Biological /Vaccine	Sterile Suspension	Refer to product labeling	0.5 mL	SC	Single dose at Visit 5	Experimental	IMP	Central or Local
Prevnar 13™	Active Comparator	HIBERIX™	Biological /Vaccine	Sterile Solution	Refer to product labeling	0.5 mL	IM	Single dose at Visit 5	Experimental	IMP	Central or Local

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
Admin=administration; IB=Investigator's Brochure; IM=intramuscular; IMP=investigational medicinal product; NIMP=non-investigational medicinal product; SC=subcutaneous. Definition: Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed. *For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ will be administered at Visits 1 and 3.											

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 receive V114 or Prevnar 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 Prevnar 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 Prevnar 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, RotaTeq™, Pentacel™, RECOMBIVAX HB™, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™) 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, Prevnar 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 ongoing study (see Section 5.2 for details). If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant'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 electronic case report form (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 schedule recommended by the U.S. ACIP (Table 2). Non-U.S. countries participating in this study must follow the U.S. vaccination schedule. The ACIP recommends that hepatitis B vaccine be given at birth; however, guidelines for non-U.S. counties may differ. For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ will be administered at ~2 and 6 months of age and not at ~4 months of age.

In addition to concomitant vaccines being provided in the study (Table 2), other non-study pediatric vaccines may be permitted according to local, regional, and/or country guidelines and according to the restrictions outlined in Section 5.2. If the fourth dose of diphtheria, tetanus, and acellular pertussis vaccination and the second dose of hepatitis A vaccination is scheduled to be given during the study, these vaccinations should be given after the final blood draw of the study (Visit 6). If the participant is scheduled to receive any other non-study pediatric vaccine, the investigator should discuss this with the Sponsor Clinical Director as soon as possible. These vaccinations should be recorded on the appropriate eCRF.

During influenza season, it is anticipated that participants 6 months of age and older may be given an influenza vaccine. Influenza vaccine should be administered at least 7 days prior to or at least 15 days after the administration of the study vaccine.

Concomitant vaccines (oral or injectable) should be administered on the same day as V114 or Prevnar 13™. RotaTeq™ is administered orally and should be given before V114 or

Prevnar 13™ and other injectable concomitant vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines. Other pediatric injectable vaccines administered concomitantly should be given after V114 or Prevnar 13™. To avoid any confounding results, concomitant injectable vaccines should not be administered in the same limb as V114 or Prevnar 13™. Recommended injection-site locations for V114 or Prevnar 13™ and concomitant injectable vaccines 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] **(Generic Name)**	**Indication**	**Visit 1 (~2 months of age)**	**Visit 2 (~4 months of age)**	**Visit 3 (~6 months of age)**	**Visit 5 (~12 to 15 months of age)**
RotaTeq™ [b] (Rotavirus Vaccine, Live, Oral, Pentavalent)	Prevention of rotavirus gastroenteritis	X	X	X	
Pentacel™ (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine)	Prevention of diphtheria, tetanus, pertussis, poliomyelitis, and invasive disease due to *Haemophilus influenzae* type b	X	X	X	
RECOMBIVAX HB™ (Hepatitis B Vaccine [Recombinant])	Prevention of hepatitis B virus infection	X	X [c]	X	
VAQTA™ (Hepatitis A Vaccine, Inactivated)	Prevention of hepatitis A infection				X
M-M-R™II (Measles, Mumps, and Rubella Virus Vaccine Live)	Prevention of measles, mumps, and rubella				X
VARIVAX™ (Varicella Virus Vaccine Live)	Prevention of varicella				X
HIBERIX™ (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate])	Prevention of invasive disease caused by *Haemophilus influenzae* type b				X

[a] Tradenames for licensed vaccines may vary depending on where clinical supplies are sourced by the Sponsor.
[b] RotaTeq™ is administered orally and should be given before V114 or Prevnar 13™ and other concomitant vaccines. Injectable vaccines administered in the study should be given after V114 or Prevnar 13™.
[c] For participants who received the first dose of hepatitis B vaccine before enrollment, RECOMBIVAX HB™ will be administered at ~2 and 6 months of age.

Table 3 Recommended Injection-site Locations for Study Interventions

Vaccine	**Recommended Injection Site**
V114 or Prevnar 13™	Right thigh
PENTACEL™	Left upper thigh
RECOMBIVAX HB™	Left lower thigh
VAQTA™	Left lower thigh
M-M-R™II	Right arm
VARIVAX™	Left arm
HIBERIX™	Left upper thigh

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 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.

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, Prevnar 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 is unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places 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 4, 5, and 6 for immunogenicity assays. The maximum amount of blood collected from each participant over the duration of the study will not exceed 15 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

Informed consent given by the participant's legally acceptable representative must be documented on a consent form. The form must include the study protocol number, protocol title, dated signature, and agreement of the participant's legally acceptable representative and of the person conducting the consent discussion.

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

The initial ICF, any subsequent revised 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 the study and the study population are to be included in the study informed consent form.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study. The investigator should consult with the Sponsor's Clinical Director for any questions about participant eligibility.

If the participant meets any of the Exclusion Criteria with an asterisk (*), Visit 1 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 documented 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 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 non-study 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 Prevnar 13™. Documentation of which limb was used for the administration of V114 or Prevnar 13™ must be recorded on the eVRC (Section 8.1.9 and 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 Prevnar 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.

Prevnar 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 2, 4, 6, and 12 to 15 months of age. The study vaccines are to be administered at the locations recommended in Table 3. Documentation of which limb was used for the administration of V114 or Prevnar 13™ should be recorded on the appropriate eCRF. This information should also be recorded on the eVRC to inform the participant's legally acceptable representative of the appropriate limb to monitor for AEs related to the V114 or Prevnar 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 Prevnar 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 Prevnar 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 Food and Drug Administration 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 non-study 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 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 vaccinations 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 6) 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.

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

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

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

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 pre-specified 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 Prevnar™. 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 Prevnar™ 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 Prevnar 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 Prevnar 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 United States World Health Organization 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 microcolony platform. The MOPA assay for all 15 V114 serotypes has undergone validation. The validation study evaluated various performance parameters of the assay including precision, relative accuracy/dilutional linearity, and specificity. The validation results were evaluated against pre-specified acceptance criteria for each of the parameters.

8.2.3 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 Micrometabolic Inhibition Test-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 micrometabolic inhibition test (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.

8.2.5 Hepatitis A Virus Enzyme Immunoassay

The Hepatitis A Virus Enzyme Immunoassay (HAV EIA) is a double antigen sandwich immunoassay developed for the quantitation of total anti-HAV antibodies in human serum. In this assay, inactivated HAV antigen is bound to solid phase microtiter plates and serum containing anti-HAV antibodies is added. The anti-HAV antibodies bind to the HAV antigen-coated plates, forming antibody-antigen complexes. The bound antibody-antigen complexes are then detected using alkaline phosphatase-labeled HAV antigen. Color development occurs as a result of the addition of an enzyme-specific substrate. The color intensity is then measured spectrophotometrically, and quantitation of the concentration of human antibody to HAV in the sample is determined by interpolation of the test sample optical density (OD) from an assay standard curve prepared from the WHO International Standard for Anti-Hepatitis A immunoglobulin. A negative control and 3 positive controls spanning a range of assay concentrations are also included on each assay plate. Antibody concentration is measured in milli-International Units per milliliter (mIU/mL).

8.2.6 Bulk Measles IgG Enzyme Immunoassay

The purpose of the Bulk Measles IgG EIA is to detect total IgG antibody to measles virus after vaccination with a measles-containing vaccine. Plates are coated using inactivated measles antigen that is bound to solid phase microtiter plates. The antigen is derived from Measles Edmonston strain-infected Vero cells. Serum or plasma is added to the coated plates and samples positive for measles antibodies will bind to the measles antigen-coated plates, forming antibody-antigen complexes. The bound antibody-antigen complexes can then be detected using an alkaline phosphatase-labeled anti-human IgG. Color development occurs as a result of the addition of an enzyme-specific substrate phenolphthalein monophosphate. The color intensity is then measured spectrophotometrically with the highest intensity of color correlating to a high level of measles antibody and lowest color intensity correlating to low levels of measles antibody. Quantitation of the human IgG antibody to measles virus or titer is determined by comparison of the resulting OD to a standard curve. The reference standard is a pool of human sera that has been calibrated against the WHO anti-measles reference

standard, lot NIBSC 66/202. The concentration of anti-measles antibody in a sample is reported in mIU/mL of serum.

8.2.7 Mumps Enzyme-linked Immunosorbent Assay

The purpose of the mumps ELISA is to detect IgG antibody to mumps virus after vaccination with a mumps virus-containing vaccine. The assay uses an earlier passage of the Jeryl Lynn® mumps virus (Jeryl Lynn® 135 [JL135], <12 passages), which is considered to be a wild-type (WT)-like strain. The reactivity of the sera to the mumps antigens prepared from uninfected Vero cells (denoted as tissue culture control [TCC] wells) is subtracted from that of JL135-infected Vero cells. JL135 mumps virus antigen or TCC is bound to solid phase microtiter plates and serum containing mumps antibody is added. The mumps antibody bound to the WT mumps antigen-coated plates forms an antibody-antigen complex. The bound antibody-antigen complex is then detected using an enzyme-labeled anti-human IgG. Color development occurs with the addition of a substrate and color intensity is measured spectrophotometrically. Results are obtained as a difference of the average duplicate of each OD of JL135 mumps antigen wells and the average duplicate OD of TCC wells for each serum sample (noted as delta optical density [DOD]). Quantitation of the human IgG antibody to mumps virus, or antibody concentration, is determined by comparison of the resulting test DOD to a standard curve. The reference standard is an individual human serum. Results for the assay are reported as the concentration of antibody in Mumps antibody units/mL.

8.2.8 Bulk Rubella IgG EIA

The purpose of the Bulk Rubella IgG EIA is to detect total IgG antibody to rubella virus after vaccination with a rubella-containing vaccine. Plates are coated in house using inactivated rubella antigen that is bound to solid phase microtiter plates. The antigen is derived from Rubella HPV-77 infected Vero cells. Serum is added to the coated plates and samples positive for rubella antibodies will bind to the rubella antigen-coated plates, forming antibody-antigen complexes. The bound antibody-antigen complexes can then be detected using an alkaline phosphatase-labeled anti-human IgG. Color development occurs as a result of the addition of an enzyme-specific substrate, phenolphthalein monophosphate. The color intensity is then measured spectrophotometrically with the highest intensity of color correlating to a high level of rubella antibody and lowest color intensity correlating to low levels of rubella antibody.

Quantitation of the human IgG antibody to rubella virus or titer is determined by comparison of the resulting analysis OD to a standard curve. The reference standard is an individual human serum that has been calibrated against the WHO anti-rubella reference standard. The concentration of anti-rubella antibody in a sample is reported in International Units per milliliter (IU/mL) of serum.

8.2.9 Glycoprotein Enzyme-linked Immunosorbent Assay

The purpose of the glycoprotein ELISA (gpELISA) is to detect IgG antibody to varicella-zoster virus (VZV) after vaccination with VZV-containing vaccine(s). This method detects

antibodies to VZV glycoprotein (gp), which have been purified from MRC-5 cells infected with the KMcC strain of VZV by lectin affinity chromatography. The assay uses the "second antibody" format with varicella gp antigen and MRC5 TCC glycoprotein coated on the solid phase microtiter plate. Diluted sera are dispensed into 2 VZV gp antigen-coated wells and 2 MRC5 gp coated wells for each standard curve point, control, and sample. Antibody to VZV in a test sample binds to the antigen-coated plate. Antibody to varicella glycoprotein in a test sample, bound to the antigen on the solid phase microtiter plate is subsequently detected using goat anti-human IgG alkaline phosphatase conjugate. After substrate addition for color development, quantitation is obtained by comparison of sample DOD to a standard curve. The DOD is determined by subtracting the average OD of the TCC coated wells from its corresponding VZV gp average OD with a standard curve. Assay results are reported as concentration of antibody in gpELISA units/mL.

8.2.10 *Haemophilus Influenza* Type b IgG ELISA

The *Haemophilus influenza* Type b IgG ELISA for the in-vitro measurement of specific IgG antibodies against *Haemophilus influenza* type b (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-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 450nm 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.

8.3 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.

The complete and targeted physical examination procedures both 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 Prevnar 13™ will be recorded in the eVRC (Note: the study will report injection-site AEs from V114 or Prevnar 13™ only; the location of V114 or Prevnar 13™ administration can be used by the participant or participant's legally acceptable representative to monitor the appropriate limb for injection-site AEs related to V114 or Prevnar 13™).

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 non-study vaccinations Day 1 to Day 14 postvaccination

8.3.4 Clinical 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 documented informed consent is provided but before allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

All AEs, SAEs, and other reportable safety events must be reported by the investigator from the day of allocation/randomization to the first vaccination and from the day of each

vaccination through 14 days postvaccination. SAEs must also be reported throughout the duration of the individual's participation in the study, regardless of whether or not related to the Sponsor's product.

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

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

OR

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 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 events of clinical interest 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 with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for 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 any 24-hour period.

No specific information is available on the treatment of overdose.

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

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

8.6 Pharmacokinetics

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 provides documented informed consent for future biomedical research, 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, Prevnar 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 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 to 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 4-dose Regimen of V114 in Healthy Infants (PNEU-PED)
Treatment Assignment	Participants will be randomly assigned in a 1:1 ratio to V114 or Prevnar 13™, respectively.
Analysis Populations	**Immunogenicity**: Per-Protocol (PP) **Safety**: All Participants as Treated (APaT)

Primary Endpoint(s)	**Immunogenicity:** • Anti-PnP serotype-specific IgG response rates (proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3) • Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 • Anti-PnPs serotype-specific IgG GMCs at 30 days PD4 **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 Prevnar 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 Prevnar 13™ • Proportion of participants with vaccine-related SAEs from Day 1 through completion of study participation
Key Secondary Endpoints	• Antigen-specific response rates for all antigens and the antigen-specific GMCs for the pertussis antigens included in Pentacel™ at 30 days PD3 when administered concomitantly with V114 or Prevnar 13™ • Anti-hepatitis A response rate at 30 days PD4 for VAQTA™ when administered concomitantly with V114 or Prevnar 13™ • Antigen-specific response rates at 30 days PD4 for all antigens included in M-M-R™II when administered concomitantly with V114 or Prevnar 13™ • Anti-VZV response rate at 30 days PD4 for VARIVAX™ when administered concomitantly with V114 or Prevnar 13™ • Anti-PRP response rate at 30 days PD4 for HIBERIX™ when administered concomitantly with V114 or Prevnar 13™ • Anti-PnPs serotype-specific IgG GMCs and IgG response rates at 30 days PD3 for the 2 unique V114 serotypes • Anti-PnPs serotype-specific IgG GMCs at 30 days PD4 for the 2 unique V114 serotypes • Anti-PnPs serotype 3 IgG response rates at 30 days PD3 • Anti-PnPs serotype 3 IgG GMCs at 30 days PD3 • Anti-PnPs serotype 3 IgG GMCs at 30 days PD4
Statistical Methods for Key Immunogenicity	To address the primary immunogenicity objectives in terms of IgG response rates (H1 and H2), the between-treatment comparison will be made based on the proportion of anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3 for 13 shared serotypes contained in V114 and Prevnar 13™ and 2 unique serotypes contained in V114. The between-treatment difference (V114 minus Prevnar 13™) and its 95% CI will be calculated using Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985]. To address the primary immunogenicity objectives in terms of serotype-specific IgG GMCs at 30 days PD3 (H3 and H4) and 30 days PD4 (H5 and H6), the between-treatment comparison will be made based on serotype-specific IgG GMCs for 13 shared serotypes contained in V114 and Prevnar 13™ and 2 unique serotypes contained in V114. The 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 concentration as the response and a single term for vaccination group.

	To address the secondary objectives for evaluating the concomitant vaccines, the between-group comparison will be made based on the response rate of the antigens contained in Pentacel™ at 30 days PD3 and the antigens contained in VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ at 30 days PD4. The between-treatment comparison will be made based on the proportion of participants achieving the antigen-specific antibody threshold value. The between-treatment difference (V114 minus Prevnar 13™) and the corresponding 95% CIs will be calculated using the M&N method. In addition, the between-group comparison will be made based on the antigen-specific GMCs of pertussis contained in Pentacel™ at 30 days PD3. Estimation of the 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. These hypothesis tests 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. To address the secondary objectives for evaluating the 2 unique V114 serotypes, between-group comparisons will be made based on the anti-PnPs serotype-specific IgG response rates and GMCs at 30 days PD3, and the anti-PnPs serotype-specific IgG GMCs at 30 days PD4, for the 2 V114 unique serotypes. Analysis of the IgG response rates will be performed using the M&N method (1985) [Miettinen, O. and Nurminen, M. 1985]. 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. To address the secondary objectives for evaluating the superiority of serotype 3, between-group comparisons will be made based on the anti-PnPs serotype 3 IgG response rates and IgG GMCs at 30 days PD3 and IgG GMCs at 30 days PD4. Analysis of the IgG response rates will be performed using the M&N method (1985) [Miettinen, O. and Nurminen, M. 1985]. 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 concentrations as the response and a single term for vaccination group.
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 (1985)[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 Data Monitoring Committee (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 objectives if non-inferiority is demonstrated for the 13 shared serotypes and for the 2 unique serotypes for IgG GMCs and response rate at 30 days PD3 and for IgG GMCs at 30 days PD4. 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. The study will be considered to have met its secondary objective for the superiority hypotheses for the 2 unique V114 serotypes if superiority is demonstrated for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. The study will be considered to have met its secondary objective for the superiority hypotheses for serotype 3 if superiority is demonstrated for IgG response rates and IgG GMCs at 30 days PD3 and IgG GMCs at 30 days PD4. No multiplicity adjustments will be made for the safety objective.
Sample Size and Power	**Immunogenicity:** The study will randomize participants in a 1:1 ratio to V114 or Prevnar 13™, respectively. The overall sample size will be approximately 1720 with 860 participants into each vaccination group. The sample size was chosen to ensure sufficient power for the multiple endpoints across both primary and secondary hypotheses. With this study sample size, the overall power for all the primary hypotheses is >95%. The overall power for the secondary hypotheses for concomitant antigens evaluation is approximately 90%, and to demonstrate superiority for the 2 unique V114 serotypes is >95%. The overall power is >95% to demonstrate the superiority for the serotype 3 IgG response rates and IgG GMCs at 30 days PD3 and 94% to demonstrate the superiority for IgG GMCs at 30 days PD4. All statistical tests will be conducted at 1-sided 2.5% alpha level. Details are provided in Section 9.9.1. **Safety:** Section 9.9.2 provides information about the ability of this study to estimate the incidence of AEs within and between the vaccination groups.

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

9.4.1 Immunogenicity Endpoints

A description of immunogenicity assessments is contained in Section 8.2.

The primary immunogenicity analysis endpoints include:

- Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD3
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD4

The secondary immunogenicity analysis endpoints include:

- Antigen-specific response rates for all antigens and antigen-specific GMCs for the pertussis antigens included in Pentacel™ at 30 days PD3 when administered concomitantly with V114 or Prevnar 13™
- Anti-hepatitis A response rate at 30 days PD4 for VAQTA™ when administered concomitantly with V114 or Prevnar 13™
- Antigen-specific response rates at 30 days PD4 for all antigens included in M-M-R™II when administered concomitantly with V114 or Prevnar 13™
- Anti-VZV response rate at 30 days PD4 for VARIVAX™ when administered concomitantly with V114 or Prevnar 13™
- Anti-PRP response rate at 30 days PD4 for HIBERIX™ when administered concomitantly with V114 or Prevnar 13™
- Anti-PnPs serotype-specific IgG GMCs and IgG response rates at 30 days PD3 for the 2 unique V114 serotypes
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD4 for the 2 unique V114 serotypes
- Anti-PnPs serotype 3 IgG response rates at 30 days PD3
- Anti-PnPs serotype 3 IgG GMCs at 30 days PD3
- Anti-PnPs serotype 3 IgG GMCs at 30 days PD4

- 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 Predose4
- Anti-PnPs serotype-specific OPA GMTs and response rates Predose 4 and at 30 days PD4.
- Anti-PRP antigen response rates with an alternative threshold value at 30 days PD3 of V114 or Prevnar 13™ when administered concomitantly with Pentacel™ and 30 days PD4 of V114 or Prevnar 13™ when administered concomitantly with HIBERIX™

Table 5 summarizes the endpoints for the concomitant antigens.

Table 5 Summary of Endpoints for Concomitant Vaccine Antigens

Concomitant Vaccine	Antigen	Endpoint	Timepoint
Secondary Endpoints for Concomitant Vaccines			
Pentacel™	Diphtheria toxoid	% ≥ 0.1 IU/mL	PD3
	Tetanus toxoid	% ≥ 0.1 IU/mL	PD3
	Pertussis – PT	% ≥ 5 EU/mL	PD3
		GMC	PD3
	Pertussis – FHA	% ≥ 5 EU/mL	PD3
		GMC	PD3
	Pertussis – FIM 2/3	% ≥ 20 EU/mL	PD3
		GMC	PD3
	Pertussis – PRN	% ≥ 5 EU/mL	PD3
		GMC	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
	Hib-PRP	% ≥ 0.15 µg/mL	PD3
VAQTA™	Hepatitis A	% ≥ 10 mIU/mL	PD4
M-M-R™II	Measles	% ≥ 255 mIU/mL	PD4
	Mumps	% ≥ 10 mumps Ab units/mL	PD4
	Rubella	% ≥ 10 IU/mL	PD4
VARIVAX™	VZV	% ≥ 5 gpELISA units/mL	PD4
HIBERIX™	Hib-PRP	% ≥ 0.15 µg/mL	PD4

Concomitant Vaccine	Antigen	Endpoint	Timepoint
Exploratory Endpoints for Concomitant Vaccines			
Pentacel™	Hib-PRP	% ≥ 1.0 µg/mL	PD3
HIBERIX™	Hib-PRP	% ≥ 1.0 µg/mL	PD4
EU=endotoxin unit; FHA=filamentous hemagglutinin; FIM=fimbriae types 2 and 3; GMC=geometric mean concentrations; gpELISA= glycoprotein enzyme-linked immunosorbent assay; Hib-PRP=*Haemophilus influenzae* type b polyribosylribitol phosphate; IU=international units; mIU=milli-International Units; NAb=neutralizing antibodies; NI=non-inferiority; PD=postdose; PRN=pertactin; PT=pertussis toxin; VZV=varicella-zoster virus.			

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 Prevnar 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 Prevnar 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 Prevnar 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 Prevnar 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 Dose 4 with V114 or Prevnar 13™
- Participants body temperature measured Day 1 (day of vaccination) through Day 7 following any vaccination with V114 or Prevnar 13™

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

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

- Failure to receive primary infant series vaccination (V114 or Prevnar 13™ Doses 1, 2, and 3) 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 immunogenicity analyses at a particular timepoint include:

- Failure to receive Dose 4 of V114 or Prevnar 13™ according to vaccination schedule required at the timepoint for the analysis
- Failure to receive Pentacel™, VAQTA™, M-M-R™II, VARIVAX™, or HIBERIX™ according to vaccination schedule required at the timepoint for the analysis
- Failure to receive the scheduled doses of V114 or Prevnar 13™ (at least 28 days between Doses 1 and 2 and between Doses 2 and 3 [for PD3 and Predose 4 analysis], 12 months to 1 day prior to 16 months of age for Dose 4 [for PD4 analyses])
- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of blood sample at the timepoint 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 Full Analysis Set (FAS) population will also be performed for the primary immunogenicity endpoints and select secondary endpoints for the evaluation of concomitant vaccines. The FAS population consists of all randomized participants who received all study vaccinations required at the timepoint 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 All Participants as Treated (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 Prevnar 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. The analyses will be conducted for each of the 15 pneumococcal serotypes in V114 and each antigen in the concomitant vaccines separately.

Primary Endpoints/Hypotheses (H1 and H2)

The first primary objective is to compare the response rates of anti-PnPs serotype-specific IgG between V114 and Prevnar 13™ at 30 days PD3. The response rate is defined as the proportion of participants with anti-PnPs serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL. The objective 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.

For the 13 shared serotypes contained in V114 and Prevnar 13™, p_1 is the response rate for the V114 group and p_2 is the response rate for the Prevnar 13™ group. For the 2 serotypes unique to V114, p_1 is the response rate of the 2 unique serotypes for the V114 group and p_2 is the lowest response rate among all 13 shared serotypes, excluding serotype 3, for the Prevnar 13™ group. V114 is non-inferior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13™) is greater than -0.1. The M&N method (1985), an unconditional, asymptotic method, will be used for this analysis [Miettinen, O. and Nurminen, M. 1985].

Primary Endpoints/Hypotheses (H3 to H6)

The second primary objective and the third primary objective are to compare the anti-PnPs serotype-specific IgG GMCs between V114 and Prevnar 13™ at 30 days PD3 and 30 days PD4, respectively. The objectives will be assessed via the following non-inferiority hypotheses:

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

For the 13 shared serotypes contained in V114 and Prevnar 13™, GMC_1 is the anti-PnPs serotype-specific IgG GMCs for the V114 group and GMC_2 is the anti-PnPs serotype-specific IgG GMCs for the Prevnar 13™ group. For the 2 serotypes unique to V114, GMC_1 is the anti-PnPs serotype-specific IgG GMCs of the 2 unique serotypes for the V114 group and GMC_2 is the lowest anti-PnPs IgG GMCs among all 13 shared serotypes, excluding serotype 3, for the Prevnar 13™ group. A ratio of 0.5 corresponds to a 2.0-fold decrease of anti-PnPs serotype-specific IgG GMCs in the V114 group as compared with the Prevnar 13™ group. V114 is non-inferior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13™) is greater than 0.5. 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/Hypotheses (H7 to H11)

To address the secondary objectives for evaluating the concomitant vaccines, between-group comparison will be made based on the response rate of the antigens contained in Pentacel™ at 30 days PD3 and the antigens contained in VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ at 30 days PD4. The response rate is defined as the proportion of participants achieving the antigen-specific threshold value (Table 5 in Section 9.4.1). Each objective will be assessed 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 Prevnar 13™ group, and δ is the pre-specified non-inferiority margin and the values of δ are listed in Table 9 in Section 9.9. The concomitant vaccine administered concomitantly with V114 is non-inferior to the concomitant vaccine administered concomitantly with Prevnar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13™) is greater than δ. The M&N method (1985) will be used for this analysis.

In addition, the between-group comparison will be made based on the antigen-specific GMCs of pertussis contained in Pentacel™ at 30 days PD3. The objective will be assessed via the following non-inferiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 0.67$ versus
H_1: $GMC_1/GMC_2 > 0.67$,

where GMC_1 is the antigen-specific pertussis GMCs for the V114 group and GMC_2 is the antigen-specific pertussis GMCs for the Prevnar 13™ group. A ratio of 0.67 corresponds to a 1.5-fold decrease of antigen-specific pertussis GMCs in the V114 group as compared with the Prevnar 13™ group. V114 is non-inferior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13™) is greater than 0.67. Estimation of the 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/Hypotheses (H12, H13, and H14)

To address the secondary objectives for evaluating the 2 unique V114 serotypes, between-group comparisons will be made based on the anti-PnPs serotype-specific IgG response rates and GMCs at 30 days PD3, and the anti-PnPs serotype-specific IgG GMCs at 30 days PD4, for the 2 V114 unique serotypes. The response rate is defined as the proportion of participants with anti-PnPs serotype-specific IgG responses achieving the threshold value of 0.35 μg/mL.

The comparison of the response rates 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 Prevnar 13™ group. V114 is superior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13™) is greater than 0.1. The M&N method (1985), an unconditional, asymptotic method, will be used for this analysis [Miettinen, O. and Nurminen, M. 1985].

The comparison of the 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 the V114 group and GMC_2 is the anti-PnPs serotype-specific IgG GMCs for the Prevnar 13™ group. A ratio of 2.0 corresponds to a 2.0-fold increase of anti-PnPs serotype-specific IgG GMCs in the V114 group as compared with the Prevnar 13™ group. V114 is superior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 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/Hypotheses (H15, H16, and H17)

To address the secondary objectives for evaluating the superiority of serotype 3, between-group comparisons will be made based on the anti-PnPs serotype 3 IgG response rates and GMCs at 30 days PD3, and the anti-PnPs serotype 3 IgG GMCs at 30 days PD4. The response rate is defined as the proportion of participants with anti-PnPs serotype 3 IgG responses achieving the threshold value of 0.35 μg/mL.

The comparison of the response rates will be assessed via the following superiority hypothesis:

H0: p1-p2 ≤0 versus
H1: p1-p2 >0,

where p1 is the response rate for the V114 group and p2 is the response rate for the Prevnar 13™ group. V114 is superior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13™) is greater than 0. The M&N (1985) method, an unconditional, asymptotic method, will be used for this analysis [Miettinen, O. and Nurminen, M. 1985].

The comparison of the GMCs will be assessed via the following superiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 1.2$ versus
H_1: $GMC_1/GMC_2 > 1.2$,

where GMC_1 is the anti-PnPs serotype 3 IgG GMCs for the V114 group and GMC_2 is the anti-PnPs serotype 3 IgG GMCs for the Prevnar 13™ group. A ratio of 1.2 corresponds to a 1.2-fold increase of anti-PnPs serotype 3 IgG GMCs in the V114 group as compared with the Prevnar 13™ group. V114 is superior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13™) is greater than 1.2. Estimation of the IgG GMC ratios and computation of the corresponding 95% CIs will be performed using the 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.

Other Secondary Endpoints/Exploratory Endpoints

Other secondary/exploratory objectives include the evaluation of anti-PnPs serotype-specific IgG GMCs Predose 4 and the evaluation of anti-PnPs serotype-specific OPA GMTs and response rates at 30 days PD3, Predose 4, and at 30 days PD4.

The exploratory objectives also include the evaluation of anti-PRP response rate using an alternative threshold value (≥1.0 μg/mL) at 30 days PD3 of V114 or Prevnar 13™ when administered concomitantly with Pentacel™ and 30 days PD4 of V114 or Prevnar 13™ when administered concomitantly with HIBERIX™.

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 and 30 days PD4 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 Endpoints (H1 and H2)				
Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Primary Endpoints (H3 and 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	
Primary Endpoints (H5 and H6)				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD4	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 Endpoints (H7)				
Antigen-specific response rates for all antigens included in Pentacel™ at 30 days PD3	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Antigen-specific GMCs for all pertussis antigens included in Pentacel™ 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 Endpoints (H8)				
Anti-hepatitis A response rate at 30 days PD4	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints (H9)				
Antigen-specific response rates for all antigens included M-M-R™II at 30 days PD4	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Secondary Endpoints (H10)				
Anti-varicella response rate at 30 days PD4	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints (H11)				
Anti-PRP response rate at 30 days PD4	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints (H12)				
Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3 for the 2 unique V114 serotypes	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Secondary Endpoints (H13)				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 2 unique V114 serotypes	P	t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Secondary Endpoints (H14)				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD4 for the 2 unique V114 serotypes	P	t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Secondary Endpoints (H15)				
Proportion of participants with anti-PnPs serotype 3 IgG ≥0.35 µg/mL at 30 days PD3	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Secondary Endpoints (H16)				
Anti-PnPs serotype 3 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
Secondary Endpoints (H17)				
Anti-PnPs serotype 3 IgG GMCs at 30 days PD4	P	t-distribution with the variance estimate from a linear model[‡] (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Other Secondary Endpoints				
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

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
CI=confidence interval; FAS=full analysis set; GMC=geometric mean concentration; GMT=geometric mean titer; IgG=immunoglobulin G; OPA=opsonophagocytic activity; PD=postdose; PnPs=pneumococcal polysaccharide; PP=Per-Protocol; PRP=polyribosylribitol phosphate. † 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 M&N method (1985). 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/somnolence, hives or welts/urticaria, and appetite loss/decreased appetite) 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]).

In this study, membership in Tier 2 requires that at least 1% of the participants in any treatment group exhibit the event. The threshold of at least 1% was chosen to draw clinical meaningful inference. When less than 1% of participants report AEs in both groups, the 95% CI for the between-group difference may exclude zero. However, the clinical significance of these differences is unknown given the small number of participants who report AEs. 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 at least 1% of 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 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
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 ≥1% of participants in one of the vaccination groups)		X	X
Tier 3	Specific AEs by SOC and PT‡ (incidence <1 of 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 adverse event categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least one AE.
‡ Includes only those endpoints not pre-specified as Tier 1 or not already prespecified 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, and gender, birth weight, and gestational age), baseline characteristics, prior and concomitant vaccinations and therapies will be summarized by vaccination group either by descriptive statistics or categorical tables.

9.7 Interim Analyses

A periodic review of safety and tolerability data across the V114 Phase 3 pediatric program will be conducted by an independent, unblinded, external DMC. A description of the structure 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 objectives if non-inferiority is demonstrated for the 13 shared serotypes and for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. 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. The study will be considered to have met its secondary objective for the superiority hypotheses for the 2 unique V114 serotypes if superiority is demonstrated for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. The study will be considered to have met its secondary objective for the superiority hypotheses for serotype 3 if superiority is demonstrated for IgG response rates and IgG GMCs at 30 days PD3 and IgG GMCs at 30 days PD4.

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 1720 with 860 participants into each vaccination group. The sample size was chosen to ensure sufficient power for the multiple endpoints across both primary and secondary hypotheses.

With this study sample size and the assumptions listed below, the overall power for all the primary hypotheses is >95% to demonstrate non-inferiority of V114 to Prevnar 13™ for the 13 shared serotypes and the 2 unique serotypes for V114. The overall power for the secondary hypotheses for concomitant antigens evaluation is approximately 90%, to demonstrate superiority for the 2 unique V114 serotypes is >95%, and to demonstrate the superiority for the serotype 3 IgG response rates and IgG GMCs at 30 days PD3 is >95%, and IgG GMCs at 30 days PD4 is 94%.

The power for each individual hypothesis is provided below.

Primary Immunogenicity Endpoints/Hypotheses (H1 and H2)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes and the 2 unique serotypes based on the proportion of participants with anti-PnP serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL at 30 days PD3. This power is calculated based on (1) 80% evaluability rate (688 evaluable participants per treatment group), (2) a non-inferiority margin of -0.1 for the difference (V114 minus Prevnar 13™), and (3) a serotype-specific true response rate for the 13 shared serotypes between V114 and Prevnar 13™ and the 2 unique V114 serotypes (Table 8).

Table 8 Assumptions of the True Response Rates for V114 and Prevnar 13™ for the 15 Pneumococcal Serotypes in V114 at 30 Days PD3

Serotype	True Response Rate	
	V114	Prevnar 13™
Prevnar 13™ Types		
1	0.95	0.95
3	0.90	0.70
4	0.95	0.95
5	0.95	0.95
6A	0.95	0.95
6B	0.90	0.90
7F	0.95	0.95
9V	0.95	0.95
14	0.95	0.95
18C	0.95	0.95
19A	0.95	0.95
19F	0.95	0.95
23F	0.90	0.90
Non- Prevnar 13™ Types		
22F	0.95	NA
33F	0.90	NA

NA=not applicable; PD=postdose.
Comparison for the 2 unique V114 serotypes will be to the lowest responder among the shared serotypes in Prevnar 13™, excluding serotype 3. Based on our assumption, the comparator could be either serotype 6B or 23F (true response rate=0.90).

Primary Immunogenicity Endpoints/Hypotheses (H3 and H4)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes and the 2 unique serotypes based on the anti-PnP serotype-specific IgG GMCs at 30 days PD3. This power is calculated based on (1) 80% evaluability rate (688 evaluable participants per treatment group), (2) a non-inferiority margin of 0.5 for the GMC ratio (V114/Prevnar 13™), (3) a true GMC ratio of 1.0 for the 13 shared serotypes between V114 and Prevnar 13™ and for the 2 unique serotypes between V114 and the lowest GMC of any of the shared serotypes in Prevnar 13™, excluding serotype 3, and (4) the standard deviation of the natural log concentrations is 1.1 for the 13 shared serotypes between V114 and Prevnar 13™ and the 2 unique serotypes in V114.

Primary Immunogenicity Endpoints/Hypotheses (H5 and H6)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes and for the 2 unique serotypes based on the anti-PnP serotype-specific IgG GMCs at 30 days PD4. This power is calculated based on (1) 75% evaluability rate (645 evaluable participants per treatment group), (2) a non-

inferiority margin of 0.5 for the GMC ratio (V114/Prevnar 13™), (3) a true GMC ratio of 1.0 for the 13 shared serotypes between V114 and Prevnar 13™ and for the 2 unique serotypes between V114 and the lowest GMC of any of the shared serotypes in Prevnar 13™, excluding serotype 3, and (4) the standard deviation of the natural log concentrations is 1.1 for the 13 shared serotypes between V114 and Prevnar 13™ and the 2 unique serotypes in V114.

Secondary Immunogenicity Endpoints/Hypotheses (H7 to H11)

This study has approximately 90% power at a 1-sided 2.5% alpha-level to demonstrate Pentacel™, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ administered concomitantly with V114 is non-inferior to these vaccines administered concomitantly with Prevnar 13™ based on the response rate of antigens included in Pentacel™ at 30 days PD3, the GMCs of the pertussis antigens included in Pentacel™ at 30 days PD3, and the response rate of antigens included in VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ at 30 days PD4. This power assumes the same underlying response rate in both the V114 group and the Prevnar 13™ group for each antigen. Detailed assumptions for concomitant antigens are provided in Table 9.

Table 9 Summary of Endpoints and Power for Concomitant Vaccine Antigens

Concomitant Vaccine	Antigen	Endpoint	Timepoint	NI Margin (δ) (V114 versus Prevnar 13™)	Evaluability Rate	Assumed True RR or SD	Power
Pentacel™	Diphtheria toxoid	% ≥ 0.1 IU/mL	PD3	-10%	80%	RR=0.90	>95%
	Tetanus toxoid	% ≥ 0.1 IU/mL	PD3	-5%	80%	RR=0.97	
	Pertussis – PT	% ≥ 5 EU/mL	PD3	-10%	80%	RR=0.90	
		GMC	PD3	0.67	80%	SD=0.69	
	Pertussis – FHA	% ≥ 5 EU/mL	PD3	-10%	80%	RR=0.90	
		GMC	PD3	0.67	80%	SD=0.66	
	Pertussis – FIM 2/3	% ≥ 20 EU/mL	PD3	-10%	80%	RR=0.90	
		GMC	PD3	0.67	80%	SD=0.82	
	Pertussis – PRN	% ≥ 5 EU/mL	PD3	-10%	80%	RR=0.90	
		GMC	PD3	0.67	80%	SD=0.83	
	Poliovirus 1	% with NAb>=1:8 dilution	PD3	-5%	80%	RR=0.97	
	Poliovirus 2	% with NAb>=1:8 dilution	PD3	-5%	80%	RR=0.97	
	Poliovirus 3	% with NAb>=1:8 dilution	PD3	-5%	80%	RR=0.97	
	Hib-PRP	% ≥ 0.15 µg/mL	PD3	-10%	80%	RR=0.90	
VAQTA™	Hepatitis A	% ≥ 10 mIU/mL	PD4	-10%	70%	RR=0.95	>95%
M-M-R™II	Measles	% ≥ 255 mIU/mL	PD4	-5%	68%	RR=0.95	90%
	Mumps	% ≥ 10 mumps Ab units/mL	PD4	-5%	68%	RR=0.95	
	Rubella	% ≥ 10 IU/mL	PD4	-5%	68%	RR=0.95	
VARIVAX™	VZV	% ≥ 5 gpELISA units/mL	PD4	-10%	70%	RR=0.90	>95%
HIBERIX™	Hib-PRP	% ≥ 0.15 µg/mL	PD4	-10%	65%	RR=0.95	>95%

EU=endotoxin unit; FHA=filamentous hemagglutinin; FIM=fimbriae types 2 and 3; GMC=geometric mean concentrations; gpELISA=glycoprotein enzyme-linked immunosorbent assay; Hib-PRP=*Haemophilus influenzae* type b polyribosylribitol phosphate; mIU=milli-International Units; NAb=neutralizing antibodies; NI non-inferiority; PD=postdose; PRN=pertactin; PRP=polyribosylribitol phosphate; PT=pertussis toxin; RR=response rate; SD standard deviation (in natural log scale); VZV=varicella-zoster virus.

Secondary Immunogenicity Endpoints/Hypotheses (H12, H13, and H14)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is superior to Prevnar 13™ for the 2 unique serotypes based on the proportion of participants with anti-PnP serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL at 30 days PD3. This power is calculated based on (1) 80% evaluability rate (688 evaluable participants per treatment group), (2) a superiority margin of 0.1 for the difference (V114 minus Prevnar 13™), and (3) a serotype-specific true response rate for the 2 V114 unique serotypes (Table 10).

Table 10 Assumptions of the True Response Rates for V114 and Prevnar 13™ for the 2 V114 Unique Pneumococcal Serotypes at 30 Days PD3

Serotype	True Response Rate	
	V114	Prevnar 13™
22F	0.95	0.02
33F	0.90	0.02

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is superior to Prevnar 13™ for the 2 V114 unique serotypes based on the anti-PnP serotype-specific IgG GMCs at 30 days PD3 and 30 days PD4. This power is calculated based on (1) 80% evaluability rate at 30 days PD3 and 75% evaluability rate at 30 days PD4, (2) a superiority margin of 2.0 for the GMC ratio (V114/Prevnar 13™), (3) a true GMC ratio of 10.0, and (4) the standard deviation of the natural log concentrations is 1.1.

Secondary Immunogenicity Endpoints/Hypotheses (H15, H16, and H17)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate that V114 is superior to Prevnar 13™ for serotype 3 based on the proportion of participants with anti-PnP serotype 3 IgG responses achieving the threshold value of 0.35 µg/mL at 30 days PD3. This power is calculated based on (1) 80% evaluability rate (688 evaluable participants per treatment group), (2) a superiority margin of 0 for the difference (V114 minus Prevnar 13™), and (3) true response rates for serotype 3 as displayed in Table 11. These assumptions are based on the most current data available from the V114 program.

Table 11 Assumptions of the True Response Rates for V114 and Prevnar 13™ for Serotype 3 at 30 Days PD3

Serotype	True Response Rate	
	V114	Prevnar 13™
3	0.95	0.76

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is superior to Prevnar 13™ for serotype 3 based on the anti-PnP serotype 3 IgG GMCs at 30 days PD3 and 94% power based on the anti-PnP serotype 3 IgG GMCs at 30 days PD4. This power is calculated based on (1) evaluability rates of 80% at 30 days PD3 and 75% at 30 days PD4, (2) a superiority margin of 1.2 for the GMC ratio (V114/Prevnar 13™), (3) true GMC ratios

of 1.94 at 30 days PD3 and 1.38 at 30 days PD4, and (4) the standard deviations of the natural log concentrations of 0.75 at 30 days PD3 and 0.73 at 30 days PD4. These assumptions are based on the most current data available from the V114 program.

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 860 participants in each of the V114 group and Prevnar 13™ group if the underlying incidence of an SAE is 0.19% (1 of every 534 participants receiving the vaccine). There is a 50% chance of observing at least one SAE among 860 participants in each of the V114 group and Prevnar 13™ group if the underlying incidence of an SAE is 0.08% (1 of every 1241 participants receiving the vaccine). If no SAEs are observed among 860 participants in each of the V114 group and Prevnar 13™ group, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.43% (one in every 233 participants).

Table 12 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 860 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 12 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 860 Participants in each Group)

Incidence of Adverse Event		**Risk Difference**
V114 (%) N=860	**Prevnar 13™ (%) N=860**	**Percentage Points**
1.2	0.1	1.1
4.4	2.0	2.4
8.4	5.0	3.4
14.4	10.0	4.4
20.1	15.0	5.1
25.7	20.0	5.7
36.4	30.0	6.4
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 select safety endpoints (summary of AEs) as well as primary and select secondary immunogenicity endpoints. 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 Prevnar 13™, Pentacel™, VAQTA™, M-M-R™II, VARIVAX™ and HIBERIX™ 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 Interim Analyses) 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 documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor 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.
- Congenital Disorders (eg, present from birth) that are detected/diagnosed in an infant participant.

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

1. 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]

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

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

4. DNA: Deoxyribonucleic acid.

5. 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:

1. The biology of how drugs/vaccines work

2. Biomarkers responsible for how a drug/vaccine enters and is removed by the body

3. Other pathways drugs/vaccines may interact with

4. 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.

1. Participants for Enrollment

   All participants enrolled in the clinical study will be considered for enrollment in future biomedical research

2. 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.

3. 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.

4. Future Biomedical Research Specimen(s)

   Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the 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

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ACIP	Advisory Committee on Immunization Practices
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
DOD	delta optical density
DTP-6IgG	diphtheria, tetanus, and pertussis 6-valent IgG
ECG	electrocardiogram
ECL	electrochemiluminescence
eCRF	electronic case report form
EDC	electronic data collection
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
eVRC	electronic Vaccination Report Card
FAS	full analysis set
FBR	future biomedical research
FDA	U.S. 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
gp	glycoprotein
H	hypothesis
HAV EIA	hepatitis A virus enzyme immunoassay
Hib	*Haemophilus influenzae* type B
Hib-PRP	*Haemophilus influenzae* type b polyribosylribitol phosphate
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IPD	invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
IU/mL	International Units per milliliter
MIT	micrometabolic inhibition test
mIU/mL	milli-International Units per milliliter
M&N	Miettinen and Nurminen
MOPA	multiplexed opsonophagocytic assay
MSD	Merck Sharp & Dohme
OD	optical density

Abbreviation	Expanded Term
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
PnPs	pneumococcal polysaccharides
PD3	postdose 3
PD4	postdose 4
PnECL	pneumococcal electrochemiluminescence
PP	per-protocol
PRN	pertactin
PRP	polyribosylribitol phosphate
PT	Pertussis toxin
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TCC	tissue culture control
US	United States
VZV	varicella-zoster virus
WHO	World Health Organization
WT	wild type

11 REFERENCES

[Anttila, M., et al 1999]	Anttila M, Voutilainen M, Jäntti V, Eskola J, Käyhty H. Contribution of serotype-specific IgG concentration, IgG subclasses and relative antibody avidity to opsonophagocytic activity against Streptococcus pneumoniae. Clin Exp Immunol 1999;118(3):402-7.	[03QY70]
[Bernstein, H. H., et al 2007]	Bernstein HH, Eves K, Campbell K, Black SB, Twiggs JD, Reisinger KS, et al. Comparison of the safety and immunogenicity of a refrigerator-stable versus a frozen formulation of ProQuad (measles, mumps, rubella, and varicella virus vaccine live). Pediatrics 2007;119(6):e1299-e1305.	[03QSRG]
[Bryant, K. A., et al 2013]	Bryant KA, Gurtman A, Girgenti D, Reisinger K, Johnson A, Pride MW, et al. Antibody responses to routine pediatric vaccines administered with 13-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2013 Apr;32(4):383-8.	[0459FX]
[Burton, Robert L. and Nahm, Moon H. 2006]	Burton RL, Nahm MH. Development and validation of a fourfold multiplexed opsonization assay (MOPA4) for pneumococcal antibodies. Clin Vaccine Immunol 2006;13(9):1004-9.	[03QT2R]
[Centers for Disease Control and Prevention 2008]	Centers for Disease Control and Prevention (CDC). Invasive pneumococcal disease in children 5 years after conjugate vaccine introduction-eight states,1998-2005. MMWR Morb Mortal Wkly Rep. 2008 Feb 15;57(6):144-8.	[04KW8S]
[Centers for Disease Control and Prevention 2010]	Centers for Disease Control and Prevention. Prevention of Pneumococcal Disease Among Infants and Children - Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine; Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59(RR-11):1-19.	[03RSB6]
[Centers for Disease Control and Prevention 2015]	Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. 13th ed. Hamborsky J, Kroger A, Wolfe S, editors. Washington (DC): Department of Health and Human Services (HHS); c2015. Chapter 6, Vaccine administration; p. 79-106.	[0508PV]

[CLOPPER, C. J. and PEARSON, E. S. 1934]	Clopper CJ, Pearson ES. The use of confidence of fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03RRVC]
[Drijkoningen, J. J 2014]	Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect. 2014 May;20 Suppl 5:45-51.	[04NFHN]
[Edwards, K. M. 2014]	Edwards KM, Berbers GAM. Immune responses to pertussis vaccines and disease. J Infect Dis. 2014;209(suppl 1):S10-5.	[0533QY]
[Farrell, D. J, et al 2007]	Farrell DJ, Klugman KP, Pichichero M. Increased antimicrobial resistance among nonvaccine serotypes of Streptococcus pneumoniae in the pediatric population after the introduction of 7-valent pneumococcal vaccine in the United States. Pediatr Infect Dis J. 2007 Feb;26(2):123-8.	[04KWD9]
[Farrington, C. P. 1990]	Farrington CP, Manning G. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk. Stat Med Vol. 9,1447-1454 (1990)	[04FS6L]
[Guevara, M., et al 2016]	Guevara M, Barricarte A, Torroba L, Herranz M, Gil-Setas A, Gil F, et al. Direct, indirect and total effects of 13-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in children in Navarra, Spain, 2001 to 2014: cohort and case-control study. Euro Surveill. 2016;21(14).	[04KSQ3]
[Hicks, L. A., et al 2007]	Hicks LA, Harrison LH, Flannery B, Hadler JL, Schaffner W, Craig AS, et al. Incidence of Pneumococcal Disease Due to Non-Pneumococcal Conjugate Vaccine (PCV7) Serotypes in the United States during the Era of Widespread PCV7 Vaccination, 1998-2004. J Infect Dis 2007;196:1346-54.	[03QT0G]
[Jokinen, J., et al 2015]	Jokinen J, Rinta-Kokko H, Siira L, Palmu AA, Virtanen MJ, Nohynek H, et al. Impact of ten-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children a population-based study. PLoS One. 2015 Mar 17;10(3):e0120290.	[04KW7F]

[Lepoutre, A., et al 2015]	Lepoutre A, Varon E, Georges S, Dorleans F, Janoir C, Gutmann L, et al. Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001-2012. Vaccine. 2015 Jan 3;33(2):359-66.	[04KW88]
[Lexau, C. A., et al 2005]	Lexau CA, Lynfield R, Danila R, Pilishvili T, Facklam R, Farley MM, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA 2005;294(16):2043-51.	[03RBPW]
[Martinelli, D., et al 2014]	Martinelli D, Pedalino B, Cappelli MG, Caputi G, Sallustio A, Fortunato F, et al Towards the 13-valent pneumococcal conjugate universal vaccination: effectiveness in the transition era between PCV7 and PCV13 in Italy, 2010-2013. Hum Vaccin Immunother. 2014;10(1):33-9.	[04KW8B]
[Metlay, J. P., et al 2006]	Metlay JP, Fishman NO, Joffe M, Edelstein PH. Impact of pediatric vaccination with pneumococcal conjugate vaccine on the risk of bacteremic pneumococcal pneumonia in adults. Vaccine 2006;24:468-75.	[03RC46]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[Moore, M. R., et al 2015]	Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis. 2015 Feb 3. [Epub ahead of print].	[043MRP]
[Palmu, A. A., et al 2015]	Palmu AA, Kilpi TM, Rinta-Kokko H, Nohynek H, Toropainen M, Nuorti JP, et al. Pneumococcal conjugate vaccine and clinically suspected invasive pneumococcal disease. Pediatrics. 2015 Jul;136(1):e22-7.	[04KVRL]
[Pilishvili, Tamara, et al 2010]	Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010;201(1):32-41.	[03R5S4]

[Plotkin, S. A. 2010]	Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol 2010;17(7):1055-65.	[03RV0S]
[Romero-Steiner, S., et al 1997]	Romero-Steiner S, Libutti D, Pais LB, Dykes J, Anderson P, Whitin JC, et al. Standardization of an opsonophagocytic assay for the measurement of functional antibody activity against streptococcus pneumoniae using differentiated HL-60 cells. Clin Diagn Lab Immunol 1997;4(4):415-22.	[03NWQ5]
[Ruckinger, S., et al 2009]	Ruckinger S, van der Linden M, Reinert RR, von Kries R, Burckhardt F, Siedler A. Reduction in the incidence of invasive pneumococcal disease after general vaccination with 7-valent pneumococcal conjugate vaccine in Germany. Vaccine 2009;27:4136-41.	[03QYQQ]
[Schmitt, H. J., et al 1996]	Schmitt HJ, Muschenborn S, Wagner S, Knuf M, Bock HL, Bogaerts H, et al. Immunogenicity and reactogenicity of a bicomponent and a tricomponent acellular pertussis-diphtheria-tetanus (DTaP) vaccine in primary immunization and as second year booster: a double-blind, randomized trial. Int J Infect Dis. 1996 Jul;1(1):6-13.	[054BR7]
[U.S. Food and Drug Administration 2009]	U.S. Food and Drug Administration (CDER, CBER, CDRH). Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims [Internet]. Washington: U.S. Department of Health and Human Services; 2009. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf	[04MG9J]
[Vesikari, T., et al 2017]	Vesikari T, Rivera L, Korhonen T, Ahonen A, Cheuvart B, Hezareh M, et al. Immunogenicity and safety of primary and booster vaccination with 2 investigational formulations of diphtheria, tetanus and Haemophilus influenzae type b antigens in a hexavalent DTPa-HBV-IPV/Hib combination vaccine in comparison with the licensed Infanrix hexa. Hum Vaccin Immunother. 2017;13(7):1505-15.	[054BVK]

[Wagenvoort, G. H., et al 2016]	Wagenvoort GH, Knol MJ, de Melker HE, Vlaminckx BJ, van der Ende A, Rozenbaum MH, et al. Risk and outcomes of invasive pneumococcal disease in adults with underlying conditions in the post-PCV7 era, The Netherlands. Vaccine. 2016 Jan 12;34(3):334-40.	[04KTDB]
[Waight, P. A., et al 2015]	Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015 May;15(5):535-43.	[04KTF2]
[Weiss, S., et al 2015]	Weiss S, Falkenhorst G, van der Linden M, Imohl M, von Kries R. Impact of 10- and 13-valent pneumococcal conjugate vaccines on incidence of invasive pneumococcal disease in children aged under 16 years in Germany, 2009 to 2012. Euro Surveill. 2015 Mar 12;20(10):21057.	[04KTFC]
[Whitney, Cynthia G., et al 2003]	Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348(18):1737-46.	[03QT0D]
[World Health Organization 2005]	World Health Organization. WHO Expert Committee on Biological Standardization: fifty-fourth report. WHO technical report series, 927; Geneva 2005.	[03QTCN]
[World Health Organization 2008]	World Health Organization. WHO/Health Canada Consultation on Serological Criteria for Evaluation and Licensing of New Pneumococcal Vaccines. 2008 Jul 7-8. Ottawa, Canada, 2008:1-39.	[03R0JC]
[World Health Organization 2013]	World Health Organization. WHO expert committee on biological standardization, sixtieth report. Geneva (Switzerland): World Health Organization (WHO); c2013. Annex 3: recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines; p. 91-151.	[0587WR]

Supplemental Statistical Analysis Plan (sSAP)

TABLE OF CONTENTS

LIST OF TABLES

1 INTRODUCTION

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

2 SUMMARY OF CHANGES

2.1 Summary of Changes from Protocol SAP

A summary of changes is provided in the table below:

Section	Description of Change	Rationale
Section 3.4.1 Immunogenicity Endpoints	Added a paragraph to define OPA subset.	Revisions made for clarity.
Section 3.4.2 Safety Endpoints	Added a paragraph to specify the timeframe associated with the reporting of AEs.	Revisions made for clarity.
Section 3.5.1 Immunogenicity Analysis Populations	Added a table (Table 2) to display the effect of dosing deviations (ie, missed dose, out-of-window dose and extra dose) on the PP population.	Added to provide additional statistical analysis details/data derivations.
Section 3.5.1 Immunogenicity Analysis Populations	Updated one sentence in this section from "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" to "The FAS population consists of all randomized participants who received all study vaccinations required at the time point for the analysis and have at least one serology result at the time point for the analysis."	Revisions made to clarify the criteria for inclusion in the FAS population.
Section 3.5.2 Safety Analysis Population	Updated a sentence in this section from "Safety analyses will be conducted in the All Participants as Treated (APaT) population,	Revisions made to clarify the criteria for inclusion in the APaT population.

	which consists of all randomized participants who received at least one dose of study vaccination" to "Safety analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study vaccination for the time point of interest. For safety analyses following any dose of PCV, participants vaccinated with PCV at any time point will be included. For safety analyses following each dose of PCV, participants vaccinated with PCV at that dose will be included. Updated another sentence from "Safety parameters for cross-treated participants (ie, those who received vaccinations of both V114 and Prevnar 13™) will be summarized separately." to "Safety parameters for cross-treated participants (ie, those who inadvertently received vaccinations of both V114 and Prevnar 13™) will be excluded from the analyses and will be summarized separately."	
Section 3.6.1 Statistical Methods for Immunogenicity Analyses	Updated one sentence to provide Reverse Cumulative Distribution Curves for OPA titers at 30 days postdose 3 (PD3) and 30 days postdose 4 (PD4).	Added to provide additional statistical analysis details/data derivations.
Section 3.6.1 Statistical Methods for Immunogenicity Analyses	Added a paragraph to provide forest plots for IgG GMCs and IgG response rates at 30 days PD3, IgG GMCs at 30 days PD4 and response rates for concomitant vaccines at 30 days PD3 and 30 days PD4.	Added to provide additional statistical analysis details/data derivations.

Section 3.6.1 Statistical Methods for Immunogenicity Analyses	Added a paragraph and a table (Table 4) to explain how values below the LLOQ or above the ULOQ should be treated in various analyses.	Added to provide additional statistical analysis details/data derivations.
Section 3.6.2 Statistical Methods for Safety Analyses	Added a paragraph to explain AEs related to the concomitant vaccines administered as part of the protocol-specified regimen will be provided.	Added to provide additional statistical analysis details/data derivations.
Section 3.6.2 Statistical Methods for Safety Analyses	Added a paragraph to explain the rationale for not including laboratory AEs in the summary tables.	Added to provide additional statistical analysis details/data derivations.
Section 3.6.2 Statistical Methods for Safety Analyses	Added a paragraph to describe an additional supportive analysis of the proportion of participants with solicited complaints using the data collected directly from participants via the VRC.	Added to provide additional statistical analysis details/data derivations.
Section 3.6.3 Summaries of Demographic and Baseline Characteristics	Added a sentence to specify the age variable used for the analyses.	Added to provide additional statistical analysis details/data derivations.
Section 3.10 Subgroup Analyses	Added details of subgroup analyses.	Added to provide additional statistical analysis details/data derivations.
Throughout	Corrected minor typographical and grammatical errors.	Revisions made for accuracy.

2.2 Summary of Changes from Previous Versions of the sSAP

Previous Version	Current Version	Section	Description of Change	Rationale
None	19 May 2021	Not Applicable	Not Applicable	This is the first version of the sSAP.

3 ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 4-dose Regimen of V114 in Healthy Infants (PNEU-PED)
Treatment Assignment	Participants will be randomly assigned in a 1:1 ratio to V114 or Prevnar 13™, respectively.
Analysis Populations	**Immunogenicity**: Per-Protocol (PP) **Safety**: All Participants as Treated (APaT)
Primary Endpoint(s)	**Immunogenicity:** • Anti-PnP serotype-specific IgG response rates (proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3) • Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 • Anti-PnPs serotype-specific IgG GMCs at 30 days PD4 **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 Prevnar 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 Prevnar 13™ Proportion of participants with vaccine-related SAEs from Day 1 through completion of study participation
Key Secondary Endpoints	• Antigen-specific response rates for all antigens and the antigen-specific GMCs for the pertussis antigens included in Pentacel™ at 30 days PD3 when administered concomitantly with V114 or Prevnar 13™ • Anti-hepatitis A response rate at 30 days PD4 for VAQTA™ when administered concomitantly with V114 or Prevnar 13™ • Antigen-specific response rates at 30 days PD4 for all antigens included in M-M-R™II when administered concomitantly with V114 or Prevnar 13™ • Anti-VZV response rate at 30 days PD4 for VARIVAX™ when administered concomitantly with V114 or Prevnar 13™ • Anti-PRP response rate at 30 days PD4 for HIBERIX™ when administered concomitantly with V114 or Prevnar 13™ • Anti-PnPs serotype-specific IgG GMCs and IgG response rates at 30 days PD3 for the 2 unique V114 serotypes • Anti-PnPs serotype-specific IgG GMCs at 30 days PD4 for the 2 unique V114 serotypes • Anti-PnPs serotype 3 IgG response rates at 30 days PD3 • Anti-PnPs serotype 3 IgG GMCs at 30 days PD3

	Anti-PnPs serotype 3 IgG GMCs at 30 days PD4
Statistical Methods for Key Immunogenicity	To address the primary immunogenicity objectives in terms of IgG response rates (H1 and H2), the between-treatment comparison will be made based on the proportion of anti-PnPs serotype-specific IgG ≥0.35 μg/mL at 30 days PD3 for 13 shared serotypes contained in V114 and Prevnar 13™ and 2 unique serotypes contained in V114. The between-treatment difference (V114 minus Prevnar 13™) and its 95% CI will be calculated using Miettinen and Nurminen (M&N) method [Ref. 5.4: 03QCDT]. To address the primary immunogenicity objectives in terms of serotype-specific IgG GMCs at 30 days PD3 (H3 and H4) and 30 days PD4 (H5 and H6), the between-treatment comparison will be made based on serotype-specific IgG GMCs for 13 shared serotypes contained in V114 and Prevnar 13™ and 2 unique serotypes contained in V114. 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 for evaluating the concomitant vaccines, the between-group comparison will be made based on the response rate of the antigens contained in Pentacel™ at 30 days PD3 and the antigens contained in VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ at 30 days PD4. The between-treatment comparison will be made based on the proportion of participants achieving the antigen-specific antibody threshold value. The between-treatment difference (V114 minus Prevnar 13™) and the corresponding 95% CIs will be calculated using the M&N method. In addition, the between-group comparison will be made based on the antigen-specific GMCs of pertussis contained in Pentacel™ at 30 days PD3. Estimation of the 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 titers as the response and a single term for vaccination group. These hypothesis tests will be based on the lower bound of the 2-sided 95% CI to be greater than the prespecified margins listed in Section 3.9. To address the secondary objectives for evaluating the 2 unique V114 serotypes, between-group comparisons will be made based on the anti-PnPs serotype-specific IgG response rates and GMCs at 30 days PD3, and the anti-PnPs serotype-specific IgG GMCs at 30 days PD4, for the 2 V114 unique serotypes. Analysis of the IgG response rates will be performed using the M&N method (1985) [Ref. 5.4: 03QCDT]. 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 concentrations as the response and a single term for vaccination group. To address the secondary objectives for evaluating the superiority of serotype 3, between-group comparisons will be made based on the anti-PnPs serotype 3 IgG response rates and IgG GMCs at 30 days PD3 and IgG GMCs at 30 days PD4. Analysis of the IgG response rates will be performed using the M&N method (1985) [Ref. 5.4: 03QCDT]. 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 concentrations as the response and a single term for vaccination group.
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 (1985)[Ref. 5.4: 03QCDT].

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 Data Monitoring Committee (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 objectives if non-inferiority is demonstrated for the 13 shared serotypes and for the 2 unique serotypes for IgG GMCs and response rate at 30 days PD3 and for IgG GMCs at 30 days PD4. 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. The study will be considered to have met its secondary objective for the superiority hypotheses for the 2 unique V114 serotypes if superiority is demonstrated for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. The study will be considered to have met its secondary objective for the superiority hypotheses for serotype 3 if superiority is demonstrated for IgG response rates and IgG GMCs at 30 days PD3 and IgG GMCs at 30 days PD4. No multiplicity adjustments will be made for the safety objective.
Sample Size and Power	**Immunogenicity:** The study will randomize participants in a 1:1 ratio to V114 or Prevnar 13™, respectively. The overall sample size will be approximately 1720 with 860 participants into each vaccination group. The sample size was chosen to ensure sufficient power for the multiple endpoints across both primary and secondary hypotheses. With this study sample size, the overall power for all the primary hypotheses is >95%. The overall power for the secondary hypotheses for concomitant antigens evaluation is approximately 90%, and to demonstrate superiority for the 2 unique V114 serotypes is >95%. The overall power is >95% to demonstrate the superiority for the serotype 3 IgG response rates and IgG GMCs at 30 days PD3 and 94% to demonstrate the superiority for IgG GMCs at 30 days PD4. All statistical tests will be conducted at 1-sided 2.5% alpha level. Details are provided in Section 3.9.1. **Safety:** Section 3.9.2 provides information about the ability of this study to estimate the incidence of AEs within and between the vaccination groups.

3.2 Responsibility for Analyses/In-house Blinding

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

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

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

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

3.3 Hypotheses/Estimation

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

3.4 Analysis Endpoints

3.4.1 Immunogenicity Endpoints

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

The primary immunogenicity analysis endpoints include:

- Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD3
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD4

The secondary immunogenicity analysis endpoints include:

- Antigen-specific response rates for all antigens and antigen-specific GMCs for the pertussis antigens included in Pentacel™ at 30 days PD3 when administered concomitantly with V114 or Prevnar 13™
- Anti-hepatitis A response rate at 30 days PD4 for VAQTA™ when administered concomitantly with V114 or Prevnar 13™
- Antigen-specific response rates at 30 days PD4 for all antigens included in M-M-R™II when administered concomitantly with V114 or Prevnar 13™
- Anti-VZV response rate at 30 days PD4 for VARIVAX™ when administered concomitantly with V114 or Prevnar 13™
- Anti-PRP response rate at 30 days PD4 for HIBERIX™ when administered concomitantly with V114 or Prevnar 13™
- Anti-PnPs serotype-specific IgG GMCs and IgG response rates at 30 days PD3 for the 2 unique V114 serotypes
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD4 for the 2 unique V114 serotypes
- Anti-PnPs serotype 3 IgG response rates at 30 days PD3
- Anti-PnPs serotype 3 IgG GMCs at 30 days PD3
- Anti-PnPs serotype 3 IgG GMCs at 30 days PD4
- Anti-PnPs serotype-specific OPA GMTs and response rates at 30 days PD3

Due to the larger serum requirements of the OPA assay, functional antibody activity (as measured by the OPA GMTs) will be assessed in the first 20% of all participants with sufficient serum volume at PD3 to evaluate OPA responses and 50% of these participants at Predose 4 and PD4 with sufficient serum volume for both assays (OPA Subset).

The exploratory immunogenicity analysis endpoints include:

- Anti-PnPs serotype-specific IgG GMCs Predose4
- Anti-PnPs serotype-specific OPA GMTs and response rates Predose 4 and at 30 days PD4.
- Anti-PRP antigen response rates with an alternative threshold value at 30 days PD3 of V114 or Prevnar 13™ when administered concomitantly with Pentacel™ and 30 days PD4 of V114 or Prevnar 13™ when administered concomitantly with HIBERIX™

Table 1 summarizes the endpoints for the concomitant antigens.

Table 1 Summary of Endpoints for Concomitant Vaccine Antigens

Concomitant Vaccine	Antigen	Endpoint	Timepoint
Secondary Endpoints for Concomitant Vaccines			
Pentacel™	Diphtheria toxoid	% ≥ 0.1 IU/mL	PD3
	Tetanus toxoid	% ≥ 0.1 IU/mL	PD3
	Pertussis – PT	% ≥ 5 EU/mL	PD3
		GMC	PD3
	Pertussis – FHA	% ≥ 5 EU/mL	PD3
		GMC	PD3
	Pertussis – FIM 2/3	% ≥ 20 EU/mL	PD3
		GMC	PD3
	Pertussis – PRN	% ≥ 5 EU/mL	PD3
		GMC	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
	Hib-PRP	% ≥ 0.15 µg/mL	PD3
VAQTA™	Hepatitis A	% ≥ 10 mIU/mL	PD4
M-M-R™II	Measles	% ≥ 255 mIU/mL	PD4
	Mumps	% ≥ 10 mumps Ab units/mL	PD4
	Rubella	% ≥ 10 IU/mL	PD4
VARIVAX™	VZV	% ≥ 5 gpELISA units/mL	PD4
HIBERIX™	Hib-PRP	% ≥ 0.15 µg/mL	PD4
Exploratory Endpoints for Concomitant Vaccines			
Pentacel™	Hib-PRP	% ≥ 1.0 µg/mL	PD3
HIBERIX™	Hib-PRP	% ≥ 1.0 µg/mL	PD4
EU=endotoxin unit; FHA=filamentous hemagglutinin; FIM=fimbriae types 2 and 3; GMC=geometric mean concentrations; gpELISA= glycoprotein enzyme-linked immunosorbent assay; Hib-PRP=*Haemophilus influenzae* type b polyribosylribitol phosphate; IU=international units; mIU=milli-International Units;			

Concomitant Vaccine	Antigen	Endpoint	Timepoint
NAb=neutralizing antibodies; NI=non-inferiority; PD=postdose; PRN=pertactin; PT=pertussis toxin; VZV=varicella-zoster virus.			

3.4.2 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 Prevnar 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 Prevnar 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 Prevnar 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 Prevnar 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 Dose 4 with V114 or Prevnar 13™
- Participants body temperature measured Day 1 (day of vaccination) through Day 7 following any vaccination with V114 or Prevnar 13™

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

3.5 Analysis Populations

3.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of 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 primary infant series vaccination (V114 or Prevnar 13™ Doses 1, 2, and 3) 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 immunogenicity analyses at a particular timepoint include:

- Failure to receive correct Dose 4 of V114 or Prevnar 13™ according to vaccination schedule required at the timepoint for the analysis

- Failure to receive Pentacel™, VAQTA™, M-M-R™II, VARIVAX™, or HIBERIX™ according to vaccination schedule required at the timepoint for the analysis

- Failure to receive the scheduled doses of V114 or Prevnar 13™ (at least 28 days between Doses 1 and 2 and between Doses 2 and 3 [for PD3 and Predose 4 analysis], 12 months to 1 day prior to 16 months of age for Dose 4 [for PD4 analyses])

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

- Collection of blood sample at the timepoint for the analysis outside of the pre-specified window (as described in Section 1.3 of the protocol)

Table 2 displays the effect of dosing deviations (ie, missed dose, out-of-window dose and extra dose) on the PP population.

Table 2 Effect of Dosing Deviations on the Per-Protocol Population

Vaccine	Dosing Deviation	Immunogenicity Analysis	Effect on Per-Protocol Population
PCV (V114 or Prevnar 13™)	Missed Dose	IgG	Participant will be excluded from the Per-Protocol population at all time points after the occurrence of the missed dose
		Concomitant Vaccines	
	Out-of-Window Dose	IgG	Participant will be excluded from the Per-Protocol population at the time point immediately following the occurrence of the out-of-window dose (only applies to Dose 3 and Dose 4)
		Concomitant Vaccines	
	Extra Dose	IgG	Participant will be excluded from the Per-Protocol population at all time points after the occurrence of the extra dose
		Concomitant Vaccines	
Concomitant Vaccines Associated With Hypothesis Tests (PENTACEL™, HIBERIX™, M-M-R™ II, VARIVAX™, or VAQTA™)	Missed Dose	IgG	Participant will be excluded from the Per-Protocol population at 30 days postdose 3 (Note: Participants who received the first dose of hepatitis B vaccine before enrollment will only receive 2 doses of RECOMBIVAX HB™, per the protocol)
		Specified Concomitant Vaccine†	
		Other Concomitant Vaccines‡	Missed dose does not affect the immunogenicity analysis of other concomitant vaccines
	Out-of-Window Dose	IgG	Participant will be excluded from the Per-Protocol population at 30 days postdose 3 (only applies to dose given at Visit 3)
		Specified Concomitant Vaccine†	
		Other Concomitant Vaccines‡	Out-of-window dose does not affect the immunogenicity analysis of other concomitant vaccines
	Extra Dose	IgG	Participant will be excluded from the Per-Protocol population at 30 days postdose 3 if the extra dose is received within the protocol-specified exclusion period (i.e., within the 14 days before receipt of PCV for non-live vaccines; within the 30 days before receipt of PCV for live virus vaccines)
		Specified Concomitant Vaccine†	Participant will be excluded from the Per-Protocol population at 30 days postdose 3

		Other Concomitant Vaccines‡	Extra dose does not affect the immunogenicity analysis of other concomitant vaccines
Concomitant Vaccines Not Associated With Hypothesis Tests (ROTATEQ™ or RECOMBIVAX HB™)	Missed Dose	IgG	Participant will be excluded from the Per-Protocol population at the time point immediately following the occurrence of the missed dose (only applies to Dose 3 and Dose 4)
		Specified Concomitant Vaccine†	Missed dose does not affect the immunogenicity analysis of the concomitant vaccines
		Other Concomitant Vaccines‡	
	Out-of-Window Dose	IgG	Participant will be excluded from the Per-Protocol population at the time point immediately following the occurrence of the out-of-window dose (only applies to Dose 3 and Dose 4)
		Specified Concomitant Vaccine†	Out-of-window dose does not affect the immunogenicity analysis of the concomitant vaccines
		Other Concomitant Vaccines‡	
	Extra Dose	IgG	Participant will be excluded from the Per-Protocol population at 30 days postdose 3 or postdose 4 if the extra dose is received within the protocol-specified exclusion period (i.e., within the 14 days before receipt of PCV for non-live vaccines; within the 30 days before receipt of PCV for live virus vaccines)
		Specified Concomitant Vaccine†	Extra dose does not affect the immunogenicity analysis of the concomitant vaccines
		Other Concomitant Vaccines‡	

† Specific concomitant vaccine pertains to the concomitant vaccine with the dosing deviation.
‡ Other concomitant vaccines pertain to the concomitant vaccines other than the one with the dosing deviation.

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

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

3.5.2 Safety Analysis Populations

Safety analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study vaccination for the time point of interest. For safety analyses following any dose of PCV, participants vaccinated with PCV at any time point will be included. For safety analyses following each dose of PCV, participants vaccinated with PCV at that dose will be included. 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 inadvertently received vaccinations of both V114 and Prevnar 13™) will be excluded from the analyses and will be summarized separately.

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

3.6 Statistical Methods

Statistical testing and inference for immunogenicity and safety analyses are described in Section 3.6.1 and Section 3.6.2, respectively. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level. Section 3.6.3 describes how demographic and baseline characteristics will be summarized.

3.6.1 Statistical Methods for Immunogenicity

This section describes the statistical methods that address the primary, secondary, and exploratory immunogenicity objectives. The analyses will be conducted for each of the 15 pneumococcal serotypes in V114 and each antigen in the concomitant vaccines separately.

Primary Endpoints/Hypotheses (H1 and H2)

The first primary objective is to compare the response rates of anti-PnPs serotype-specific IgG between V114 and Prevnar 13™ at 30 days PD3. The response rate is defined as the proportion

of participants with anti-PnPs serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL. The objective will be assessed via the following non-inferiority hypotheses:

H_0: p_1-p_2 ≤-0.1 versus
H_1: p_1-p_2 >-0.1.

For the 13 shared serotypes contained in V114 and Prevnar 13™, p_1 is the response rate for the V114 group and p_2 is the response rate for the Prevnar 13™ group. For the 2 serotypes unique to V114, p_1 is the response rate of the 2 unique serotypes for the V114 group and p_2 is the lowest response rate among all 13 shared serotypes, excluding serotype 3, for the Prevnar 13™ group. V114 is non-inferior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13™) is greater than -0.1. The M&N method (1985), an unconditional, asymptotic method, will be used for this analysis [Ref. 5.4: 03QCDT].

Primary Endpoints/Hypotheses (H3 to H6)

The second primary objective and the third primary objective are to compare the anti-PnPs serotype-specific IgG GMCs between V114 and Prevnar 13™ at 30 days PD3 and 30 days PD4, respectively. The objectives will be assessed via the following non-inferiority hypotheses:

H_0: GMC_1/GMC_2 ≤0.5 versus
H_1: GMC_1/GMC_2 >0.5.

For the 13 shared serotypes contained in V114 and Prevnar 13™, GMC_1 is the anti-PnPs serotype-specific IgG GMCs for the V114 group and GMC_2 is the anti-PnPs serotype-specific IgG GMCs for the Prevnar 13™ group. For the 2 serotypes unique to V114, GMC_1 is the anti-PnPs serotype-specific IgG GMCs of the 2 unique serotypes for the V114 group and GMC_2 is the lowest anti-PnPs IgG GMCs among all 13 shared serotypes, excluding serotype 3, for the Prevnar 13™ group. A ratio of 0.5 corresponds to a 2.0-fold decrease of anti-PnPs serotype-specific IgG GMCs in the V114 group as compared with the Prevnar 13™ group. V114 is non-inferior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13™) is greater than 0.5. 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 concentrations as the response and a single term for vaccination group.

Secondary Endpoints/Hypotheses (H7 to H11)

To address the secondary objectives for evaluating the concomitant vaccines, between-group comparison will be made based on the response rate of the antigens contained in Pentacel™ at 30 days PD3 and the antigens contained in VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ at 30 days PD4. The response rate is defined as the proportion of participants achieving the antigen-specific threshold value (Table 1 in Section 3.4.1). Each objective will be assessed via the following non-inferiority hypotheses:

H_0: p_1-p_2 ≤δ versus
H_1: p_1-p_2 >δ,

where p_1 is the response rate for the V114 group, p_2 is the response rate for the Prevnar 13™ group, and δ is the pre-specified non-inferiority margin and the values of δ are listed in 7 in Section 3.9. The concomitant vaccine administered concomitantly with V114 is non-inferior to the concomitant vaccine administered concomitantly with Prevnar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13™) is greater than δ. The M&N method (1985) will be used for this analysis.

In addition, the between-group comparison will be made based on the antigen-specific GMCs of pertussis contained in Pentacel™ at 30 days PD3. The objective will be assessed via the following non-inferiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 0.67$ versus
H_1: $GMC_1/GMC_2 > 0.67$,

where GMC_1 is the antigen-specific pertussis GMCs for the V114 group and GMC_2 is the antigen-specific pertussis GMCs for the Prevnar 13™ group. A ratio of 0.67 corresponds to a 1.5-fold decrease of antigen-specific pertussis GMCs in the V114 group as compared with the Prevnar 13™ group. V114 is non-inferior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13™) is greater than 0.67. Estimation of the 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 concentrations as the response and a single term for vaccination group.

Secondary Endpoints/Hypotheses (H12, H13, and H14)

To address the secondary objectives for evaluating the 2 unique V114 serotypes, between-group comparisons will be made based on the anti-PnPs serotype-specific IgG response rates and GMCs at 30 days PD3, and the anti-PnPs serotype-specific IgG GMCs at 30 days PD4, for the 2 V114 unique serotypes. The response rate is defined as the proportion of participants with anti-PnPs serotype-specific IgG responses achieving the threshold value of 0.35 μg/mL.

The comparison of the response rates 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 Prevnar 13™ group. V114 is superior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13™) is greater than 0.1. The M&N method (1985), an unconditional, asymptotic method, will be used for this analysis [Ref. 5.4: 03QCDT].

The comparison of the 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 the V114 group and GMC_2 is the anti-PnPs serotype-specific IgG GMCs for the Prevnar 13™ group. A ratio of 2.0 corresponds to a 2.0-fold increase of anti-PnPs serotype-specific IgG GMCs in the V114 group as compared

with the Prevnar 13™ group. V114 is superior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13™) is greater than 2.0. 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 concentrations as the response and a single term for vaccination group.

Secondary Endpoints/Hypotheses (H15, H16, and H17)

To address the secondary objectives for evaluating the superiority of serotype 3, between-group comparisons will be made based on the anti-PnPs serotype 3 IgG response rates and GMCs at 30 days PD3, and the anti-PnPs serotype 3 IgG GMCs at 30 days PD4. The response rate is defined as the proportion of participants with anti-PnPs serotype 3 IgG responses achieving the threshold value of 0.35 µg/mL.

The comparison of the response rates will be assessed via the following superiority hypothesis:

H0: p1-p2 ≤0 versus
H1: p1-p2 >0,

where p1 is the response rate for the V114 group and p2 is the response rate for the Prevnar 13™ group. V114 is superior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13™) is greater than 0. The M&N (1985) method, an unconditional, asymptotic method, will be used for this analysis [Ref. 5.4: 03QCDT].

The comparison of the GMCs will be assessed via the following superiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 1.2$ versus
H_1: $GMC_1/GMC_2 > 1.2$,

where GMC_1 is the anti-PnPs serotype 3 IgG GMCs for the V114 group and GMC_2 is the anti-PnPs serotype 3 IgG GMCs for the Prevnar 13™ group. A ratio of 1.2 corresponds to a 1.2-fold increase of anti-PnPs serotype 3 IgG GMCs in the V114 group as compared with the Prevnar 13™ group. V114 is superior to Prevnar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13™) is greater than 1.2. Estimation of the IgG GMC ratios and computation of the corresponding 95% CIs will be performed using the 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.

Other Secondary Endpoints/Exploratory Endpoints

Other secondary/exploratory objectives include the evaluation of anti-PnPs serotype-specific IgG GMCs Predose 4 and the evaluation of anti-PnPs serotype-specific OPA GMTs and response rates at 30 days PD3, Predose 4, and at 30 days PD4.

The exploratory objectives also include the evaluation of anti-PRP response rate using an alternative threshold value (≥1.0 µg/mL) at 30 days PD3 of V114 or Prevnar 13™ when administered concomitantly with Pentacel™ and 30 days PD4 of V114 or Prevnar 13™ when administered concomitantly with HIBERIX™.

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 [Ref. 5.4: 03RRVC].

Reverse Cumulative Distribution Curves for IgG concentrations and OPA titers at 30 days PD3 and 30 days PD4 will be graphically displayed by serotype.

Forest plots for IgG GMCs and IgG response rates at 30 days PD3 and forest plots for IgG GMCs at 30 days PD4 will be provided by serotype. Antigen specific response rates for Pentacel™ at 30 days PD3 and response rates for VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ at 30 days PD4 will be also graphically represented with forest plots.

A detailed analysis strategy for immunogenicity endpoints is listed in Table 3.

Table 3 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints (H1 and H2)				
Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Primary Endpoints (H3 and 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	
Primary Endpoints (H5 and H6)				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD4	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 Endpoints (H7)				
Antigen-specific response rates for all antigens included in Pentacel™ at 30 days PD3	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	

Antigen-specific GMCs for all pertussis antigens included in Pentacel™ 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 Endpoints (H8)				
Anti-hepatitis A response rate at 30 days PD4	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints (H9)				
Antigen-specific response rates for all antigens included M-M-R™II at 30 days PD4	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints (H10)				
Anti-varicella response rate at 30 days PD4	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints (H11)				
Anti-PRP response rate at 30 days PD4	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoints (H12)				
Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3 for the 2 unique V114 serotypes	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Secondary Endpoints (H13)				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 2 unique V114 serotypes	P	t-distribution with the variance estimate from a linear model‡ (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Secondary Endpoints (H14)				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD4 for the 2 unique V114 serotypes	P	t-distribution with the variance estimate from a linear model‡ (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Secondary Endpoints (H15)				
Proportion of participants with anti-PnPs serotype 3 IgG ≥0.35 µg/mL at 30 days PD3	P	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Secondary Endpoints (H16)				
Anti-PnPs serotype 3 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

Secondary Endpoints (H17)				
Anti-PnPs serotype 3 IgG GMCs at 30 days PD4	P	t-distribution with the variance estimate from a linear model‡ (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
Other Secondary Endpoints				
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; IgG=immunoglobulin G; OPA=opsonophagocytic activity; PD=postdose; PnPs=pneumococcal polysaccharide; PP=Per-Protocol; PRP=polyribosylribitol phosphate.
† P=Primary approach; S=Supportive approach.
‡ 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 titers as the response and a single term for vaccination group.

The detectable ranges for OPA and IgG responses differ across serotypes. The limits of quantitation define the range of responses over which the assays provide precise and accurate measurements. Table 4 gives the limits of quantitation defined for each serotype for OPA and IgG responses. For responses smaller than the lower limit of quantitation (LLOQ), half of the LLOQ is used for analysis when calculating the OPA GMTs and IgG GMCs, and in the graphical displays of the Reverse Cumulative Distribution Curves for OPA titers and IgG concentrations. For OPA and IgG responses that are larger than the upper limit of quantitation (ULOQ), a value equal to ULOQ + 1 is used for analysis.

Table 4 Limits of Quantitation for OPA and IgG Serotype-specific Responses

	OPA		**IgG**	
Serotype	**LLOQ (1/dil)**	**ULOQ (1/dil)**	**LLOQ (µg/mL)**	**ULOQ (µg/mL)**
1	9	30,213	0.05	850
3	19	30,564	0.05	145
4	34	137,160	0.05	173
5	27	119,016	0.1	368
6A	232	210,600	0.05	393
6B	40	105,840	0.05	341
7F	61	251,235	0.05	830
9V	151	224,316	0.05	644
14	62	281,637	0.05	1,520
18C	115	445,230	0.05	730
19A	31	128,304	0.05	1,387

	OPA		IgG	
Serotype	**LLOQ (1/dil)**	**ULOQ (1/dil)**	**LLOQ (µg/mL)**	**ULOQ (µg/mL)**
19F	113	158,841	0.05	1,461
22F	15	229,338	0.05	1,054
23F	55	251,829	0.05	595
33F	20	399,600	0.05	833
IgG = immunoglobulin G; LLOQ = lower limit of quantitation; OPA= opsonophagocytic activity; ULOQ = upper limit of quantitation.				

3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements. Additional summaries on key safety parameters will also be provided following each vaccination.

The analysis of safety results will follow a tiered approach (Table 5). 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 M&N method (1985). 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/somnolence, hives or welts/urticaria, and appetite loss/decreased appetite) 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]).

In this study, membership in Tier 2 requires that at least 1% of the participants in any treatment group exhibit the event. The threshold of at least 1% was chosen to draw clinical meaningful inference. When less than 1% of participants report AEs in both groups, the 95% CI for the between-group difference may exclude zero. However, the clinical significance of these differences is unknown given the small number of participants who report AEs. 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 at least 1% of 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 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 5 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
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

Safety Tier	Safety Endpoint†	p-Value	95% CI for Between-Group Comparison	Descriptive Statistics
	Specific AEs by SOC and PT‡ (incidence ≥1% of participants in one of the vaccination groups)		X	X
Tier 3	Specific AEs by SOC and PT‡ (incidence <1 of 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 adverse event categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least one AE.

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

Summary tables for AEs related to the concomitant vaccines administered as part of the protocol-specified regimen will be provided.

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

A supportive analysis comparing the proportion of participants reporting each of the solicited complaints on the VRC will be conducted in support of the primary safety analyses that are based on solicited AEs. This supportive analysis will use the methodology specified in Table 5 for solicited AEs. The analysis will be conducted on the subset of the APaT population who entered solicited complaints data on the VRC.

3.6.3 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, and gestational age), baseline characteristics, prior and concomitant vaccinations and therapies will be summarized by vaccination group either by descriptive statistics or categorical tables.

Calculated age based on the difference in months between the birthdate and randomization date will be used for summaries of age.

3.7 Interim Analyses

A periodic review of safety and tolerability data across the V114 Phase 3 pediatric program will be conducted by an independent, unblinded, external DMC. A description of the structure 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 of the protocol. 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 of the protocol for details on the Committees Structure for this study). If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this Executive Oversight Committee (EOC) of the Sponsor (and potentially other limited Sponsor personnel) may be unblinded to results at the intervention level 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.

3.8 Multiplicity

The study will be considered to have met its primary objectives if non-inferiority is demonstrated for the 13 shared serotypes and for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. 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. The study will be considered to have met its secondary objective for the superiority hypotheses for the 2 unique V114 serotypes if superiority is demonstrated for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. The study will be considered to have met its secondary objective for the superiority hypotheses for serotype 3 if superiority is demonstrated for IgG response rates and IgG GMCs at 30 days PD3 and IgG GMCs at 30 days PD4.

No multiplicity adjustments will be made for the safety comparisons.

3.9 Sample Size and Power Calculations

3.9.1 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 1720 with 860 participants into each vaccination group. The sample size was chosen to ensure sufficient power for the multiple endpoints across both primary and secondary hypotheses.

With this study sample size and the assumptions listed below, the overall power for all the primary hypotheses is >95% to demonstrate non-inferiority of V114 to Prevnar 13™ for the 13 shared serotypes and the 2 unique serotypes for V114. The overall power for the secondary hypotheses for concomitant antigens evaluation is approximately 90%, to demonstrate superiority for the 2 unique V114 serotypes is >95%, and to demonstrate the superiority for the serotype 3 IgG response rates and IgG GMCs at 30 days PD3 is >95%, and IgG GMCs at 30 days PD4 is 94%.

The power for each individual hypothesis is provided below.

Primary Immunogenicity Endpoints/Hypotheses (H1 and H2)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes and the 2 unique serotypes based on the proportion of participants with anti-PnP serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL at 30 days PD3. This power is calculated based on (1) 80% evaluability rate (688 evaluable participants per treatment group), (2) a non-inferiority margin of -0.1 for the difference (V114 minus Prevnar 13™), and (3) a serotype-specific true response rate for the 13 shared serotypes between V114 and Prevnar 13™ and the 2 unique V114 serotypes (Table 6).

Table 6 Assumptions of the True Response Rates for V114 and Prevnar 13™ for the 15 Pneumococcal Serotypes in V114 at 30 Days PD3

Serotype	True Response Rate	
	V114	Prevnar 13™
Prevnar 13™ Types		
1	0.95	0.95
3	0.90	0.70
4	0.95	0.95
5	0.95	0.95
6A	0.95	0.95
6B	0.90	0.90
7F	0.95	0.95
9V	0.95	0.95
14	0.95	0.95
18C	0.95	0.95
19A	0.95	0.95
19F	0.95	0.95
23F	0.90	0.90
Non- Prevnar 13™ Types		
22F	0.95	NA
33F	0.90	NA

NA=not applicable; PD=postdose.
Comparison for the 2 unique V114 serotypes will be to the lowest responder among the shared serotypes in Prevnar 13™, excluding serotype 3. Based on our assumption, the comparator could be either serotype 6B or 23F (true response rate=0.90).

Primary Immunogenicity Endpoints/Hypotheses (H3 and H4)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes and the 2 unique serotypes based on the anti-PnP serotype-specific IgG GMCs at 30 days PD3. This power is calculated based on (1) 80% evaluability rate (688 evaluable participants per treatment group), (2) a non-inferiority margin of 0.5 for the GMC ratio (V114/Prevnar 13™), (3) a true GMC ratio of 1.0 for the 13 shared serotypes between V114 and Prevnar 13™ and for the 2 unique serotypes between V114 and the lowest GMC of any of the shared serotypes in Prevnar 13™, excluding serotype 3, and (4) the standard deviation of the natural log concentrations is 1.1 for the 13 shared serotypes between V114 and Prevnar 13™ and the 2 unique serotypes in V114.

Primary Immunogenicity Endpoints/Hypotheses (H5 and H6)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is non-inferior to Prevnar 13™ for the 13 shared serotypes and for the 2 unique serotypes based on the anti-PnP serotype-specific IgG GMCs at 30 days PD4. This power is calculated based on (1) 75% evaluability rate (645 evaluable participants per treatment group), (2) a non-inferiority margin of 0.5 for the GMC ratio (V114/Prevnar 13™), (3) a true GMC ratio of 1.0 for the 13 shared serotypes between V114 and Prevnar 13™ and for the 2 unique serotypes between V114 and the

lowest GMC of any of the shared serotypes in Prevnar 13™, excluding serotype 3, and (4) the standard deviation of the natural log concentrations is 1.1 for the 13 shared serotypes between V114 and Prevnar 13™ and the 2 unique serotypes in V114.

Secondary Immunogenicity Endpoints/Hypotheses (H7 to H11)

This study has approximately 90% power at a 1-sided 2.5% alpha-level to demonstrate Pentacel™, VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ administered concomitantly with V114 is non-inferior to these vaccines administered concomitantly with Prevnar 13™ based on the response rate of antigens included in Pentacel™ at 30 days PD3, the GMCs of the pertussis antigens included in Pentacel™ at 30 days PD3, and the response rate of antigens included in VAQTA™, M-M-R™II, VARIVAX™, and HIBERIX™ at 30 days PD4. This power assumes the same underlying response rate in both the V114 group and the Prevnar 13™ group for each antigen. Detailed assumptions for concomitant antigens are provided in Table 7.

Table 7 Summary of Endpoints and Power for Concomitant Vaccine Antigens

Concomitant Vaccine	Antigen	Endpoint	Timepoint	NI Margin (δ) (V114 versus Prevnar 13™)	Evaluability Rate	Assumed True RR or SD	Power
Pentacel™	Diphtheria toxoid	% ≥ 0.1 IU/mL	PD3	-10%	80%	RR=0.90	>95%
	Tetanus toxoid	% ≥ 0.1 IU/mL	PD3	-5%	80%	RR=0.97	
	Pertussis – PT	% ≥ 5 EU/mL	PD3	-10%	80%	RR=0.90	
		GMC	PD3	0.67	80%	SD=0.69	
	Pertussis – FHA	% ≥ 5 EU/mL	PD3	-10%	80%	RR=0.90	
		GMC	PD3	0.67	80%	SD=0.66	
	Pertussis – FIM 2/3	% ≥ 20 EU/mL	PD3	-10%	80%	RR=0.90	
		GMC	PD3	0.67	80%	SD=0.82	
	Pertussis – PRN	% ≥ 5 EU/mL	PD3	-10%	80%	RR=0.90	
		GMC	PD3	0.67	80%	SD=0.83	
	Poliovirus 1	% with NAb>=1:8 dilution	PD3	-5%	80%	RR=0.97	
	Poliovirus 2	% with NAb>=1:8 dilution	PD3	-5%	80%	RR=0.97	
	Poliovirus 3	% with NAb>=1:8 dilution	PD3	-5%	80%	RR=0.97	
	Hib-PRP	% ≥ 0.15 µg/mL	PD3	-10%	80%	RR=0.90	
VAQTA™	Hepatitis A	% ≥ 10 mIU/mL	PD4	-10%	70%	RR=0.95	>95%
M-M-R™II	Measles	% ≥ 255 mIU/mL	PD4	-5%	68%	RR=0.95	90%
	Mumps	% ≥ 10 mumps Ab units/mL	PD4	-5%	68%	RR=0.95	
	Rubella	% ≥ 10 IU/mL	PD4	-5%	68%	RR=0.95	
VARIVAX™	VZV	% ≥ 5 gpELISA units/mL	PD4	-10%	70%	RR=0.90	>95%
HIBERIX™	Hib-PRP	% ≥ 0.15 µg/mL	PD4	-10%	65%	RR=0.95	>95%

EU=endotoxin unit; FHA=filamentous hemagglutinin; FIM=fimbriae types 2 and 3; GMC=geometric mean concentrations; gpELISA=glycoprotein enzyme-linked immunosorbent assay; Hib-PRP=*Haemophilus influenzae* type b polyribosylribitol phosphate; mIU=milli-International Units; NAb=neutralizing antibodies; NI non-inferiority; PD=postdose; PRN=pertactin; PRP=polyribosylribitol phosphate; PT=pertussis toxin; RR=response rate; SD standard deviation (in natural log scale); VZV=varicella-zoster virus.

Secondary Immunogenicity Endpoints/Hypotheses (H12, H13, and H14)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is superior to Prevnar 13™ for the 2 unique serotypes based on the proportion of participants with anti-PnP serotype-specific IgG responses achieving the threshold value of 0.35 µg/mL at 30 days PD3. This power is calculated based on (1) 80% evaluability rate (688 evaluable participants per treatment group), (2) a superiority margin of 0.1 for the difference (V114 minus Prevnar 13™), and (3) a serotype-specific true response rate for the 2 V114 unique serotypes (Table 8).

Table 8 Assumptions of the True Response Rates for V114 and Prevnar 13™ for the 2 V114 Unique Pneumococcal Serotypes at 30 Days PD3

Serotype	True Response Rate	
	V114	Prevnar 13™
22F	0.95	0.02
33F	0.90	0.02

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is superior to Prevnar 13™ for the 2 V114 unique serotypes based on the anti-PnP serotype-specific IgG GMCs at 30 days PD3 and 30 days PD4. This power is calculated based on (1) 80% evaluability rate at 30 days PD3 and 75% evaluability rate at 30 days PD4, (2) a superiority margin of 2.0 for the GMC ratio (V114/Prevnar 13™), (3) a true GMC ratio of 10.0, and (4) the standard deviation of the natural log concentrations is 1.1.

Secondary Immunogenicity Endpoints/Hypotheses (H15, H16, and H17)

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate that V114 is superior to Prevnar 13™ for serotype 3 based on the proportion of participants with anti-PnP serotype 3 IgG responses achieving the threshold value of 0.35 µg/mL at 30 days PD3. This power is calculated based on (1) 80% evaluability rate (688 evaluable participants per treatment group), (2) a superiority margin of 0 for the difference (V114 minus Prevnar 13™), and (3) true response rates for serotype 3 as displayed in Table 9. These assumptions are based on the most current data available from the V114 program.

Table 9 Assumptions of the True Response Rates for V114 and Prevnar 13™ for Serotype 3 at 30 Days PD3

Serotype	True Response Rate	
	V114	Prevnar 13™
3	0.95	0.76

This study has >95% power at a 1-sided 2.5% alpha-level to demonstrate V114 is superior to Prevnar 13™ for serotype 3 based on the anti-PnP serotype 3 IgG GMCs at 30 days PD3 and 94% power based on the anti-PnP serotype 3 IgG GMCs at 30 days PD4. This power is calculated based on (1) evaluability rates of 80% at 30 days PD3 and 75% at 30 days PD4, (2) a superiority margin of 1.2 for the GMC ratio (V114/Prevnar 13™), (3) true GMC ratios of 1.94 at 30 days PD3 and 1.38 at 30 days PD4, and (4) the standard deviations of the natural log

concentrations of 0.75 at 30 days PD3 and 0.73 at 30 days PD4. These assumptions are based on the most current data available from the V114 program.

3.9.2 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 860 participants in each of the V114 group and Prevnar 13™ group if the underlying incidence of an SAE is 0.19% (1 of every 534 participants receiving the vaccine). There is a 50% chance of observing at least one SAE among 860 participants in each of the V114 group and Prevnar 13™ group if the underlying incidence of an SAE is 0.08% (1 of every 1241 participants receiving the vaccine). If no SAEs are observed among 860 participants in each of the V114 group and Prevnar 13™ group, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.43% (one in every 233 participants).

Table 10 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 860 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) [Ref. 5.4: 04FS6L]; no multiplicity adjustments were made.

Table 10 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 860 Participants in each Group)

Incidence of Adverse Event		**Risk Difference**
V114 (%) N=860	**Prevnar 13™ (%) N=860**	**Percentage Points**
1.2	0.1	1.1
4.4	2.0	2.4
8.4	5.0	3.4
14.4	10.0	4.4
20.1	15.0	5.1
25.7	20.0	5.7
36.4	30.0	6.4
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) [Ref. 5.4: 04FS6L]		

3.10 Subgroup Analyses

Subgroup analyses based on sex (female vs male) and race will be performed for select safety endpoints (summary of AEs) as well as primary and select secondary immunogenicity endpoints. Details of subgroup analyses will be documented in the supplemental Statistical Analysis Plan.

An overall summary of AEs and a summary of solicited AEs following any vaccination will be provided for each subgroup (point estimates only) with ≥5% of the total number of randomized participants in each vaccination group.

The following subgroups are planned for evaluation:

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (Asian, Black or African American, Multiple, White)
- Sex (Female, Male)

To determine whether the intervention effect is consistent across various subgroups, the estimate of the between-group intervention effect (with a nominal 95% CI) will be summarized for the following primary immunogenicity endpoints with ≥5% of the total number of participants in each vaccination group:

- Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL at 30 days PD3
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 and PD4

The following subgroups are planned for evaluation:

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (Asian, Black or African American, Multiple, White)
- Sex (Female, Male)

3.11 Compliance (Medication Adherence)

The number and proportion of randomized participants receiving each vaccination will be summarized (Section 3.12).

3.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V114 or Prevnar 13™, Pentacel™, VAQTA™, M-M-R™II, VARIVAX™ and HIBERIX™ at each vaccination schedule.

4 LIST OF REFERENCES

[Ref. 5.4: 03QCDT] Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.

[Ref. 5.4: 03RRVC] Clopper CJ, Pearson ES. The use of confidence of fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.

[Ref. 5.4: 04FS6L] Farrington CP, Manning G. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk. Stat Med Vol. 9,1447-1454 (1990)