Official Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Japanese Infants
NCT number:	NCT04384107
Document Date:	07-Aug-2020

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 V114 in Healthy Japanese Infants

Protocol Number: 033-01

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	Not Applicable
EudraCT	2019-003644-68

Approval Date: 07 August 2020

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	07-AUG-2020	Amendment to change to the primary objectives for the evaluation of this study
Original Protocol	09-MAR-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

The purpose for this amendment is to change the objectives to more closely align with World Health Organization [World Health Organization 2013] guidelines for the assessment of immune responses to PCVs.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 3 Hypotheses, Objectives, and Endpoints	• Changed hypothesis 2 (H2) to evaluate non-inferiority of V114 to Prevenar 13™ for the 2 unique V114 serotypes instead of an evaluation of superiority. • Changed the evaluation of anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) for the 13 shared serotypes compared with Prevenar 13™ to the primary objective, and added hypothesis 3 (H3).	Revisions were made to more closely align with World Health Organization guidelines for the assessment of immune responses to PCVs.
Section 4.2.1.1 Immunogenicity Endpoints	Changed the percentage of participants for whom OPA responses at 30 days PD3 and 30 days PD4 will be evaluated.	Larger numbers of participants contributing to the OPA analysis will enable better precision in the evaluation of functional antibody responses.

Section # and Name	Description of Change	Brief Rationale
Section 9.1 Statistical Analysis Plan Summary Section 9.3 Hypotheses/Estimation Section 9.4.1 Immunogenicity Endpoints Section 9.6.1 Statistical Methods for Immunogenicity Analyses Section 9.8 Multiplicity Section 9.9.1 Sample Size and Power for Immunogenicity Analyses	Updated these sections to align with changes to hypothesis 2 (H2) and addition of hypothesis 3 (H3)	Revisions were made to incorporate changes to the statistical analyses for the evaluation of the IgG response rates for the 2 unique V114 serotypes and the IgG GMCs for the 13 shared serotypes, compared with Prevenar 13™.
Section 9.10 Subgroup Analyses	Added the analysis of IgG GMCs at 30 days PD3.	Revisions were made to incorporate changes to the subgroup analyses.
Throughout	Editorial revisions	Minor editorial changes to the text.

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 V114 in Healthy Japanese Infants

Short Title: A Phase 3 study of V114 in healthy Japanese infants

Acronym: Not applicable

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 Japanese infants enrolled at 2 to 6 months of age (from 2 months to 1 day prior to 7 months of age [inclusive]) administered V114 or Prevenar 13™.

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 (the day of vaccination is considered 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 Prevenar 13™.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3)

Objectives	Endpoints
Hypothesis (H1): V114 is non-inferior to Prevenar 13™ for the 13 shared serotypes between V114 and Prevenar 13™ based on response rates at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in the response rates [V114 minus Prevenar 13™] to be greater than -0.1). **Hypothesis (H2)**: V114 is non-inferior to Prevenar 13™ for the 2 serotypes unique to V114 based on the response rate of the 2 unique V114 serotypes compared with the lowest response rate of any of the shared serotypes in Prevenar 13™ 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 Prevenar 13™] to be greater than -0.1).	
• **Objective 3**: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) for the 13 shared serotypes between V114 and Prevenar 13™ at 30 days following Dose 3 for participants administered V114 versus participants administered Prevenar 13™. • **Hypothesis (H3):** V114 is non-inferior to Prevenar 13™ for the 13 shared serotypes between V114 and Prevenar 13™ based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of two-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratios (V114/Prevenar 13™) to be greater than 0.5.)	• Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes between V114 and Prevenar 13™ at 30 days PD3

Objectives	Endpoints
Secondary	
• **Objective 1**: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) for the 2 unique V114 serotypes at 30 days following Dose 3 for participants administered V114 versus participants administered Prevenar 13™.	• Anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days PD3
• **Objective 2**: To compare the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 30 days following Dose 4 for participants administered V114 versus participants administered Prevenar 13™.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4)
• **Objective 3**: To compare anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4 for participants administered V114 versus participants administered Prevenar 13™.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD4
• **Objective 4**: To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) response rates and Geometric Mean Titers (GMTs) 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
• **Objective 5 (OPA Subset)**: To evaluate the anti-PnPs serotype-specific OPA response rates and GMTs at 30 days following Dose 4 by each vaccination group.	• Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at 30 days PD4

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Pneumococcal disease
Population	Healthy Japanese 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
Blinding Roles	Participants or Subjects Care Provider Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 23 months from the time that written informed consent is provided for the first participant until the last participant's last study-related telephone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 660 participants will be randomized with approximately 330 in each intervention group.

Intervention Groups and Duration:

Intervention Groups	See table below
Total Number	2 intervention groups
Duration of Participation	Each participant will participate in the study for approximately 7 to 14 months from the time the participant's legally acceptable representative signs the Informed Consent Form (ICF) through the final contact.

Intervention Group Name	Vaccine	Dose Strength	Dose Frequency	Route of Admin.	Vaccination Regimen	Use
V114	V114	Refer to IB	4 doses	SC	Single dose at Visits 1, 2, 3, and 5	Experimental
Prevenar 13™	Prevenar 13™	Refer to product labeling	4 doses	SC	Single dose at Visits 1, 2, 3, and 5	Experimental
Admin.: Administration, IB: Investigator's Brochure, SC: Subcutaneous						

Study Governance Committees:

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

Study Accepts Healthy Volunteers: Yes

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

1.2 Schema

The study design is depicted in Figure 1.

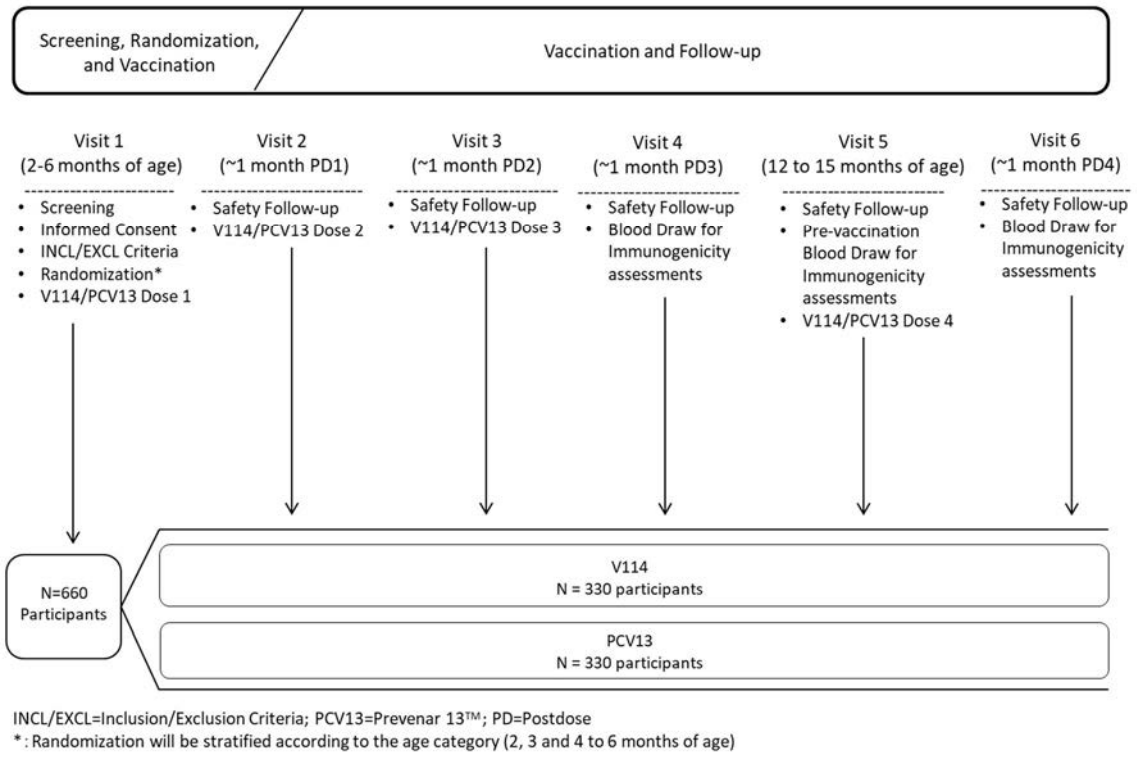

Figure 1 V114-033 Study Design

1.3 Schedule of Activities

Study Period	Screening／Intervention						Notes
Visit Number:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	See Section 8.1.10 for details on discontinuation.
Scheduled Time:	**Age: 2-6 months (Dose 1)**	**~1 month after Dose 1 (Dose 2)**	**~1 month after Dose 2 (Dose 3)**	**~1 month after Dose 3**	**Age: 12 to 15 months (Dose 4)**	**~1 month after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window:	**2 months of age to 1 day prior to 7 months of age**	**28 to 56 days after Dose 1**	**28 to 56 days after Dose 2**	**28 to 42 days after Dose 3**	**12 months of age to 1 day prior to 16 months of age**	**28 to 42 days after Dose 4**	Visit 2 (Dose 2) and Visit 3 (Dose 3) could be later than the upper limit of visit window but Visit 3 (Dose 3) must be before 12 months of age and at least 60 days interval is needed between Visit 3 (Dose 3) and Visit 5 (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 (FBR)	X						Participation in FBR 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						
Prior/Concomitant Medication and Non-Study Vaccination Review	X	X	X	X	X	X	

Study Period	Screening／Intervention						Notes
Visit Number:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	See Section 8.1.10 for details on discontinuation.
Scheduled Time:	**Age: 2-6 months (Dose 1)**	**~1 month after Dose 1 (Dose 2)**	**~1 month after Dose 2 (Dose 3)**	**~1 month after Dose 3**	**Age: 12 to 15 months (Dose 4)**	**~1 month after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window:	**2 months of age to 1 day prior to 7 months of age**	**28 to 56 days after Dose 1**	**28 to 56 days after Dose 2**	**28 to 42 days after Dose 3**	**12 months of age to 1 day prior to 16 months of age**	**28 to 42 days after Dose 4**	Visit 2 (Dose 2) and Visit 3 (Dose 3) could be later than the upper limit of visit window but Visit 3 (Dose 3) must be before 12 months of age and at least 60 days interval is needed between Visit 3 (Dose 3) and Visit 5 (Dose 4).
V114 or Prevenar 13™ Administration (Blinded)	X	X	X		X		Before each vaccine administration, the investigator must review medical history to ensure the participant has no new contraindication to the vaccine(s) scheduled to be given (Section 8.1.8).
Non-study Pediatric Vaccines	(X)	(X)	(X)	(X)	(X)	(X)	Non-study pediatric vaccines are permitted. If given at the same time, oral vaccines are recommended to be given prior to the study vaccine and other injectable vaccines. Other injectable vaccines are administered after the study vaccine and in a separate limb. See Section 6.5 for details on concomitant vaccines.
Provide VRC	X	X	X		X		
Review VRC data		X	X	X		X	See Section 8.1.9 for details.
Collect VRC		X	X	X		X	
Safety Procedures							
Complete Physical Examination	X						To be performed by the investigator before vaccine is administered (see Section 8.3.1).
Targeted Physical Examination		X	X		X		To be performed by the investigator 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.

Study Period	Screening／Intervention						Notes
Visit Number:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	See Section 8.1.10 for details on discontinuation.
Scheduled Time:	**Age: 2-6 months (Dose 1)**	**~1 month after Dose 1 (Dose 2)**	**~1 month after Dose 2 (Dose 3)**	**~1 month after Dose 3**	**Age: 12 to 15 months (Dose 4)**	**~1 month after Dose 4**	Months of age is calculated according to the participant's birth date.
Visit Window:	**2 months of age to 1 day prior to 7 months of age**	**28 to 56 days after Dose 1**	**28 to 56 days after Dose 2**	**28 to 42 days after Dose 3**	**12 months of age to 1 day prior to 16 months of age**	**28 to 42 days after Dose 4**	Visit 2 (Dose 2) and Visit 3 (Dose 3) could be later than the upper limit of visit window but Visit 3 (Dose 3) must be before 12 months of age and at least 60 days interval is needed between Visit 3 (Dose 3) and Visit 5 (Dose 4).
30-Minute Postvaccination Observation Period	X	X	X		X		To be performed by blinded study site personnel only.
AE Monitoring	X	X	X	X	X	X	Nonserious AEs are to be reported from Days 1 through 14 following each vaccination. SAEs, deaths and medical device incidents are to be reported throughout the duration of an individual's study participation. See Section 8.4, 10.3 and 10.4 for details.
Immunogenicity Procedures							
Collect Blood (Serum) for Immunogenicity Assays				X	X	X	Blood samples must be collected before vaccination where applicable.
Future Biomedical Research							
Collect Buccal Swabs for FBR	X						Buccal swab DNA samples for analysis should be obtained prior to vaccination at Visit 1, on randomized and FBR consented participants only.

AE = adverse event; DNA = deoxyribonucleic acid; VRC = Vaccination Report Card; FBR = Future Biomedical Research; SAE = serious adverse event

2 INTRODUCTION

Merck Sharp & Dohme Corp. (MSD) is developing an investigational 15-valent pneumococcal conjugate vaccine (PCV) (referred to as V114) for 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 and 23F) present in the licensed vaccine Prevenar 13™ (pneumococcal 13-valent conjugate vaccine [diphtheria CRM_{197} protein], Wyeth Pharmaceuticals, a subsidiary of Pfizer, Inc., Philadelphia, PA), plus 2 additional serotypes (22F and 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 gradually 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 comparable immunogenicity to licensed PCVs for shared serotypes and expanded serotype coverage. V114 includes an additional 2 key serotypes compared with Prevenar 13™ and will address an unmet medical and public health need for a PCV with expanded coverage.

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 Prevenar 13™. Country-specific routine immunization regimens vary by schedule and number of doses. In Japan, a 4-dose schedule, consisting of a 3-dose primary series at approximately 2, 3 and 4 months of age followed by a toddler dose at 12 to 15 months of age, is currently recommended by Japan Pediatric Society. In this study, the first dose is given at 2 to 6 months of age and 2nd and 3rd dose is given with an interval of ≥27 days from the prior doses.

It is generally recommended that Prevenar 13™ is to be given at the same time as other National Immunization Program (NIP) pediatric vaccines. The concomitant administration of V114 with most NIP pediatric vaccines will be allowed in this Phase 3 clinical study at the discretion of investigators.

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 include both invasive infections (meningitis, bacteremic pneumonia, and bacteremia), and noninvasive infections (acute otitis media, non-bacteremic pneumonia, and sinusitis).

Infection surveillance in Japan (2017) indicates that the total number of reports of IPD was 3,139, and prevalence was 9.37 per 100,000 population for children <5 years of age and 5.34 per 100,000 population for adults 65 years of age and older.

Currently, many countries worldwide have incorporated licensed PCVs (eg, Prevenar 13™) into their infant immunization programs. In Japan emergency promotion fund project with Prevenar™ was initiated in November 2010 and introduced into pediatric NIP in April 2013. Prevenar™ was then replaced by Prevenar 13™ in November 2013. Since PCVs have been introduced into the NIP, the overall burden of IPD in children caused by vaccine serotypes has decreased by 97% in 2017. On the other hand, the proportion of IPD in children caused by serotypes not included in Prevenar 13™ is increasing.

The investigational Merck Sharp & Dohme Corp. (MSD), PCV, V114 is a 15-valent vaccine, containing pneumococcal polysaccharide conjugates of the 13 serotypes in Prevenar 13™ (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) plus 2 additional serotypes (22F and 33F).

In Japan, the rate of serotypes 22F and 33F isolates from children <15 years with IPD in 2014 were 11.1% and 0.8% [Nakano S., et al 2016]. Both 22F and 33F have been associated with serious clinical outcomes, including IPD, as demonstrated by their high degree of invasiveness compared with other serotypes not currently covered by licensed PCVs. Furthermore, serotypes 22F and 33F have shown relative resistance to certain antibiotics used in the treatment of community acquired pneumonia [Golden AR., et al 2016]. Thus, it is anticipated that vaccination with V114 will contribute further to prevention of disease in both children and adults due to clinically important strains of *S. pneumoniae* compared to Prevenar 13™.

2.2.2 Preclinical and Clinical Studies

A Phase 1 study evaluating the safety and immunogenicity of V114 administered subcutaneously or intramuscularly to healthy Japanese infants (V114-028) is still ongoing.

A Phase 1 study has demonstrated the safety and immunogenicity of V114 administered intramuscularly to healthy Japanese adults 50 years of age and older (V114-015) has completed. A Phase 3 study involving healthy Japanese adults 65 years of age and older (V114-019) is still ongoing.

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

2.2.3 Information on Other Study-related Therapy

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

Prevenar 13™ will be EU commercial product in this study. Refer to approved labeling for detailed background information on Prevenar 13™.

2.3 Benefit/Risk Assessment

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

Approximately 50% of participants will be assigned to Prevenar 13™ and receive 4 doses of Prevenar 13™, the standard of care, as the active comparator in this study. V114 is expected to provide comparable immune responses and a comparable safety profile to Prevenar 13™ for the shared pneumococcal serotypes while providing additional coverage for the 2 serotypes (22F and 33F) unique to V114. It is unknown if the investigational V114 will have the same benefit/risk profile as Prevenar 13™. V114 has the potential to prevent IPD caused by serotype 22F and 33F.

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 Japanese infants enrolled at 2 to 6 months of age (from 2 months to 1 day prior to 7 months of age [inclusive]) administered V114 or Prevenar 13™.

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 (the day of vaccination is considered 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 Prevenar 13™. **Hypothesis (H1)**: V114 is non-inferior to Prevenar 13™ for the 13 shared serotypes between V114 and Prevenar 13™ based on response rates at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in the response rates [V114 minus Prevenar 13™] to be greater than -0.1). **Hypothesis (H2)**: V114 is non-inferior to Prevenar 13™ for the 2 serotypes unique to V114 based on the response rate of the 2 unique V114 serotypes compared with the lowest response rate of any of the shared serotypes in Prevenar 13™ 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 Prevenar 13™] to be greater than -0.1).	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3)

Objectives	Endpoints
• **Objective 3**: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) for the 13 shared serotypes between V114 and Prevenar 13™ at 30 days following Dose 3 for participants administered V114 versus participants administered Prevenar 13™. • **Hypothesis (H3):** V114 is non-inferior to Prevenar 13™ for the 13 shared serotypes between V114 and Prevenar 13™ based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of two-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratios (V114/Prevenar 13™) to be greater than 0.5.)	• Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes between V114 and Prevenar 13™ at 30 days PD3
Secondary	
• **Objective 1**: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) for the 2 unique V114 serotypes at 30 days following Dose 3 for participants administered V114 versus participants administered Prevenar 13™.	• Anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days PD3
• **Objective 2**: To compare the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 μg/mL) at 30 days following Dose 4 for participants administered V114 versus participants administered Prevenar 13™.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4)
• **Objective 3**: To compare anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4 for participants administered V114 versus participants administered Prevenar 13™.	• Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD4
• **Objective 4**: To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) response rates and Geometric Mean Titers (GMTs) 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
• **Objective 5 (OPA Subset)**: To evaluate the anti-PnPs serotype-specific OPA response rates and GMTs at 30 days following Dose 4 by each vaccination group.	• Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 at 30 days PD4
Exploratory	
• **Objective 1**: To evaluate anti-PnPs serotype-specific IgG response rates and 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 response rates and GMTs immediately prior to Dose 4 by each vaccination group.	• Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in V114 Predose 4

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active comparator-controlled, parallel-group, multi-site, double-blind, study of V114 in healthy Japanese infants enrolled at 2 to 6 months of age. Approximately 660 infants will be randomly assigned, in 1:1 ratio with stratification into 3 categories by age category (2 months,3 months and 4 to 6 months of age), to receive either V114 (330 participants) or Prevenar 13™ (330 participants).

A 0.5 mL subcutaneous dose of V114 or Prevenar 13™ will be administered (blinded) to healthy Japanese infants with the 1st dose given at 2 to 6 months of age and 2nd and 3rd dose is given at an interval of ≥27 days from the prior dose. Then, the 4th dose at 12 to 15 months of age is administered.

Participants will be followed for injection-site and systemic AEs through Day 14 following each vaccination with V114 or Prevenar 13™. Information for SAEs and deaths, regardless of whether the events are considered vaccine-related by the investigator, will be collected from the time consent is signed through completion of participation in the study.

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 is a Phase 3 study to assess the safety, tolerability, and immunogenicity of V114 in healthy Japanese infants. Prevenar 13™ is indicated for healthy infants from 2 months to 5 years of age in Japan with official funding (NIP) since 2013. In Japan, the first dose of Prevenar 13™ should be given by 6 months of age.

The safety and immunogenicity in subcutaneous administration of V114 will be assessed in this study because subcutaneous administration is typically selected for most pediatric vaccines in Japan.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

Sera from participants will be used to measure vaccine-induced, serotype-specific immune responses for all 15 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) included in V114 using the pneumococcal electrochemiluminescence (PnECL) assay and the Multiplexed Opsonophagocytic Assay (MOPA). PnECL assay measures serotype-specific IgG response rates and IgG GMC. MOPA measures serotype-specific OPA response rates and GMTs. OPA GMTs represent functional antibodies capable of inhibiting growth of *S. pneumoniae* in culture. Additional information on the immunogenicity assays can be found in Section 8.2.

The PnECL will be used to test the primary immunogenicity hypotheses in this study. 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].

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 2013] [World Health Organization 2008]. The response rate (ie, the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 µg/mL) is one of primary endpoints 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 response rates, IgG GMCs, OPA response rates and OPA GMTs)
- Immediately prior to Dose 4 to evaluate the persistence of protective immunity (IgG response rates, IgG GMCs, OPA response rates and OPA GMTs)
- Approximately 30 days following Dose 4 to evaluate anamnestic antibody responses (IgG response rates, IgG GMCs, OPA response rates and OPA GMTs)

Functional antibody activity (as measured by OPA GMTs) will be assessed in all participants with sufficient serum volume at PD3 to evaluate OPA responses. Additionally, evaluation of OPA responses will be conducted at Predose 4 for the first 25% of the participants who had OPA performed at PD3, for whom there is sufficient volume, and at PD4 for the first 50% of the participants who had OPA performed at PD3, for whom there is sufficient volume.

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. The paper Vaccination Report Card (VRC) used to record AEs during the postvaccination periods, as defined in Section 8.1.9.

Details on the safety endpoints evaluated in this study can be found in Section 8.3.3 and Section 9.4.2.

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

4.2.1.3 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of 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. Prevenar 13™ is currently the only recommended vaccine for the prevention of pneumococcal disease in Japanese infants and is also used in many other countries worldwide. It will be used as the active comparator in this study.

Refer to package insert for detailed background information on Prevenar 13™.

4.3 Justification for Dose

The dose and dosing schedule of V114 is similar to that used in previous pediatric V114 clinical studies, which demonstrated safety and comparable immune responses to those of Prevenar 13™. Refer to V114 IB for details on dosing schedule. Subcutaneous route is typically selected for most pediatric vaccines in Japan and subcutaneous route is the same as Prevenar 13™.

4.4 Beginning and End of Study Definition

The overall study begins when written informed consent is provided for the first participant. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Healthy Japanese male and female infants at 2 to 6 months of age (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 Japanese male or female, 2 months of age to 6 months of age inclusive, at the time of randomization.

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, or any diphtheria toxoid-containing vaccine.

3. *Had a recent febrile illness (axillary temperature ≥37.5°C) occurring within 72 hours prior to receipt of study vaccine.

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

5. Has a history of congenital or acquired immunodeficiency.

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

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

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

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

10. 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).

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

Prior/Concomitant Therapy

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

13. *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 each study vaccination.

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

14. *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 14 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.

15. *Has received a licensed live vaccine within 28 days before receipt of study vaccines or is scheduled to receive any live vaccine within 14 days following receipt of study vaccines.

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

Prior/Concurrent Clinical Study Experience

17. 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

18. 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 far away during the study.

19. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

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

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants 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 CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (V114 and Prevenar 13™) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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

Table 1 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin.	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
V114	Experimental	V114	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to IB	0.5 mL	SC	Single dose at Visits 1, 2, 3, and 5	Experimental	IMP	Central
Prevenar 13™	Active Comparator	Prevenar 13™*	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to product labeling	0.5 mL	SC	Single dose at Visits 1, 2, 3, and 5	Experimental	IMP	Central

Admin. = administration; IB = Investigator's Brochure; SC = Subcutaneous; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

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.

*: Pneumococcal 13-valent conjugate vaccine (diphtheria CRM_{197} protein), EU commercial product

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.

6.1.1 Medical Devices

Study vaccine will be provided as a single dose pre-filled syringe, which is defined as a combination product (syringe device and vaccine). A syringe device corresponds to a medical device.

Medical device incidents for a syringe device, including those resulting from malfunctions of a syringe, must be reported to the Sponsor in Japan. Refer to Section 8.4.8 and Appendix 4 for details.

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 randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to receive V114 or Prevenar 13™.

6.3.2 Stratification

Intervention randomization will be stratified according to the age category (2 months, 3 months and 4 to 6 months of age).

Each age category is defined as follows:

- 2 months of age category：2 months of age to 1 day prior to 3 months of age
- 3 months of age category：3 months of age to 1 day prior to 4 months of age
- 4 to 6 months of age category：4 months of age to 1 day prior to 7 months of age

6.3.3 Blinding

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

Because V114 and Prevenar 13™ have a different appearance, a member of the study site staff will be unblinded for the purposes of receiving, maintaining, preparing, and administering these study vaccines. 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 and the participant's parent/guardian will remain blinded such as not to be present in the same room or to be separated with a curtain when study vaccines are administered. Contact between participants or the participant's parent/guardian and unblinded study

personnel after vaccination administration is strictly prohibited. Blinded site personnel will be responsible for all safety and immunogenicity follow-up procedures after vaccine administration.

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

See Section 8.1.11 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 and Prevenar 13™ vaccination 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 time periods specified by this protocol for that medication or vaccination (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 prohibitive steroid regimen, immunoglobulin, blood, or blood products during a participant's participation in this study, one of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible. Any concurrent medication or medical treatment must be recorded on the appropriate electronic Case Report Form (eCRF). It is important to record the use of any analgesic or antipyretic medication that occurs on the day of vaccination on the VRC and appropriate eCRF.

During influenza season, it is anticipated that participants 6 months of age and older may be given inactivated influenza vaccine. Inactivated influenza vaccine should be administered either 7 days prior to or 15 days after the administration of V114 or Prevenar 13™. The influenza vaccine should not be administered at the same time as V114 or Prevenar 13™.

Other non-study pediatric vaccines (oral or injectable) including NIP vaccines can be administered on the same time as V114 or Prevenar 13™. Rotavirus vaccine administered orally is recommended to be given before V114 or Prevenar 13™ and other injectable concomitant vaccines. Other pediatric injectable vaccines are administered after V114 or

Prevenar 13™ and in a separate limb. When the non-live or live vaccine is administered on a different day from V114 or Prevenar 13™, these vaccines can be administered from 15 days after V114 or Prevenar 13™. These vaccines should be recorded on the appropriate eCRF.

V114 or Prevenar 13™ are administered in either arm. To avoid any confounding results, non-study injectable vaccines should not be administered in the same limb as V114 or Prevenar 13™. Documentation of which limb was used for the administration of V114 or Prevenar 13™ must be recorded on the VRC and appropriate eCRF.

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

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification is allowed in this study.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

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

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.11 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 and Section 8.11.3.

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 8.1.10 and Section 8.11.3.

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

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

For participants who are discontinued from study intervention but continue to be monitored in the study, see Section 1.3 and Section 8.11.3 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 8.1.10. 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 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 (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

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

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

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant'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 approximately 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 participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

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

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

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

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study. The investigator should consult with the Sponsor's Clinical Director for any questions about 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 written informed consent is provided. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee before vaccination at Visit 1. Birth weight and gestational age will be recorded on the appropriate eCRF.

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 from birth and medications taken by the participant within 30 days before the first dose of study vaccine at Visit 1.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record vaccination and 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 VRC and appropriate eCRF. Concomitant medications taken after Visit 1 and non-study vaccines received since Visit 1 will be recorded with the VRC as specified in Section 8.3.3.

Non-study pediatric vaccines administered during the study should be recorded on the appropriate eCRF. Injectable vaccines should not be administered in the same limb as V114 or Prevenar 13™. Documentation of which limb was used for the administration of V114 or Prevenar 13™ must be recorded on the VRC (Section 8.3.3) and appropriate eCRF.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.1.

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 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 administered by appropriately qualified members of the study personnel (physician or nurse). Procedures for handling, preparing, and administering the unblinded vaccines are provided in the Investigator Trial File Binder. Unblinded study personnel should follow the preparation and administration instructions for Prevenar 13™ as specified in the product label.

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

The V114 is provided as a single dose pre-filled syringe. Prior to administration of study vaccine, the unblinded study personnel should shake vigorously to obtain a homogenous white suspension. If white colored insoluble particle appears, the unblinded study personnel 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. The vaccine should not be used if the vaccine cannot be resuspended.

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

A 0.5-mL subcutaneous administration of study vaccine will be administered to healthy Japanese infants at Visit 1, 2, 3 and 5. The study vaccines are administered in the either arm.

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 and participant's parent/guardian will be blinded to the study vaccine received by the participant during the study. Vaccination information, such as Component Identification Number and time of vaccination, must be recorded on the appropriate eCRF as per the data entry guidelines.

8.1.8.1 Timing of Dose Administration

V114 or Prevenar 13™ will be administered as indicated in Section 1.3. All participants will be observed for at least 30 minutes following each vaccination for any immediate reactions. This observation must be performed by blinded site personnel for V114 and Prevenar 13™ (Section 1.3 and Section 6.3.3).

Participants must be afebrile (axillary temperature <37.5°C) for at least 72 hours prior to each vaccine administration (Section 1.3 and Section 8.3.2).

Blood samples at Visit 5 must be collected before study vaccination.

8.1.9 Vaccination Report Card

The investigator or delegate will train the participant's legally acceptable representative (parent/guardian) in the use of the paper VRC 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 VRC as described in Section 1.3 and Section 8.3.3. The investigator or delegate will review the data captured on the VRC with the participant's parent/guardian.

For the AEs outlined above, the investigator will use the information provided by the participant's parent/guardian on the VRC, and verbally at the time of VRC review, to apply the appropriate assessment of intensity as described in Appendix 3.

8.1.10 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 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit (Visit 6) 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.

8.1.10.1 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.

8.1.11 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 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 that is part of the study design 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 non-study treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

8.1.12 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 vaccineinduced, 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 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 Prevenar™. In 2012 and 2014, the Sponsor formally bridged the original PnECL assay (v1.0) to the WHO IgG ELISA in order to determine the PnECL threshold values that correspond to 0.35 µg/mL in the WHO ELISA for each of the 7 Prevenar™ serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) and for each of the additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A) in Prevenar 13™.

A confirmatory study was also performed to formally bridge the optimized PnECL assay (v2.0) to the WHO reference ELISA, and to assess the PnECL threshold values that correspond to 0.35 µg/mL measured using the WHO ELISA for each of the serotypes in V114, including the Prevenar 13™ serotypes and serotypes 22F and 33F, which were not previously assessed. The bridging of the PnECL v2.0 to the WHO ELISA has been completed, and the data showed concordance between the PnECL and WHO ELISA around the 0.35 µg/mL threshold value for all 15 serotypes. Thus, 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 by the laboratory of Professor Moon Nahm at University of Alabama (World Health Organization Pneumococcal Serology Reference Laboratory), is a multiplexed OPA assay capable of measuring 4 serotypes at a time, against a total of 16 serotypes of pneumococci [Burton, Robert L. and Nahm, Moon H. 2006]. The OPA is an antibody-mediated killing assay that measures the ability of human serum to kill *S. pneumoniae* serotypes with the help of complement and phagocytic effector cells. The ability of the assay to simultaneously test 4 serotypes/run reduces the amount of serum needed for testing. The assay readout is the opsonization index, which is the reciprocal of the highest dilution that gives ≥50% bacterial killing, as determined by comparison to assay background controls. The Sponsor has developed and optimized the MOPA in a high throughput micro-colony platform. The MOPA assay for all 15 V114 serotypes has undergone validation. The validation study evaluated various performance parameters of the assay including precision, relative accuracy/dilutional linearity, and specificity. The validation results were evaluated against pre-specified acceptance criteria for each of the parameters.

8.3 Safety Assessments

The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in study assessments and procedures 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 at Visit 1 for all participants. A targeted physical examination will be performed at subsequent vaccination visits (Visit 2, 3, and 5). Any clinically significant abnormality will be recorded on the appropriate eCRF.

The complete and targeted physical examination procedures both include obtaining vital signs (eg, heart rate, respiratory rate, and axillary 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 axillary temperatures will be taken by study personnel as indicated in Section 1.3. Participants who have febrile illness (axillary temperature ≥37.5°C) at or within 72 hours of Visit 1, 2, 3, and 5 must be rescheduled.

Temperature readings should be taken at approximately the same time each day if possible. Use of temporal or tympanic thermometers to collect temperature for this study is prohibited. The participant's parent/guardian will be asked to record the participant's temperature reading on the VRC from Day 1 through Day 7 following each vaccination. Temperature measurement must be recorded in the VRC if fever is suspected during Day 8 through Day 14.

8.3.3 Safety Assessment and Use of the VRC

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

Participant's parent/guardian will use the VRC (Section 8.1.9) to document the following information:

- Axillary 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
- Concomitant medications and non-study vaccinations Day 1 to Day 14 postvaccination

8.3.4 Clinical Safety Laboratory Assessments

There are no laboratory safety evaluations required by the protocol.

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before 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, or a procedure.

From the time of allocation/randomization through 14 days (42 days for live attenuated vaccines) following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days (42 days for live attenuated vaccines) thereafter, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

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

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

OR

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

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

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.

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 2.

Table 2 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:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. - any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
ECI	There are no ECI 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

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in

randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

There are no events of clinical interest in this study.

8.4.8 Combination Products – Medical Device Incident

The procedure for documenting and reporting for medical device incident in combination products is shown below and in Appendix 4.

In order to fulfill Japan regulatory reporting obligations, medical device incident (as defined in Section 10.4.1) will be collected and reported to the sponsor in the same time frame as serious adverse events as per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines. The paper CRF is to be used only when electronic CRF system is down. All medical device incidents will be followed until resolution, stabilization, until the event is otherwise explained, or the participant or associated person is lost to follow-up (as defined in Section 7.3).

Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities as needed about certain safety information relating to medical devices being used in clinical studies.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality between the adverse event and the medical device.

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.

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

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.8.1 Planned Genetic Analysis Sample Collection

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

8.9 Future Biomedical Research Sample Collection

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

- Buccal swab DNA for future research
- Leftover main study serum from immunogenicity assay stored for future research

8.10 Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening

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

8.11.2 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.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

A participant may discontinue from study intervention (including receipt of V114, Prevenar 13™) 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 unblinding, changes are made to primary 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 (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Japanese Infants
Treatment Assignment	Participants will be randomly assigned in a 1:1 ratio to V114 or Prevenar 13™, stratified by age category (2 months, 3 months, 4 to 6 months of age).
Analysis Population	Immunogenicity: Per-Protocol (PP) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	Immunogenicity: • Anti-PnPs 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 for the 13 shared serotypes contained in V114 and Prevenar 13™ Safety: • Proportion of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™ • Proportion of participants with solicited systemic AEs (irritability, drowsiness/somnolence, appetite lost/decreased appetite, and hives or welts/urticaria) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™ • Proportion of participants with vaccine-related SAEs from Day 1 through completion of study participation
Statistical Methods for Key Immunogenicity Analyses	The between-group differences (V114 minus Prevenar 13™) in the response rates of anti-PnPs serotype-specific IgG at 30 days PD3, along with corresponding 95% CIs based on the method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985] stratified by age category (2 months of age, ≥3 months of age), will be estimated. The Cochran-Mantel-Haenszel weight will be used to obtain stratum-adjusted proportion difference. The lower bound of the 95% CIs will be compared against the pre-specified margin of -0.1 to test the non-inferiority hypotheses. Anti-PnPs serotype-specific IgG concentrations at 30 days PD3 for the 13 shared serotypes in V114 and Prevenar 13™ will be natural log-transformed and analyzed using a linear model with factors for vaccination group and age category. Between-group differences (V114 minus Prevenar 13™) and corresponding 95% CIs will be estimated on the log scale using the model above, and the results will be transformed back to the original scale to obtain the IgG GMC ratios (V114/Prevenar 13™). The lower bound of the 95% CIs will be compared against the pre-specified margin of 0.5 to test the non-inferiority hypotheses.
Statistical Methods for Key Safety Analyses	The analysis of safety endpoints will follow a tiered approach. p-Values (Tier 1 endpoints) for between-group comparisons and 95% CIs (Tier 1 and Tier 2 endpoints) for between-group differences in the percentage of participants with the respective events will be provided. These analyses will be performed using the unstratified Miettinen and Nurminen method.
Interim Analysis	No interim analysis is planned.

Multiplicity	The study will be considered to have met its primary immunogenicity objectives if non-inferiority is demonstrated in the IgG response rates for the 15 serotypes and in the IgG GMCs for the 13 shared serotypes, both at 30 days PD3. Successful achievement of the primary immunogenicity objective requires that all individual serotypes within the hypotheses satisfy the pre-specified non-inferiority criteria at a 1-sided α level of 0.025. This approach will control the 1-sided type I error rate at 0.025, thus no multiplicity adjustment will be required. No multiplicity adjustments will be made for the safety objective.
Sample Size and Power	A total of 660 participants will be randomized in a 1:1 ratio to V114 or Prevenar 13™ to have 300 participants per arm in the PP population at 30 days PD3. The study will have an overall power of ~83% for all the primary hypotheses at a 1-sided α level of 0.025, with the underlying serotype-specific IgG response rates as observed in V114 Protocol 008, as well as the true IgG GMC ratios of 1.0 and the true standard deviation of natural log IgG concentration of 1.1 for all shared serotypes.

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 (or equivalent).

9.3 Hypotheses/Estimation

The primary immunogenicity objectives are described below.

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 Prevenar 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 Prevenar 13™, p_1 is the response rate for the V114 group and p_2 is the response rate for the Prevenar 13™ group. The 2 unique serotypes in V114 will be compared with the shared serotype with the lowest response rate in the Prevenar 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 for the Prevenar 13™ group. V114 is non-inferior to Prevenar 13™ if the lower bound of the 2-sided 95% CI for the between-group differences (V114 minus Prevenar 13™) is greater than -0.1.

Primary endpoints/hypotheses (H3)

The second primary objective is to compare the anti-PnPs serotype-specific IgG GMCs between V114 and Prevenar 13™ at 30 days PD3 for the 13 shared serotypes contained in V114 and Prevenar 13™. The objective will be assessed via the following non-inferiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 0.5$ versus

H_1: $GMC_1/GMC_2 > 0.5$,

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 Prevenar 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 Prevenar 13™ group. V114 is non-inferior to Prevenar 13™ if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevenar 13™) is greater than 0.5.

9.4 Analysis Endpoints

9.4.1 Immunogenicity Endpoints

The primary immunogenicity endpoints include:

- Proportion of participants with anti-PnPs serotype-specific IgG ≥0.35 µg/mL (response rate) at 30 days PD3 for the 13 shared serotypes in V114 and Prevenar 13™, and for the 2 serotypes unique to V114
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 13 shared serotypes in V114 and Prevenar 13™

The secondary immunogenicity endpoints include:

- Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 2 serotypes unique to V114
- Anti-PnPs serotype-specific IgG response rates at 30 days PD4
- Anti-PnPs serotype-specific IgG GMCs at 30 days PD4
- Anti-PnPs serotype-specific OPA GMTs at 30 days PD3
- Anti-PnPs serotype-specific OPA GMTs at 30 days PD4

- Anti-PnPs serotype-specific OPA response rates at 30 days PD3
- Anti-PnPs serotype-specific OPA response rates at 30 days PD4

The exploratory endpoints include:

- Anti-PnPs serotype-specific IgG response rates at Predose 4
- Anti-PnPs serotype-specific IgG GMCs at Predose 4
- Anti-PnPs serotype-specific OPA GMTs at Predose 4
- Anti-PnPs serotype-specific OPA response rates at Predose 4

9.4.2 Safety Endpoints

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

The safety endpoints include:

- Proportion of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain, and hard lump/induration) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportion of participants with solicited systemic AEs (irritability, drowsiness/somnolence, hives or welts/urticaria, and appetite loss/decreased appetite) from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportions of participants with the broad AE categories consisting of any AE and a vaccine-related AE from Day 1 through Day 14 following any vaccination with V114 or Prevenar 13™
- Proportions of participants with an SAE, a vaccine-related SAE, and discontinuation due to an AE, and death from Day 1 (day of Dose 1) through completion of study participation
- Participants body temperature measured from Day 1 (day of vaccination) through Day 7 following any vaccination with V114 or Prevenar 13™

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Population

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 Prevenar 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 Prevenar 13™ according to vaccination schedule required at the timepoint for the analysis
- Failure to receive the scheduled doses of V114 or Prevenar 13™ with the specified intervals / time window (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 unblinding of the database.

A supportive analysis using the Full Analysis Set (FAS) population may also be performed for the primary immunogenicity endpoints. 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.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study vaccination. Participants will be included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. This will be the group to which they are randomized except for participants who take incorrect study vaccination; such participants will be included in the vaccination group corresponding to the study vaccination actually received. Safety parameters for cross-treated participants (ie, those who received vaccinations of both V114 and Prevenar 13™) will be summarized separately.

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

9.6 Statistical Methods

Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

9.6.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the primary and secondary immunogenicity objectives. Further details will be described in the sSAP. The analyses will be conducted for each of the 15 pneumococcal serotypes in V114 separately.

The between-group differences (V114 minus Prevenar 13™) in the response rates of anti-PnPs serotype-specific IgG at 30 days PD3, along with corresponding 95% CIs based on the method of Miettinen and Nurminen stratified by age category (2 months of age, ≥3 months of age), will be estimated. The Cochran-Mantel-Haenszel weight will be used to obtain stratum-adjusted proportion difference. The lower bound of the 95% CIs will be compared against the pre-specified margin of -0.1 to test the non-inferiority hypotheses. Other response rate analyses in immunogenicity endpoints will be performed using the same model as above. Note that the strata of 3 months of age and 4 to 6 months of age will be combined into a single stratum for the purpose of statistical analysis as the number of participants in the 4 to 6 months of age is anticipated to be very small.

Anti-PnPs serotype-specific IgG concentrations at 30 days PD3 for the 13 shared serotypes in V114 and Prevenar 13™ will be natural log-transformed and analyzed using a linear model with factors for vaccination group and age category. Between-group differences (V114 minus Prevenar 13™) and corresponding 95% CIs will be estimated on the log scale using the model above, and the results will be transformed back to the original scale to obtain the IgG GMC ratios (V114/Prevenar 13™). The lower bound of the 95% CIs will be compared against the pre-specified margin of 0.5 to test the non-inferiority hypotheses. The same model will be used to analyze IgG concentrations at 30 days PD3 for the 2 serotypes unique to V114, IgG concentrations at other timepoints, as well as OPA titers.

Table 3 Summarizes key immunogenicity analyses.

Table 3 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Anti-PnPs serotype-specific IgG response rates at 30 days PD3	P	Stratified Miettinen and Nurminen (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 13 shared serotypes	P	Linear model (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
Secondary				
Anti-PnPs serotype-specific IgG GMCs at 30 days PD3 for the 2 unique serotypes	P	Linear model (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific IgG response rates at 30 days PD4	P	Stratified Miettinen and Nurminen (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific IgG GMCs at 30 days PD4	P	Linear model (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific OPA GMTs at: • 30 days PD3 • 30 days PD4	P	Linear model (estimate, 95% CI)	PP	Missing data will not be imputed
Anti-PnPs serotype-specific OPA response rates at: • 30 days PD3 • 30 days PD4	P	Stratified Miettinen and Nurminen (estimate, 95% CI)	PP	Missing data will not be imputed

PnPs = pneumococcal polysaccharide, IgG = immunoglobulin G, PD = postdose, PP = Per-Protocol, FAS = Full Analysis Set, CI = confidence interval, OPA = opsonophagocytic activity

† P = primary approach, S = supportive approach

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 4). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and other safety parameters 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 participants with events.

Tier 1 Events

Safety parameters or AEs of special interest that are identified *a priori* 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-group differences in the proportion of participants with events. These analyses will be performed using the unstratified Miettinen and Nurminen method. 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-group differences. 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 unstratified Miettinen and Nurminen method).

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

In addition to individual events that occur in at least 4 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 particular points (≥37.5 °C, ≥38.0 °C, ≥39.0 °C, ≥40.0 °C) 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.

Medical device incidents due to syringe, if any, will be listed.

Table 4 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)			
	Injection-site tenderness/pain (Days 1 to 14)			
	Injection-site hard lump/induration (Days 1 to 14)			
	Irritability (Days 1 to 14)			
	Drowsiness/somnolence (Days 1 to 14)			
	Hives or welts/urticaria (Days 1 to 14)			
	Appetite loss/decreased appetite (Days 1 to 14)			
Tier 2	Any AE†		X	X
	Any Vaccine-related AE†			
	Any SAE†			
	Any Vaccine-related SAE†			
	Discontinuation due to AE†			
	Death†			
	Maximum temperature measurements meeting cut points (≥37.5 °C, ≥38.0 °C, ≥39.0 °C, ≥40.0 °C; Days 1 to 7)			
	Specific AEs by SOC and PT‡ (incidence ≥4 participants in at least one of the vaccination groups)			
Tier 3	Specific AEs by SOC and PT‡ (incidence <4 participants in all of the vaccination groups)			X

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

† These endpoints are broad 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 pre-specified as Tier 2 endpoints.

9.6.3 Summary 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, 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

No interim analysis is planned for the study.

9.8 Multiplicity

The study will be considered to have met its primary immunogenicity objective if non-inferiority is demonstrated in the IgG response rates for the 15 serotypes and in the IgG GMCs for the 13 shared serotypes, both at 30 days PD3. Successful achievement of the primary immunogenicity objective requires that all individual serotypes within the hypotheses satisfy the pre-specified non-inferiority criteria at a 1-sided α level of 0.025. This approach will control the 1-sided type I error rate at 0.025, thus no multiplicity adjustment will be required.

No multiplicity adjustments will be made for the safety objective.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

A total of 660 participants will be randomized in a 1:1 ratio to V114 or Prevenar 13™ to have 300 participants per arm in the PP population at 30 days PD3 (~90% evaluability rate). The study will have an overall power of ~83% for all the primary hypotheses at a 1-sided α level of 0.025. The power calculations for the individual hypotheses are provided below.

Primary endpoints/hypotheses (H1 and H2)

The study will have a power of ~83% at a 1-sided α level of 0.025 to demonstrate that V114 is non-inferior to Prevenar 13™ for the 13 shared serotypes and the 2 unique serotypes in the anti-PnP serotype-specific IgG responses rates at 30 days PD3. The underlying serotype-specific response rates are based on the results from V114 Protocol 008 (safety and immunogenicity of two different lots of V114 were evaluated; Lot 1 and Lot 2 pooled for V114), as listed in Table 5 below.

Table 5 Assumptions of the True Response Rates at 30 Days PD3

Serotype	True Response Rate	
	V114	Prevenar 13™
Prevenar 13™ Types		
1	0.972	0.969
3	0.951	0.718
4	0.976	0.951
5	0.960	0.966
6A	0.931	0.962
6B	0.914	0.914
7F	0.995	0.990
9V	0.975	0.958
14	0.984	0.972
18C	0.975	0.955
19A	0.987	0.986
19F	0.995	0.997
23F	0.936	0.907
Non-Prevenar 13™ Types		
22F	0.987	0.907[†]
33F	0.889	0.907[†]

[†] Serotype 23F; Based on Phase 2 data, serotype 3 had the lowest response rate for PCV13, however, for the purpose of power calculation, the serotype with the next lowest response rate, 23F, was used.

Primary endpoints/hypotheses (H3)

This study will have a power of >99% at a 1-sided α level of 0.025 to demonstrate V114 is noninferior to Prevenar 13™ for the 13 shared serotypes based on the anti-PnP serotype-specific IgG GMCs at 30 days PD3. The power calculations are based on the true IgG GMC ratio of 1.0 and the true standard deviation of natural log IgG concentration of 1.1 for all shared serotypes.

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 330 participants in each of the V114 group and Prevenar 13™ group if the underlying incidence of an SAE is approximately 0.49% (1 of every 206 participants receiving the vaccine). There is a 50% chance of observing at least one SAE among 330 participants in each of the V114 group and Prevenar 13™ group if the underlying incidence of an SAE is approximately 0.21% (1 of every 477 participants receiving the vaccine). If no SAEs are observed among 330 participants in each of the V114 group and Prevenar 13™ group, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is approximately <1.1% (one in every 90 participants).

Table 6 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 330 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 [Farrington, C. P. 1990]; no multiplicity adjustments were made.

Table 6 Differences in Incidence of Adverse Events Between the 2 Vaccination Groups That Can be Detected With an ~80% Probability (Assuming 2-sided 5% Alpha Level With 330 Participants in Each Group)

Incidence of Adverse Event		**Risk Difference**
V114 (%) N=330	**Prevenar 13™ (%) N=330**	**Percentage Points**
2.6	0.1	2.5
6.4	2.0	4.4
10.9	5.0	5.9
17.5	10.0	7.5
23.6	15.0	8.6
29.4	20.0	9.4
40.4	30.0	10.4
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 [Farrington, C. P. 1990]		

9.10 Subgroup Analyses

The IgG response rates and IgG GMCs at 30 days PD3 will be analyzed separately by age category (2 months of age, ≥3 months of age; 2 months of age, 3 months of age, 4 to 6 months of age). The IgG response rates will be analyzed using the unstratified Miettinen and Nurminen method, and IgG GMCs will be analyzed using a linear model with a term for vaccination group. Additional subgroup analyses, if any, will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

The number and proportion of randomized participants receiving each vaccination will be summarized.

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

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.
- Congenital disorders (eg, present from birth) that are detected/diagnosed in an infant participant.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

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

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

Assessment of intensity

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

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

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

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

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

- Injection site redness, 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 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: Combination Products: Medical Device Incident: Definitions, Recording and Follow-up

The recording and follow-up procedures described in the protocol apply to all medical devices as described below. For purposes of this section, medical devices in scope for device information collection include devices intended to be used by a study participant according to the study protocol, that are manufactured by the Sponsor or for the Sponsor by a third party, procured by the Sponsor for human use and/or combination products, regardless of investigational or marketed product.

10.4.1 Definition of Medical Device Incident

Combination product is a product comprised of two or more regulated components, i.e., a drug and a device; a device and a cellular and tissue-based products; a cellular and tissue-based products and a drug; or a drug, a device, and a cellular and tissue-based products according to Japan regulations.

Malfunction – Failure of quality, safety and performance, etc. of investigational device in a broad sense such as damage or operational failure.

Medical Device Incident is any malfunction in the characteristics and/or performance of a device (this study is a pre-filled syringe) as well as any inadequacy in the labeling or the instructions for use which might lead to or might have led to the death of a participant and/or the associated person or to a serious deterioration in his/her state of health. A medical device incident also includes events that did not actually cause anything to a participant and/or the associated person.

10.4.2 Recording, Assessment and Follow-up of Medical Device Incident Recording

- When medical device incident occurs, it is the responsibility of the investigator to review all documentation (e.g. Hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- Any medical device incident occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the EDC data entry guidelines (or equivalent). The paper CRF is to be used only when electronic CRF system is down.

- It is important that the investigator provides his/her assessment of causality (relationship to the medical device) at the time of the initial report.

Assessment of Causality

- The investigator will consider a reasonable possibility and use clinical judgment to determine the causality.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes should also be considered and investigated.

Follow-up

- The investigator will 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 event as fully as possible.

10.5 Appendix 5: Contraceptive Guidance

Not applicable.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

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

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

13. References

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

2. International Council on Harmonisation [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
AE	adverse event
APaT	All Participants as Treated
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
eCRF	electronic Case Report Form
ECL	Electrochemiluminescence
ECG	Electrocardiogram
EDC	electronic data collection
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IPD	invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
MOPA	Multiplexed Opsonophagocytic activity
NIP	National Immunization Program
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
PD3	Postdose 3
PD4	Postdose 4
PnECL	pneumococcal electrochemiluminescence
PnPs	pneumococcal polysaccharide
PP	Per-Protocol
RNA	ribonucleic acid
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
VRC	Vaccination Report Card
WHO	World Health Organization

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
[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 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
[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
[Golden AR., et al 2016]	Golden AR, Adam HJ, Zhanel GG, et al. Invasive Streptococcus pneumoniae in Canada, 2011–2014: Characterization of new candidate 15-valent pneumococcal conjugate vaccine serotypes 22F and 33F. Vaccine. 2016;34:2527-30.	04KWF0

[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	03QCDT
[Nakano S., et al 2016]	Nakano S, Fujisawa T, Ito Y, et al. Serotypes, antimicrobial susceptibility, and molecular epidemiology of invasive and non-invasive Streptococcus pneumoniae isolates in pediatric patients after the introduction of 13-valent conjugate vaccine in a nationwide surveillance study conducted in Japan in 2012-2014. Vaccine. 2016;34:67-76.	057R40
[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
[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);2013. Annex 3: Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines; p. 91-151.	0587WR