Protocol B7471003

A PHASE 2, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A MULTIVALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY INFANTS

Statistical Analysis Plan (SAP)

Version: 1.0

Author: PPD

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LIST OF TABLES

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7471003 is based on B7471003 Final Protocol Amendment 1, dated 05 January 2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable

NOTE: Abbreviations are defined at first occurrence in this document.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7471003. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

PF-06482077, 20-valent pneumococcal conjugate vaccine (20vPnC), is being developed for active immunization to prevent disease caused by the Streptococcus pneumoniae serotypes in the vaccine.

Pfizer is developing a new 20vPnC candidate to expand protection against pneumococcal disease beyond that covered by current pneumococcal vaccines in children and adults. 20vPnC has the same composition as Prevnar 13® (13vPnC), but contains an additional 7 pneumococcal conjugates to protect against serotypes responsible for a substantial burden of remaining pneumococcal disease. A meta-analysis of serotypes causing invasive pneumococcal disease (IPD) in children <5 years of age in regions of the world that have introduced higher-valent pneumococcal conjugate vaccines (such as 13vPnC) showed that, overall, these 7 serotypes accounted for approximately 70% of disease not due to the 13vPnC vaccine types. 20vPnC uses the same platform as Prevnar and 13vPnC and contains components that have undergone extensive clinical research. A Phase 1 study has been conducted with 20vPnC in healthy adults 18 to 49 years of age, and the safety and immunogenicity results support further development of 20vPnC in older adults and infants.

The purpose of this Phase 2 study is to describe the safety and immunogenicity of 20vPnC in infants administered vaccine (20vPnC or 13vPnC control) at 2, 4, 6, and 12 months of age. Safety and immunogenicity data from this study will inform further clinical development of 20vPnC in pediatric populations.

2.1. Study Objectives

2.1.1. Primary Objective

- To describe the safety profile of 20vPnC in healthy infants.

2.1.2. Secondary Objective

- To describe the immunogenicity of 20vPnC in healthy infants.

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2.2. Study Design

This is a Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design, conducted at investigator sites in the United States.

Approximately 460 infants ≥42 to ≤98 days of age at the time of consent (signed by the legally acceptable representative [LAR] for the participant) will be enrolled and randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (as the active control vaccine). At 2, 4, 6, and 12 months of age (Doses 1, 2, 3, and 4, respectively), subjects will receive 20vPnC or 13vPnC (investigational products). The investigational products will have the same appearance in this study. Blood will be drawn for immunogenicity assessments 1 month after Dose 3 (7 months of age), prior to receipt of Dose 4 (12 months of age), and 1 month after Dose 4 (13 months of age). Subjects will be observed for 30 minutes after vaccination with 20vPnC or 13vPnC and other concomitantly administered vaccines. Prompted local reactions (pain, redness, and swelling at the injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and use of antipyretic/pain medications occurring within 7 days after vaccination will be collected each day in the electronic diary (e-diary; device or application). SAEs and NDCMCs will be collected for the entire duration of the study. Adverse Events (AEs, including nonserious AEs, SAEs, and newly diagnosed chronic medical conditions (NDCMCs)) will be collected from the signing of the informed consent document to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4. Approximately 6 months after Dose 4, the sites will contact the subject's legally acceptable representative via telephone to inquire about SAEs and NDCMCs.

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

The primary, secondary CCI [redacted] endpoints pertain to the vaccination with 20vPnC, as described in the objectives. Any reference to subjects reporting an event in this SAP should be understood to mean LAR reporting the event for the subject.

3.1. Primary Endpoints

- Proportions of subjects reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days of each dose.
- Proportions of subjects reporting prompted systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep) within 7 days of each dose.
- Proportions of subjects reporting adverse events (AEs) from Dose 1 to 1 month after Dose 3, and from Dose 4 to 1 month after Dose 4.
- Proportions of subjects reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) from Dose 1 to 6 months after Dose 4.

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Redness and swelling will be measured and recorded in measuring device units (range: 1 to >14; an entry in the e-diary of 15 will denote >14), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 4 below. Measuring device units can be converted to centimeters according to the following scale:
1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the subject as mild, moderate, or severe according to the grading scale in Table 4.

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Table 4. Grading Scales for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
Redness (synonymous with erythema)	1 to 4 caliper units (or measuring device units) = >0.0 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis or exfoliative dermatitis
Swelling (synonymous with edema)	1 to 4 caliper units (or measuring device units) = >0.0 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis
Pain at injection site (tenderness)	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched, with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe pain (tenderness) at injection site

Note: If the size of the redness and/or swelling falls between 2 measuring device units, the higher measuring device unit number will be recorded in the e-diary.
Note: Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but as an AE on the CRF.

For each local reaction, the maximum severity grade will be derived for the e-diary collection period (Day 1 to Day 7, where Day 1 is the day of each vaccination) as follows:

= missing and =0, CCI [redacted]

= highest grade (maximum severity) within 7 days of each vaccination (Day 1 to Day 7) among severity grades where the answers are neither “no” nor missing for at least 1 day during Days 1 to 7.

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Table 5. Grading Scales for Systemic Events

Systemic Event	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4
Decreased appetite (loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to feed	Emergency room visit or hospitalization for severe decreased appetite (loss of appetite)
Drowsiness (increased sleep)	Increased or prolonged sleeping bouts	Slightly subdued, interfering with daily activity	Disabling, not interested in usual daily activity	Emergency room visit or hospitalization for severe drowsiness (increased sleep)
Irritability (fussiness) (synonymous with restless sleep; decreased sleep)	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted	Emergency room visit or hospitalization for severe irritability (fussiness)

Abbreviations: CRF = case report form; e-diary = electronic diary.
Note: Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but as an AE on the CRF.

Rectal temperature will be collected in the evening daily for 7 days after each vaccination (Days 1 through 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as a rectal temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 100.4°F [38.0°C]) in order to collect a stop date in the CRF. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 6 below:

Table 6. Ranges for Fever

100.4°F to 101.1°F (38.0°C to 38.4°C)
101.2°F to 102.0°F (38.5°C to 38.9°C)
102.1°F to 104.0°F (39.0°C to 40.0°C)
>104.0°F (>40.0°C)

Maximum temperature range over Days 1-7 will be mapped into the ranges described in Table 6.

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AEs will be assessed from the time of informed consent through 1 month after Dose 3 and from Dose 4 through 1 month after Dose 4.

The primary endpoint "Proportions of subjects reporting adverse events (AEs) from Dose 1 to 1 month after Dose 3, and from Dose 4 to 1 month after Dose 4." will be computed as follows:

- Computations made for each System Organ Class and Preferred Term (and "Any Event"), separately.

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NDCMCs and SAEs will be collected from signing of the informed consent through 6 months after Dose 4.

The primary endpoint "Proportions of subjects reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) from Dose 1 to 6 months after Dose 4." will be computed in a way similar to adverse events CCI [redacted].

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3.2. Secondary Endpoints

- Pneumococcal serotype-specific immunoglobulin G (IgG) concentrations 1 month after Dose 3.

- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4.

3.2.1. IgG Concentration

Concentrations of anticapsular IgG for the 20 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) will be determined in all subjects at all time points using the Luminex assay. Results will be reported as IgG concentrations.

CCI [redacted] Antibody concentrations above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ, denoted as below the limit of quantification (BLQ), will be set to 0.5 × LLOQ for analysis.

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To support the secondary endpoints, geometric mean concentrations (GMCs) will be calculated and summarized for 1 month after Dose 3 and 1 month after Dose 4.

CCI [redacted] Proportions of subjects with serotype-specific IgG concentrations equal to or above the reference concentrations noted below will be calculated.

Serotype-specific IgG reference concentrations are defined below.

- ≥0.35 µg/mL will be used for serotypes 1, 3, 4, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19F, 22F, 23F, and 33F.
- ≥0.23 µg/mL will be used for serotype 5.
- ≥0.10 µg/mL will be used for serotype 6B.
- ≥0.12 µg/mL will be used for serotype 19A.

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3.4. Baseline and Other Variables

Baseline variables include the following data as part of the baseline characteristics:

- Demographics
- Medical history
- Physical examination

Other variables to be summarized include:

- E-diary completion
- Prior/concomitant vaccines

3.4.1. Demographics, Medical History and Physical Examination

The demographic variables are age at first vaccination (in days), sex, race, and ethnicity. Age at first vaccination in days will be derived as (1st vaccination date – date of birth + 1).

For subjects assigned to receive vaccine, but who are not vaccinated, the enrollment date will be used in place of the date of first vaccination

Medical history will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).

A physical examination will be performed. It will evaluate any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Clinically significant abnormal results will be recorded in the CRF.

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3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

The subject may receive vaccines with inactivated poliovirus, hepatitis B, or *Haemophilus influenzae* type b (either separately or in combination with diphtheria, tetanus, and pertussis antigens) at 2, 4, and 6 months of age, Measles, mumps, and rubella (MMR) vaccine may be administered concomitantly at 12 months of age with Dose 4 or more than 1 month after Dose 4. Rotavirus vaccine may be administered orally at any time. Vaccines licensed and recommended for this age group other than the combination diphtheria, tetanus, and pertussis combination vaccine may be administered with 20vPnC or 13vPnC, or as specified in the protocol.

Concomitant medications will be recorded only if they were used to treat SAEs and NDCMCs. Concomitant and prior vaccines, and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODD).

3.5. Safety Endpoints

Local reactions, systemic events, antipyretic/pain medication, AEs, SAEs and NDCMCs have been described above in the primary endpoints.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to each analysis planned for this study (see Section 7). Classifications will be documented per standard operating procedures.

See Appendix 1.1 for an outline of handling protocol deviations.

4.1. Safety Analysis Population

The **overall safety population** will include all subjects who receive at least 1 dose of study vaccine (20vPnC or 13vPnC) and have safety data reported in the study. Subjects will be assigned to vaccine group corresponding to the vaccine actually received. The safety population will be the analysis population for safety and reactogenicity endpoints.

Separate safety populations will be defined for each vaccination as follows:

Dose 1 to Dose 3 Safety Population - Subjects receiving Dose 1 and having safety data between Dose 1 and the blood draw visit 1 month after Dose 3

Dose 4 Safety Population - Subjects receiving Dose 4 and having safety data between Dose 4 and 6 months after Dose 4

If a subject's actual vaccine dose varies within a particular safety population (eg, overall or Dose 1 to Dose 3), the subject data will be either analyzed for any by-dose presentation, or data will be presented in listings as appropriate.

4.2. Evaluable Immunogenicity Populations

The evaluable immunogenicity population will be defined for Dose 3 and Dose 4 separately.

The Dose 3 evaluable immunogenicity population will include any subject:

1. Who was eligible for the study.
2. Who was randomly assigned to receive the vaccine.
3. Who was 42 to 98 days of age, inclusive, on the day of first vaccination.
4. Who received the vaccine to which he or she was randomly assigned at the first 3 doses.
5. Who had a valid and determinate IgG concentration for at least 1 serotype from 1 month after Dose 3 visit (Visit 4).
6. Whose blood collection was within 27 to 56 days, inclusive, after Dose 3.
7. Who received no prohibited vaccines before the blood draw at 1 month after Dose 3.
8. Who had no other major protocol deviations as determined by the clinician or medical monitor.

The Dose 3 evaluable immunogenicity population will be the primary analysis population for immunogenicity results from the blood collected at 1 month after Dose 3.

The Dose 4 evaluable immunogenicity population will include any subject:

1. Who was eligible for the study.
2. Who was randomly assigned to receive the vaccine.
3. Who was 42 to 98 days of age, inclusive, on the day of first vaccination.
4. Who received the assigned vaccine, as randomized, within the defined window for Dose 4 (365-386 days of age; see Protocol Schedule of Activities).
5. Who received the vaccine to which he or she was randomly assigned at all 4 doses.
6. Who had a valid and determinate IgG concentration for at least 1 serotype after Dose 4.
7. Whose blood collection was within 27 to 56 days, inclusive, after Dose 4.
8. Who received no prohibited vaccines before the blood draw at 1 month after Dose 4.
9. Who had no other major protocol deviations as determined by the clinician or medical monitor.

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The Dose 4 evaluable immunogenicity population will be the primary analysis population for immunogenicity results before and after Dose 4.

The blood collection window has been expanded by 1 extra day before, and 14 days after (see #6 above located under the Dose 3 evaluable immunogenicity population definition and #7 above for the Dose 4 evaluable immunogenicity population definition) the protocol-specified blood collection window of 28 to 42 days defined in the protocol, for consistency with established rules in the Prevnar 13 development program.

Subjects will be summarized according to their randomized vaccine in the immunogenicity analysis based on evaluable immunogenicity populations.

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5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses

No hypothesis testing will be performed, and also no formal statistical decision rules apply in this study. A descriptive estimation approach will be used to assess all safety and immunogenicity objectives. Nominal 95% confidence intervals will be calculated for all proposed endpoints.

5.2. General Methods

Time points for local reactions and systemic events refer to data within 7 days of each dose.

5.2.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%) and the numerator (n), the denominator (N) used in the percentage calculation, with 95% CIs.

The exact 95% confidence interval (CI) for binary endpoints will be computed using the F distribution (Clopper-Pearson[1]). If r is the number of responses and n is the number of subjects, then it follows that $p = r / n$ is the estimate of the proportion of response. An exact 95% CI can be computed by solving the following 2 equations. For the lower limit p_L,

$$p_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$

and for the upper limit p_U,

$$p_U = \frac{(r+1)F_U}{(n-r) + (r+1)F_U}$$

where F_L is the quantile from the F distribution for α=0.025, with numerator degrees of freedom equal to 2r and denominator degrees of freedom equal to 2(n-r+1). F_U is the quantile from the F distribution for α=0.975, with numerator degrees of freedom equal to 2(r+1) and denominator degrees of freedom equal to 2(n-r). When r equals 0, F_L should be set equal to 1.0 so p_L equals 0. When r equals n, F_L should be set equal to 1.0 so p_U equals 1.0.

5.2.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Mean (GM)

Geometric means will be computed along with associated 95% CIs. The GM will be calculated as the mean of the assay results after making the logarithm transformation and then back transformation to its original scale. Two-sided 95% CIs will be obtained by taking log transforms of concentrations, calculating the 95% CI with reference to the t-distribution, then exponentiating the confidence limits.

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5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied (eg, partial dates for AEs will be imputed according to Pfizer standard algorithms).

Methods for handling missing local reactions and systemic events are described in Section 3.1 CCI [redacted].

Methods for handling IgG concentrations CCI [redacted] below the limit of quantitation are described in Section 3.2 CCI [redacted]. All immunogenicity analyses will be performed after the imputation of the IgG concentrations CCI [redacted] that are below the LLOQ. Missing immunogenicity values will be retained as missing.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Local Reactions

6.1.1.1. Primary Analysis

Endpoints: Proportions of subjects reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days of each dose

- Analysis time points**:** Within 7 Days – Dose 1; Within 7 Days – Dose 2; Within 7 Days – Dose 3; Within 7 Days – Dose 4
- Analysis population**:** Dose 1 to Dose 3 safety population for Doses 1 to 3, Dose 4 safety population for Dose 4
- Analysis methodology**:** Descriptive statistics
- Supporting objective: Primary Objective

Reporting results:

Proportions of subjects reporting prompted local reactions will be summarized by maximum severity level. The percentage (%) and the numerator (n) and the denominator (N) used in the percentage calculation, and corresponding 95% Clopper-Pearson CI will be presented for each vaccine group at all time points. The same descriptive statistics will be compiled across all 4 doses.

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6.1.2. Systemic Events

6.1.2.1. Primary Analysis

Endpoints: Proportions of subjects reporting prompted systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep) within 7 days of each dose.

- Analysis time points**:** Within 7 Days – Dose 1; Within 7 Days – Dose 2; Within 7 Days – Dose 3; Within 7 Days – Dose 4
- Analysis population**:** Dose 1 to Dose 3 safety population for Doses 1 to 3, Dose 4 safety population for Dose 4
- Analysis methodology**:** Descriptive statistics
- Supporting objective: Primary Objective

[redacted]

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Reporting results:

The percentage (%) and the numerator (n) and the denominator (N) used in the percentage calculation, and corresponding 95% Clopper-Pearson CI will be presented for each vaccine group at all time points. The same descriptive statistics will be compiled across all 4 doses.

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6.1.3. Adverse Events

6.1.3.1. Primary Analysis

Endpoint: Proportions of subjects reporting AEs

- Analysis time points: Dose 1 to 1 month after Dose 3, and from Dose 4 to 1 month after Dose 4
- Analysis population: Dose 1 to Dose 3 safety population, Dose 4 safety population.
- Analysis methodology: Descriptive statistics
- Supporting objective: Primary Objective

Reporting results:

The percentage (%), number of subjects and the denominator (N) used in the percentage calculation, and corresponding 95% Clopper-Pearson CI will be presented for each vaccine group.

Figures: None

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6.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

6.1.4.1. Primary Analysis

Endpoint: Proportions of subjects reporting SAEs and NDCMCs

- Analysis time points: Dose 1 to 6 months after Dose 4
- Analysis population: Safety analysis population
- Analysis methodology: Descriptive statistics
- Supporting objective: Primary Objective

Reporting results:

The percentage (%), number of subjects and the denominator (N) used in the percentage calculation, and corresponding 95% Clopper-Pearson CI will be presented for each vaccine group.

Figures: None

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6.2. Secondary Endpoints

The ordering of the pneumococcal serotypes in summaries will be as follows and will appear on the same table:

- 13vPnC serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F; and
- Additional Serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F.

6.2.1. Pneumococcal Serotype-specific Immunoglobulin G (IgG) Concentrations 1 Month after Dose 3

Endpoint: Pneumococcal serotype-specific IgG concentrations 1 month after Dose 3

- Time points: 1 month after Dose 3
- Analysis population: Dose 3 evaluable immunogenicity CCI [redacted]
- Analysis methodology: Descriptive statistics
- Supporting objective: Secondary Objective

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Reporting results:

IgG GMCs with their associated 95% CIs will be summarized separately at 1 month after Dose 3 for each pneumococcal serotype by each vaccine group.

The percentage (%) and the number of subjects with serotype-specific IgG concentrations ≥ reference concentrations (n) and the denominator (N) used in the percentage calculation, and corresponding 95% Clopper-Pearson CI will be presented for each vaccine group 1 month after Dose 3.

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6.2.2. Pneumococcal Serotype-specific Immunoglobulin G (IgG) Concentrations 1 Month after Dose 4

Endpoint: Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4

- Time points: 1 month after Dose 4
- Analysis population: Dose 4 evaluable immunogenicity CCI [redacted]
- Analysis methodology: Descriptive statistics
- Supporting objective: Secondary Objective

Reporting results:

IgG GMCs with their associated 95% CIs will be summarized separately at 1 month after Dose 4 for each pneumococcal serotype by each vaccine group.

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6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct and Subject Disposition

6.5.1.1. Subject Disposition

Disposition of subjects relative to Dose 1 to Dose 3 will be summarized for all subjects as follows: The number of consented subjects and the number and percentage of randomized subjects who are randomized, receive each vaccination (Dose 1, Dose 2, Dose 3), complete Dose 1 to Dose 3, withdraw during Dose 1 to Dose 3 and the specific reasons (LAR request, lost to follow-up, failed to return, adverse event, protocol violation, other) will be summarized by vaccine group (according to randomized group assignment). A similar summarization of disposition relative to Dose 4 will also be prepared, including the number and percentage of randomized subjects who completed through 1 month after Dose 3,

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withdrew after 1 month after Dose 3 but prior to Dose 4 by reason, received Dose 4, and withdrew after Dose 4 but before blood draw 1 month after Dose 4 by reason.

The number of consented subjects and the number and percentage of randomized subjects who are randomized, vaccinated, completed, and withdrawn through 1 month after Dose 4 will be presented for each vaccine group (according to randomized group assignment) and overall.

The above information will also summarized for the time period from 1 month after Dose 4 through 6 months after Dose 4.

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6.5.1.2. Demographic Characteristics

Demographic characteristics will be summarized for all subjects, as well as for the Dose 4 safety populations, and separately for the Dose 3 and Dose 4 evaluable immunogenicity populations by vaccine group and overall.

6.5.1.3. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to MedDRA. The number and percentage of subjects with an assigned vaccine having at least one diagnosis, overall and at each system organ class and preferred term level, will be summarized by vaccine group and overall for the overall safety population.

6.5.1.4. Physical Examination

Significant physical examination findings will be recorded on Medical History or AE pages, as relevant, and reporting done under those endpoints for the overall safety population.

6.5.1.5. Blood Samples for Assay

The number and percentage of randomized subjects providing blood samples within and outside of protocol pre-specified time frames will be tabulated separately for Dose 1 to Dose 3 and Dose 4.

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6.5.2. Study Treatment Exposure

6.5.2.1. Vaccination Timing and Administration

The number and percentage of subjects randomized and receiving each vaccine (20vPnC or 13vPnC) within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and overall for all randomized subjects. The denominator for the percentages is the total number of subjects in the given vaccine group or overall. In addition, the relation of randomized vaccine to actual vaccine received will be presented as a cross tabulation of the actual vaccine received versus the randomized vaccine.

6.5.3. Prior/Concomitant Vaccination and Concomitant Medications Used to Treat SAEs and NDCMCs

Each prior/concomitant vaccine will be summarized according to the Anatomic Therapeutic Chemical (ATC) 4th level classification. The number and percentage of randomized subjects receiving each vaccine (including DTaP-IPV-HebB (Pediarix, supplied to study sites, containing diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and hepatitis B antigens), rotavirus, Hib, MMR, varicella, influenza, others) will be cross tabulated according to assigned vaccine regimen. Summarization will be done separately for before Dose 1, between Dose 1 and 1 month after Dose 3, between 1 month after Dose 3 and Dose 4, and between Dose 4 and 1 month after Dose 4. The Dose 1 to Dose 3 safety population will be used for first three tables while the Dose 4 safety population will be used for the last one.

Concomitant medications used to treat SAEs and NDCMCs will be summarized for the time points Dose 1 to 6 months after Dose 4 (safety population), and for the separate time points Dose 1 through 1 month after Dose 3 (Dose 1 to Dose 3 safety population), from 1 month after Dose 3 to Dose 4 (Dose 1 to Dose 3 safety population), Dose 4 to 1 month after Dose 4 (Dose 4 safety population), and from 1 month after Dose 4 to 6 months after Dose 4 (After Dose 4 safety population).

6.6. Safety Summaries and Analyses

The safety measures local reactions, systemic events, AEs, SAEs and NDCMCs summaries and analyses are described under the Primary Endpoints (see Section 6.1).

CCI [redacted]

8. REFERENCES

1. Collett D. Chapter 2. Statistical inference for binary data. In: Modelling binary data. London, England: Chapman & Hall; 1991: p. 17-42

9. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Appendix 1.1. Definition of Protocol Deviations that Relate to Statistical Analyses/Populations

Appendix 1.1.1. Deviations Assessed Prior to Randomization

Any significant deviation from the protocol, including inclusion and exclusion criteria, will be reviewed prior to database lock and a decision made regarding evaluation for each analysis population.

Appendix 1.1.1. Deviations Assessed After Randomization

Any significant deviation from the protocol, including inclusion and exclusion criteria, will be reviewed prior to database lock and a decision made regarding evaluation for each analysis population.