Protocol C3571002

A PHASE 2, RANDOMIZED, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A MULTIVALENT PNEUMOCOCCAL CONJUGATE VACCINE GIVEN WITH, OR SEPARATELY FROM, 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY INFANTS

Statistical Analysis Plan
(SAP)

Version: 1.0

Author: PPD

Date: 24MAY2018

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3571002 is based on C3571002 Final Protocol, dated 21 December 2017.

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 C3571002. This document may modify and/or supplement 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-06842433, complementary 7-valent pneumococcal conjugate vaccine (c7vPnC), is being developed for active immunization to prevent disease caused by the *Streptococcus pneumoniae* serotypes in the vaccine.

c7vPnC is being developed to augment current pneumococcal coverage in children and adults. c7vPnC contains pneumococcal conjugates of 7 different serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) individually conjugated to CRM_{197}. c7vPnC uses the same platform and contains the same excipients as Prevnar® and Prevnar 13®. These 7 additional serotypes were selected based on their relative prevalence as a cause of IPD, their generalized geographic distribution, and other factors that would support inclusion, such as the presence of antibiotic resistance and greater disease severity (eg, meningitis, mortality). These 7 serotypes have a long-standing association with serious pneumococcal disease. The incidence of IPD due to these 7 serotypes in children <5 years of age has remained relatively stable or slightly increased over the past several years, and these serotypes cause a significant amount of IPD in children. Additional epidemiology data for the 7 serotypes and the preclinical program are described in the c7vPnC investigator's brochure (IB).

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The purpose of this Phase 2 study is to assess the safety and immunogenicity of c7vPnC in infants, and to generate a safety and immunogenicity data set with c7vPnC to support and inform the design of the Phase 3 clinical development program. The targeted age of the population for this study, infants 2 months of age, has been selected as this is the indicated and recommended age of Prevnar 13 immunization in infants. Subjects will receive a 4-dose series of: c7vPnC coadministered with Prevnar 13 in Group 1; c7vPnC administered 1 month after Prevnar 13 in Group 2; or Prevnar 13 administered alone in Group 3 (control group). Additionally, the safety CCI of a single dose of c7vPnC (supplemental dose) administered at 13 months of age, after 4 doses of Prevnar 13 (in Group 3), will be described. CCI

2.1. Study Objectives

2.1.1. Primary Objective

- To describe the safety profile of c7vPnC in healthy infants.

2.1.2. Secondary Objective

- To describe the immunogenicity of c7vPnC in healthy infants.

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2.2. Study Design

This is a Phase 2, multicenter, randomized, active-controlled, open-label study with a 3-arm parallel design, conducted at investigator sites in the United States. Approximately 690 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 1:1:1 ratio to receive a vaccine series with:

- c7vPnC coadministered with Prevnar 13 (Group 1 - coadministration);
- c7vPnC given 1 month after Prevnar 13 (Group 2 - staggered administration); or

- Prevnar 13 alone as the active control group (Group 3 - control with Supplemental Dose). A single dose of c7vPnC will be administered after the Prevnar 13 series is completed in this group.

In all groups, Prevnar 13 will be administered at 2, 4, 6, and 12 months of age. c7vPnC will be administered at 2, 4, 6, and 12 months of age in Group 1; at 3, 5, 7, and 13 months of age in Group 2; and at 13 months of age in Group 3. **Note:** In this document, and related study documents, vaccine (investigational product) Doses 1, 2, 3, and 4 specifically refer to the doses of c7vPnC administered in Groups 1 and 2, or the doses of Prevnar 13 administered in the control group (Group 3). The dose of c7vPnC administered in Group 3 will be referred to as the Supplemental Dose. See Table 2 for a summary of study groups and key procedures.

Table 2. Summary of Study Groups and Key Procedures

	2 mo/o	3 mo/o	4 mo/o	5 mo/o	6 mo/o	7 mo/o	8 mo/o	12 mo/o	13 mo/o	14 mo/o	18 mo/o	19 mo/o
Group 1 Coadmin. c7vPnC (n=230)	c7vPnC Dose 1 Prev13		c7vPnC Dose 2 Prev13		c7vPnC Dose 3 Prev13	Blood draw		Blood draw c7vPnC Dose 4 Prev13	Blood draw		Phone contact	
Group 2 Staggered c7vPnC (n=230)	Prev13	c7vPnC Dose 1	Prev13	c7vPnC Dose 2	Prev13	Blood draw c7vPnC Dose 3	Blood draw	Prev13	Blood draw c7vPnC Dose 4	Blood draw		Phone contact
Group 3 Control (n=230)	Prev13 Dose 1		Prev13 Dose 2		Prev13 Dose 3	Blood draw		Blood draw Prev13 Dose 4	Blood draw c7vPnC Suppl. Dose	CCI		Phone contact

Abbreviations: Coadmin. = coadministered; mo/o = months old; Prev13 = Prevnar 13; Suppl. = supplemental.

Vaccine containing diphtheria, tetanus, and acellular pertussis antigens will be administered at 2, 4, and 6 months of age. This is given as part of routine standard of care in the United States, CCI [redacted] Other routine pediatric vaccines may be administered in this study, with or without certain restrictions.

Subjects will be observed for 30 minutes after each dose of c7vPnC in Groups 1 and 2, and after Prevnar 13 and the Supplemental Dose of c7vPnC in Group 3. In all groups, occurrence

of prompted local reactions (pain, redness, and swelling at the injection site), and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and use of antipyretic/pain medications within 7 days after Doses 1 to 4 and the Supplemental Dose will be collected each day in the electronic diary (e-diary). SAEs and NDCMCs will be collected for the entire duration of the study. AEs (including nonserious AEs, SAEs, and 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 or 1 month after the Supplemental Dose in Group 3. Approximately 6 months after Dose 4 or the Supplemental Dose, the sites will contact the subject's LAR via telephone to inquire about SAEs and NDCMCs. Blood will be drawn for immunogenicity assessments 1 month after Dose 3, prior to receipt of Dose 4, and 1 month after Dose 4, CCI In Group 2, blood will also be collected prior to Dose 3.

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

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 following Dose 3 and from Dose 4 to 1 month following Dose 4/Supplemental Dose.
- Proportions of subjects reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) from Dose 1 to 6 months following Dose 4/Supplemental Dose.

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

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/Supplemental Dose." will be computed in a way similar to adverse events CCI

3.2. Secondary Endpoints

- Pneumococcal serotype-specific immunoglobulin G (IgG) concentrations of the c7vPnC serotypes at 1 month after Dose 3.

- Pneumococcal serotype-specific IgG concentrations of the c7vPnC serotypes at 1 month after Dose 4.

IgG Concentration

Concentrations of anticapsular IgG for the c7vPnC pneumococcal serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) will be determined in all subjects at specified time points using the Luminex assay. Results will be reported as IgG concentrations.

CCI 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.

To support the secondary endpoints, proportions of subjects with serotype-specific IgG concentrations equal to or above the reference concentrations at 1 month after Dose 3 noted below will be calculated.

Serotype-specific IgG reference concentrations are defined below.

- ≥0.35 µg/mL will be used for serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F.

Geometric mean concentrations (GMCs) will be calculated and summarized for 1 month after Dose 3 and 1 month after Dose 4.

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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 Dose 1 (in days), sex, race, and ethnicity. Age at Dose 1 vaccination in days will be derived as (Dose 1 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 at 12 months of age. 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 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.

4.1. Safety Analysis Population

The **overall safety population** will include all subjects who receive at least 1 dose of c7vPnC (in Groups 1 and 2) or Prevnar 13 (in Group 3) and have safety data reported in the study. Subjects will be reported according to the vaccine actually received. The safety population will be the analysis population for safety and reactogenicity endpoints.

Additional safety populations will be defined as follows:

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

Dose 4 Safety Population - Subjects receiving Dose 4 and having safety data between Dose 4 and 1 month after Dose 4 for Groups 1 and 2 and having safety data between Dose 4 and Supplemental Dose for Group 3.

Supplemental Dose Safety Population - Subjects receiving Supplemental Dose and having safety data between Supplemental Dose and 1 month after Supplemental Dose.

If a subject's actual vaccine dose deviates from the planned vaccination 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 according to the vaccine dose actually received.

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 Dose 1 for Groups 1 and 3 or who was 63 to 133 days of age, inclusive on the day of Dose 1 for Group 2.
4. Who received the vaccine to which he or she was randomly assigned, through Dose 3.
5. Who had a valid and determinate IgG concentration for at least 1 serotype from 1 month after Dose 3.
6. Whose blood collection was within 27 to 56 days, inclusive, after Dose 3.
7. 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 Dose 1 for Groups 1 and 3 or who was 63 to 133 days of age, inclusive on the day of Dose 1 for Group 2.

4. Who received the assigned vaccine, as randomized, within the defined window for Dose 4 (365-386 days of age for Groups 1 and 3 and 386-421 days of age for Group 2; 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 1 month after Dose 4.

7. Whose blood collection was within 27 to 56 days, inclusive, after Dose 4.

8. Who had no other major protocol deviations as determined by the clinician or medical monitor.

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.

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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).

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Methods for handling IgG concentrations CCI below the limit of quantitation are described in Section 3.2 CCI, respectively. All immunogenicity analyses will be performed after the imputation of the IgG concentrations CCI 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; Within 7 Days - Supplemental Dose
- Analysis population**:** Dose 1 to Dose 3 safety population for Doses 1 to 3, Dose 4 safety population for Dose 4, Supplemental dose safety population for supplemental Dose
- 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 each time point.

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

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 each time points.

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6.1.3. Adverse Events

6.1.3.1. Primary Analysis

Endpoint: Proportions of subjects reporting AEs from Dose 1 to 1 month following Dose 3, from Dose 4 to 1 month following Dose 4, and from Supplemental Dose to 1 month following Supplemental Dose

- Analysis time points**:** Dose 1 to 1 month after Dose 3, and from Dose 4 to 1 month after Dose 4/Supplemental Dose
- Analysis population**:** Dose 1 to Dose 3 safety population, Dose 4 safety population, Supplemental dose safety population for supplemental Dose
- 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 from Dose 1 to 6 months following Dose 4/Supplemental Dose

- Analysis time points**:** Dose 1 to 6 months after Dose 4/Supplemental Dose
- Analysis population**:** Overall 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:

- c7vPnC serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F.

6.2.1. Pneumococcal serotype-specific immunoglobulin G (IgG) concentrations of the c7vPnC serotypes 1 month after Dose 3

Endpoint: Pneumococcal serotype-specific IgG concentrations of the c7vPnC serotypes 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

Reporting results:

IgG GMCs with their associated 95% CIs will be summarized separately at 1 month after Dose 3 for each of the 7 pneumococcal serotypes 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 of the c7vPnC serotypes 1 month after Dose 4

Endpoint: Pneumococcal serotype-specific IgG concentrations of the c7vPnC serotypes 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 of the 7 pneumococcal serotypes 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 1 month after 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 from Dose 1 to the visit 1 month after Dose 3, withdraw between Dose 1 to the visit 1 month after Dose 3 and the specific reasons for withdrawal (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/Supplemental Dose will also be prepared, including the number and percentage of randomized subjects who completed through 1 month after Dose 3, withdrew after 1 month after Dose 3 but prior to Dose 4 by reason, received Dose 4, and withdrew after Dose 4 but before the visit 1 month after Dose 4 by reason. For Group 3, disposition will also include those receiving the Supplemental Dose and those who withdrew after the Supplemental Dose but before the visit 1 month after the Supplemental Dose.

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 3 will be presented for each vaccine group (according to randomized group assignment) and overall.

The above information will also be summarized for the time period from 1 month after Dose 3 through 6 months after Dose 4 (Group 1 and Group 2)/Supplemental Dose (Group 3).

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6.5.1.2. Demographic Characteristics

Demographic characteristics will be summarized for the overall safety population, CCI [redacted] 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 1 month after Dose 3, before and 1 month after Dose 4, and before and after the Supplemental Dose.

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6.5.2. Study Vaccination Exposure

6.5.2.1. Vaccination Timing and Administration

The number and percentage of subjects randomized and receiving each vaccine (c7vPnC and/or Prevnar 13) 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 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/Supplemental Dose. 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/Supplemental Dose (Dose 4 safety population), and from 1 month after Dose 4 to 6 months after Dose 4/Supplemental Dose (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).

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8. REFERENCES

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

2. Chan ISF, Zhang Z. (1999). Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics*, 55:1201–1209.

9. APPENDICES

None