Protocol B7471006

A PHASE 3, RANDOMIZED, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN ADULTS ≥65 YEARS OF AGE WITH PRIOR PNEUMOCOCCAL VACCINATION

Statistical Analysis Plan (SAP)

Version: 2

Author: PPD

Date: 23 Mar 2020

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TABLE OF CONTENTS

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LIST OF TABLES

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1. VERSION HISTORY

This statistical analysis plan (SAP) for Study B7471006 is based on the final B7471006 protocol, dated 22 Oct 2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	C C I [redacted] [redacted] [redacted] • Sections 3.1, 3.5, 4, and 6: miscellaneous clarification of text	C C I [redacted] [redacted] [redacted] • To provide clarification based on team feedback received during the tables, listings, and figures (TLFs) mock reviews of other Phase 3 studies and blinded data reviews (BDRs)

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 B7471006. This document may modify and/or supplement the plans outlined in the protocol; however, any major modifications of the primary endpoints and their analyses will also be reflected in a protocol amendment.

2.1. Study Objectives

2.1.1. Primary Safety Objective

- To describe the safety profile of 20-valent pneumococcal conjugate vaccine (20vPnC).

2.1.2. Primary Immunogenicity Objective

- To describe the immune responses to 20vPnC in adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPSV23), previously vaccinated with 13-valent pneumococcal conjugate vaccine (13vPnC), or previously vaccinated with both 13vPnC and PPSV23.

2.1.3. Secondary Objective

- To further describe the immune responses to 20vPnC in adults previously vaccinated with PPSV23, previously vaccinated with 13vPnC, or previously vaccinated with both 13vPnC and PPSV23.

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2.2. Study Design

This Phase 3, multicenter, randomized, open-label study will be conducted at investigator sites in the United States and Sweden. The purpose of the study is to describe the safety and immunogenicity of 20vPnC administered to adults ≥65 years of age who have been previously vaccinated with various pneumococcal vaccines.

A total of ~875 adults ≥65 years of age will be enrolled into 3 cohorts based on their prior pneumococcal vaccination history.

Subjects who have received PPSV23 ≥1 to ≤5 years previously, but have not been vaccinated with 13vPnC, will be assigned to Cohort A and will be randomized (2:1) to receive either 20vPnC or 13vPnC.

Subjects who have received 13vPnC ≥6 months previously, but have not been vaccinated with PPSV23, will be assigned to Cohort B and will be randomized (2:1) to receive either 20vPnC or PPSV23.

Subjects who have previously received 13vPnC followed by PPSV23 (PPSV23 vaccination must have been given ≥1 year prior to vaccination in this study) will be assigned to Cohort C and will receive 20vPnC.

Vaccine assignment is summarized in Table 2 below.

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Table 2. Vaccine Assignment

Cohort	Prior Vaccination History	Vaccine Assignment	Sample Size
A	Received PPSV23 vaccination in prior ≥1 to ≤5 years, but no 13vPnC	20vPnC	250
		13vPnC	125
B	Received 13vPnC vaccination in prior ≥6 months, but no PPSV23	20vPnC	250
		PPSV23	125
C	Received 13vPnC followed by PPSV23 vaccination (PPSV23 vaccination ≥1 year prior)	20vPnC	125

On Day 1 (Visit 1), subjects will be assessed for eligibility, have blood drawn for immunogenicity assessments in the 20vPnC group and for purposes of vaccine research in all subjects, and receive the study vaccination. Subjects will be observed for at least 30 minutes after vaccination and adverse events (AEs) occurring during that time (immediate AEs) will be recorded. Subjects will also receive safety follow-up and electronic diary (e-diary) instructions at the visit. Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 7 days after vaccination, and prompted local reactions (redness, swelling, and pain at the injection site) occurring at the assigned vaccine (20vPnC, 13vPnC, or PPSV23) injection site within 10 days after vaccination, will be collected daily in the e-diary. Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days after vaccination.

Subjects will return for Visit 2 (28 to 42 days after Visit 1). Information will be collected from the subjects on AEs, serious AEs (SAEs), newly diagnosed chronic medical conditions (NDCMCs), and e-diary follow-up (as needed). Blood will be drawn for immunogenicity assessments in the 20vPnC group and for purposes of vaccine research in all subjects.

At Visit 3 (approximately 6 months [168 to 196 days] after Visit 1), the sites will contact the subjects via telephone to inquire about SAEs, NDCMCs, nonstudy vaccinations, and concomitant medications used to treat SAEs or NDCMCs.

Opsonophagocytic activity (OPA) titers for serotypes present in 20vPnC (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) will be determined on all sera collected prior to study vaccination and 1 month after vaccination from 20vPnC recipients. CCI

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Safety Endpoints

- Reported prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination.
- Reported prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination.
- Reported AEs within 1 month after vaccination.
- Reported SAEs and NDCMCs within 6 months after vaccination.

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Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21 and >21), 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.

Table 4. Grading Scales for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Redness	5 to 10 measuring device units = >2.0 to 5.0 cm	11 to 20 measuring device units = >5.0 to 10.0 cm	>20 measuring device units = >10.0 cm	Necrosis or exfoliative dermatitis
Swelling	5 to 10 measuring device units = >2.0 to 5.0 cm	11 to 20 measuring device units = >5.0 to 10.0 cm	>20 measuring device units = >10.0 cm	Necrosis

Table 4. Grading Scales for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Pain at injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity[b]	Emergency room visit or hospitalization for severe pain at the injection site

Abbreviations: CRF = case report form; e-diary = electronic diary.

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.

a. Grade 4 assessment should be made by the investigator; Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF. The severity of the local reaction should be graded using the AE severity grading scale.
b. Prevents daily activity, eg, results in missed days of work or school or is otherwise incapacitating.

For each local reaction, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 10, where Day 1 is the day of vaccination) as follows:

> maximum severity grade = highest grade (maximum severity) within 10 days after vaccination (Day 1 through Day 10) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 10.

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The systemic events of fatigue, headache, muscle pain, and joint pain will be assessed by subjects as mild, moderate, or severe according to the grading scale in Table 5 below.

Table 5. Grading Scales for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Fatigue (tiredness)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

Abbreviations: CRF = case report form; e-diary = electronic diary.

a. Prevents daily routine activity, eg, results in missed days of work or school or is otherwise incapacitating; includes use of narcotics for analgesia.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF. The severity of the systemic event should be graded using the AE severity grading scale.

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Oral temperature will be collected in the evening daily for 7 days following 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 an oral temperature of ≥38.0°C (≥100.4°F). 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 38.0°C [100.4°F]) in order to collect a stop date in the CRF. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius first for reporting. Fever will be grouped into ranges for the analysis according to Table 6 below.

Table 6. Ranges for Fever

≥38°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C

Note: Fever is defined as temperature ≥38.0°C.

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AE reporting will be based on the specific reporting period. Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer Vaccine data standard rules.

AE reporting will be based on the start date, which will indicate the specific reporting period. Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in the Pfizer Vaccine data standard rules.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers:

- Tier 1 events (Cohorts A and B only): These are prespecified events of clinical importance and are identified in a list in the product's safety review plan. No Tier 1 events have been identified to date for 20vPnC.

- Tier 2 events (Cohorts A and B only): These are events that are not Tier 1, but are considered "relatively common." A Medical Dictionary for Regulatory Activities (MedDRA) preferred term is defined as a Tier 2 event for a cohort if there are at least 4 subjects with the AE term in at least 1 vaccine group in that cohort.

- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

Cohort C is excluded from Tier 1 and Tier 2 because it has exactly 1 vaccine group and tier analyses include comparison of 2 vaccine groups.

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3.2. Primary Immunogenicity Endpoint

The primary immunogenicity endpoints are the pneumococcal serotype-specific OPA titers 1 month after vaccination.

OPA titers 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 for the blood samples obtained at Visit 1 (Day 1) and at Visit 2 (approximately 1 month after Visit 1). OPA titers will be determined only for subjects receiving 20vPnC.

OPA titers above the lower limit of quantitation (LLOQ) are considered accurate and their quantitated values will be reported. CCI [redacted] OPA titers below the corresponding LLOQ or denoted as below the limit of quantitation (BLQ) will be set to 0.5 × LLOQ for analysis. Missing assay results will not be imputed.

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3.3. Secondary Endpoints

- Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
- ≥4-Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
- Serotype-specific OPA titers ≥ LLOQ 1 month after vaccination.

[redacted]

3.5. Baseline and Other Variables

Day 1 is defined as the day of vaccination. Measurements or samples collected prior to vaccination on Day 1 are considered the baseline data for the assessments.

Baseline variables include the following:

- Demographics
- Medical history
- [redacted]
- Prior pneumococcal vaccine

Other variables to be summarized include the following:

- E-diary completion
- Pneumococcal vaccines at enrollment
- Concomitant medications to treat SAEs or NDCMCs

[redacted]

[redacted]

3.5.1. Demographics, Medical History [redacted]

The demographic variables are age at vaccination (in years), sex (male or female), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white) and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported). In cases where more than 1 category is selected for race, the subject would be counted under the category "multiracial" for analysis. Age at vaccination at Visit 1 will be derived based on the subject's birthday. For example, if the vaccination date is 1 day before the subject's 19th birthday, the subject is considered to be 18 years old.

For subjects who were randomized but not vaccinated, the randomization date will be used in place of the vaccination date for age calculation. If the randomization date is also missing, then the informed consent date will be used for age calculation.

Medical history of clinical significance will be collected and categorized according to the current version (at the time of reporting) of MedDRA. Significant findings from any physical examination performed at baseline will also be collected on the Medical History page of the CRF and summarized with medical history.

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3.5.3. Nonstudy Vaccinations and Concomitant Medications

The name and date of administration for any nonstudy vaccinations received and medications taken to treat SAEs or NDCMCs from the time of signing of the ICD to the final visit will be collected and recorded in the CRF. Details of any medications that the subject is currently taking for medical conditions at enrollment and throughout the study will be recorded in the CRF. Concomitant medications and nonstudy vaccinations will be coded according to the World Health Organization Drug Dictionary (WHODD).

4. ANALYSIS SETS

Every subject will be assessed to determine who meets the criteria for inclusion in each analysis population prior to each analysis planned for this study (see Section 6). Classifications will be documented per standard operating procedures.

4.1. Safety Population

The safety population will include any subject who

- receives 1 dose of 20vPnC, PPSV23, or 13vPnC and
- has safety follow-up after vaccination.

Subjects will be included in the vaccine group corresponding to the vaccine actually received. The safety population will be the analysis population for safety and reactogenicity endpoints.

4.2. Evaluable Immunogenicity Populations

The evaluable immunogenicity population will include any subject who

- receives 20vPnC as randomized,
- is enrolled in the appropriate cohort based on prior pneumococcal vaccination history,
- has the Visit 2 blood collection within 27 to 49 days after vaccination,
- has at least 1 valid and determinate OPA titer for any serotype for Visit 2, and
- does not have any other major protocol deviations as determined by the clinician.

Major protocol deviations will be determined by clinical review. A major protocol deviation is a protocol deviation that, in the opinion of the sponsor's study clinician, would materially affect assessment of immunogenicity, eg, subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The evaluable immunogenicity population will be the primary analysis population for immunogenicity results.

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5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses

No hypothesis testing between vaccine groups will be performed, and also no formal statistical decision rules apply in this study. However, 95% confidence intervals (CIs) between vaccine groups on AE proportions will be applied to Tier 1 and Tier 2 AEs (see Section 6.1.3). Otherwise, a descriptive estimation approach will be used to assess all safety and immunogenicity objectives. Nominal 95% CIs will be calculated for all proposed data summaries.

5.2. General Methods

Safety results will be summarized separately for each cohort. Immunogenicity results of serotype-specific OPA titers will be determined only for subjects who receive 20vPnC in each cohort. Immunogenicity results from the 20vPnC groups will be summarized side by side from all 3 cohorts.

Time points for local reactions and systemic events refer to data within 10 days after vaccination for local reactions and within 7 days after vaccination for systemic events.

AEs within 1 month (Visit 2) and SAEs and NDCMCs through 6 months after vaccination (Visit 3) will be summarized. If any nonserious AEs are reported to occur before vaccination or more than 1 month after vaccination (outside of the protocol-specified reporting window), they will not be summarized, but will be included in the AE listings.

5.2.1. Analyses for Binary Data

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

The exact 95% CI for binary endpoints will be computed using the F distribution (Clopper-Pearson[1] method).

The 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, the 95% CIs for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen[2] method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group within each group will be provided. No Tier 1 events have been identified to date for 20vPnC.

5.2.2. Analyses for Continuous Data

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

Continuous immunogenicity outcomes of serotype-specific OPA titers will be analyzed on the natural log scale. The results will be reported in the original scale after back transformation.

5.2.2.1. Geometric Mean Titers

For immunogenicity results of serotype-specific OPA titers, geometric mean titers (GMTs) will be computed along with associated 95% CIs. The GMT will be calculated as the mean of the assay results after making the logarithm transformation and then transformed back to its original scale. Two-sided 95% CIs will be obtained by taking log transforms of OPA titers, calculating the 95% CI with reference to the t-distribution, then exponentiating the confidence limits.

5.2.2.2. Geometric Mean Fold Rises

For immunogenicity results of serotype-specific OPA titers, fold rise in OPA titer is defined as the Visit 2 (1 month after vaccination) result divided by the Visit 1 (prior to vaccination) result. The geometric mean fold rises (GMFRs) and associated CIs will be calculated using the same method as for GMTs, but performed on the defined ratios. GMFRs will be limited to subjects with nonmissing values at both time points.

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5.3. Methods to Manage Missing Data

Missing data handling rules are described in corresponding endpoint sections.

6. ANALYSES AND SUMMARIES

All safety analyses will be performed separately for each cohort. Safety analyses within each cohort will be compiled for each vaccine group in the cohort. No between-group comparisons are planned except for Tier 1 (if any) and Tier 2 AEs.

Immunogenicity analyses within each cohort will be limited to the 20vPnC group. Descriptive immunogenicity results from subjects receiving 20vPnC will be summarized together by cohort. No between-cohort comparisons of immunogenicity results are planned.

6.1. Primary Endpoints

6.1.1. Local Reactions

6.1.1.1. Primary Analysis

Endpoint: Proportions of subjects reporting prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination

- Analysis time point: Within 10 days after vaccination
- Analysis population: Safety population
- Analysis methodology: Descriptive statistics
- Supporting objective: Primary objective

Reporting results:

Proportions of subjects reporting prompted local reactions will be summarized by maximum severity level. Confirmed e-diary errors will be excluded from the analysis. The percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI will be presented for each cohort by vaccine group (as applicable).

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6.1.2. Systemic Events

6.1.2.1. Primary Analysis

Endpoints: Proportions of subjects reporting prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination.

- Analysis time point: Within 7 days after vaccination
- Analysis population: Safety population
- Analysis methodology: Descriptive statistics
- Supporting objective: Primary objective

Reporting results:

Proportions of subjects reporting prompted local reactions will be summarized by maximum severity level. Confirmed e-diary errors will be excluded from the analysis. The percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI will be presented for each cohort by vaccine group (as applicable).

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6.1.3. Adverse Events

6.1.3.1. Primary Analysis

Endpoint: Proportions of subjects reporting AEs within 1 month after vaccination

- Analysis time point: 1 Month after vaccination
- Analysis population: Safety population
- Analysis methodology: 3-Tiered approach as described in Section 5.2.1
- Supporting objective: Primary objective

Reporting results:

The percentage (%), the number of subjects and the denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI for subjects reporting any AE, each system organ class, and each preferred term within system organ class will be presented for each cohort by vaccine group.

In addition, for AEs classified as Tier 2 events (Cohort A and Cohort B only), the difference in percentages and associated 2-sided 95% CI for between-group comparisons (20vPnC – 13vPnC for Cohort A, 20vPnC – PPSV23 for Cohort B) will be provided using the Miettinen and Nurminen method. Further, for Tier 1 events (Cohort A and Cohort B only), if any are identified, the difference in percentages, the associated 95% CI for the risk difference, and the corresponding p-value will also be provided.

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Figures:

A forest plot of the risk difference with 95% CI will be presented if the number of preferred terms classified as Tier 2 events is greater than 5.

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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 point: Within 6 months after vaccination
- Analysis population: Safety population
- Analysis methodology: Descriptive statistics
- Supporting objective: Primary objective

Reporting results:

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

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6.2. Primary Immunogenicity Endpoint

The ordering of the pneumococcal serotypes in summaries will be as follows:

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

6.2.1. Pneumococcal Serotype-Specific OPA Titers

Endpoint: Pneumococcal serotype-specific OPA titers

- Time point: Before vaccination and 1 month after vaccination
- Analysis population: Evaluable immunogenicity [redacted]
- Analysis methodology: Descriptive statistics
- Supporting objective: Primary objective

Reporting results:

OPA GMTs with their associated 95% CIs will be provided before vaccination (Visit 1) and 1 month after vaccination (Visit 2) for each cohort.

[redacted]

6.3. Secondary Immunogenicity Endpoints

6.3.1. Fold Rise in Pneumococcal Serotype-Specific OPA Titers From Before Vaccination to 1 Month After Vaccination

Endpoint: Fold rise in serotype-specific OPA titers

- Time point: 1 Month after vaccination
- Analysis population: Evaluable immunogenicity [redacted]
- Analysis methodology: Descriptive statistics
- Supporting objective: Secondary objective

[redacted]

[redacted]

Reporting results:

The OPA GMFRs and the associated 95% CIs from before vaccination (Visit 1) to 1 month after vaccination (Visit 2) will be provided for each cohort.

6.3.2. ≥4-Fold Rise in Pneumococcal Serotype-Specific OPA Titers From Before Vaccination to 1 Month After Vaccination

Endpoint: Proportion of subjects with ≥4-fold rise in serotype-specific OPA titers

- Time point: 1 Month after vaccination.
- Analysis population: Evaluable immunogenicity, CCI [redacted].
- Analysis methodology: Descriptive statistics
- Supporting objective: Secondary objective

Reporting results:

The proportion of subjects with ≥4-fold rises and the associated 95% CI from before vaccination to 1 month after vaccination will be calculated for each cohort.

6.3.3. Pneumococcal Serotype-Specific OPA Titers ≥ LLOQ 1 Month After Vaccination

Endpoint: Proportion of subjects with serotype-specific OPA titers ≥ LLOQ

- Time point: Before vaccination and 1 month after vaccination
- Analysis population: Evaluable immunogenicity, CCI [redacted]
- Analysis methodology: Descriptive statistics
- Supporting objective: Secondary objective

Reporting results:

The proportions of subjects with serotype-specific OPA titers ≥ LLOQ and the associated 95% CIs will be calculated before vaccination and 1 month after vaccination for each cohort.

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6.6. Baseline and Other Summaries and Analyses

6.6.1. Study Conduct and Subject Disposition

6.6.1.1. Subject Disposition

The number and percentage of randomized subjects who receive vaccination, complete Visit 2, complete the study, and withdraw from the study will be summarized for each cohort by vaccine group (as applicable). The specific reasons for withdrawal (lost to follow-up, AE, protocol deviation, other) will also be presented.

[redacted]

6.6.1.2. Demographic Characteristics

Demographic characteristics will be summarized for all subjects in the safety population by cohort and vaccine group (as applicable). Summary statistics for sex and race will be the number and percentage of subjects within each cohort and by vaccine group (as applicable). Age at the time of vaccination will be summarized by mean, median, minimum, maximum, and standard deviation by vaccine group within cohort. Age at vaccination will also be categorized into 65 through 69 years, 70 through 79 years, and 80 years and older for each vaccine group within each cohort.

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6.6.1.4. 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 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized for each cohort and by vaccine group (as applicable) for the safety population.

6.6.1.5. Blood Samples for Assay

The number and percentage of randomized subjects providing blood samples within and outside of the protocol-prespecified window of 28 and 42 days, inclusive, after vaccination will be tabulated for all randomized subjects.

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6.6.2. Vaccine Exposure

6.6.2.1. Vaccine Administration

Randomized subjects receiving each vaccine (20vPnC, 13vPnC, or PPSV23) will be listed. Subjects who received incorrect vaccine will also be listed.

6.6.3. Nonstudy Vaccination and Concomitant Medications Used to Treat SAEs and NDCMCs

Nonstudy vaccines received and concomitant medications taken to treat SAEs and NDCMCs during the study will be listed.

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[redacted]

8. REFERENCES

1. Collett D. Statistical inference for binary data. In: *Modelling Binary Data*. London, England: Chapman & Hall; 1991:17-42.

2. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med.* 1985;4(2):213-226.

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