Protocol B7471007

A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN PNEUMOCOCCAL VACCINE–NAÏVE ADULTS 18 YEARS OF AGE AND OLDER

Statistical Analysis Plan

(SAP)

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Author: PPD

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1. VERSION HISTORY

This statistical analysis plan (SAP) for Study B7471007 is based on protocol Amendment 2, dated 11 Feb 2019.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	CCI [redacted] • Sections 3.1, 3.4, 4.2, and 6 to address the feedback from the team based on the tables, listings, and figures (TLFs) mock reviews and blinded data reviews (BDRs). CCI [redacted]	CCI [redacted] To provide clarification based on feedback received during TLF mock reviews and BDRs; CCI [redacted]

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471007. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

2.1. Study Objectives

2.1.1. Primary Objectives

2.1.1.1. Primary Safety Objective (All Cohorts)

- To describe the safety profile of 20-valent pneumococcal conjugate vaccine (20vPnC) in adults 18 years of age and older.

2.1.1.2. Primary Immunogenicity Objectives – Cohort 1 (60 Years of Age and Older)

- To demonstrate that the immune responses to the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in 13-valent pneumococcal conjugate vaccine (13vPnC) induced by 20vPnC in adults 60 years of age and older are noninferior to the immune response induced by 13vPnC.

- To demonstrate that the immune responses to the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by 20vPnC in adults 60 years of age and older are noninferior to the immune response induced by 23-valent pneumococcal polysaccharide vaccine (PPSV23).

2.1.2. Secondary Objectives

2.1.2.1. Secondary Objective – Cohort 2 (50 Through 59 Years of Age)

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 50 through 59 years of age are noninferior to the immune responses induced by 20vPnC in adults 60 through 64 years of age.

2.1.2.2. Secondary Objective – Cohort 3 (18 Through 49 Years of Age)

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 18 through 49 years of age are noninferior to the immune responses induced by 20vPnC in adults 60 through 64 years of age.

2.1.2.3. Secondary Objective – All Cohorts

- To describe the immune responses to 20vPnC in adults 60 years of age and older, 50 through 59 years of age, and 18 through 49 years of age.

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2.2. Study Design

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in the United States and Sweden. Approximately 3880 adults 18 years of age and older with no history of pneumococcal vaccination will be enrolled into 1 of 3 cohorts based on their age at enrollment. Subjects enrolled in Cohort 1 will be randomized to 1 of 2 vaccine groups, 20vPnC/saline or 13vPnC/PPSV23. Subjects enrolled in Cohort 2 and Cohort 3 will be randomized into 1 of 2 vaccine groups, 20vPnC or 13vPnC.

Cohort 1: Approximately 3000 subjects 60 years of age and older at enrollment will be randomized (1:1) into 1 of 2 vaccine groups. Each subject will receive either 20vPnC or 13vPnC at Vaccination 1. Subjects who received 20vPnC at Vaccination 1 will receive saline at Vaccination 2. Subjects who received 13vPnC at Vaccination 1 will receive PPSV23 at Vaccination 2. Approximately 2000 subjects 60 through 64 years of age and 1000 subjects 65 years of age and older will be enrolled and stratified by age.

Cohort 2: Approximately 440 subjects 50 through 59 years of age at enrollment will be randomized (3:1) to receive 20vPnC or 13vPnC at Visit 1.

Cohort 3: Approximately 440 subjects 18 through 49 years of age at enrollment will be randomized (3:1) to receive 20vPnC or 13vPnC at Visit 1.

On Day 1 (Visit 1), subjects will be assessed for eligibility, have blood drawn for immunogenicity assessments, and receive 20vPnC or 13vPnC. Subjects will be observed for at least 30 minutes after vaccination by blinded site staff, who will record any acute (immediate) adverse events (AEs) occurring during that time. 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 at Visit 1 and prompted local reactions (redness, swelling, and pain) occurring at the 20vPnC or 13vPnC injection site within 10 days after vaccination at Visit 1 will be collected daily in the e-diary. Use of antipyretic/pain medications will be collected daily in an e-diary for 7 days after vaccination.

Subjects in Cohort 1 will return for Visit 2 (28 to 42 days after Visit 1), and information will be collected from the subjects on AEs, serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), and e-diary follow-up (as needed). Blood will be

drawn for immunogenicity assessments. Saline will be administered to subjects who previously received 20vPnC, and PPSV23 will be administered to subjects who previously received 13vPnC, by a third-party unblinded site staff member. Subjects will be observed for at least 30 minutes after vaccination by blinded site staff, who will record AEs occurring during that time (immediate AEs). Subjects will also be reminded about safety follow-up. The subjects in Cohort 1 will return for Visit 3 (28 to 42 days after Visit 2) and information will be collected from the subjects on AEs, SAEs, and NDCMCs. Blood will be drawn for immunogenicity assessments.

Subjects in Cohorts 2 and 3 will return for Visit 2 (28 to 42 days after Visit 1), and information will be collected from the subjects on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Blood will be drawn for immunogenicity assessments.

Cohorts 1, 2, and 3 will have a final visit, approximately 6 months (168 to 196 days) after Visit 1; for this visit, the sites will contact the subjects in all cohorts via telephone to inquire about SAEs, NDCMCs, and nonstudy vaccinations, as well as concomitant medications used to treat SAEs or NDCMCs.

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints (All Cohorts)

- 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 3 below. Measuring device units will 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 3.

Table 3. 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
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 at Visit 1) as follows:

> maximum severity grade = highest grade (maximum severity) within 10 days after vaccination at Visit 1 (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 4 below.

Table 4. 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 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.

Oral temperature will be collected in the evening daily for 7 days following vaccination at Visit 1 (Days 1 through 7, where Day 1 is the day of vaccination at Visit 1) 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 <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 5 below.

Table 5. Ranges for Fever

≥38.0°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.

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

- Tier 1 events: 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: 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.

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3.1.2. Primary Immunogenicity Endpoint – Cohort 1 (60 Years of Age and Older)

- Serotype-specific opsonophagocytic activity (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 all subjects prior to vaccination at Visit 1 and at Visit 2 (approximately 1 month after Visit 1). OPA titers will be determined only for the 7 additional serotypes at Visit 3 (approximately 1 month after Vaccination 2).

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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3.2. Secondary Endpoints

3.2.1. Secondary Endpoint – Cohort 2 (50 Through 59 Years of Age)

- 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 all subjects prior to vaccination at Visit 1 and at Visit 2 (approximately 1 month after Visit 1).

LLOQ values for each serotype and rules for imputing values below LLOQ will be followed as specified in Section 3.1.2.

3.2.2. Secondary Endpoint – Cohort 3 (18 Through 49 Years of Age)

- 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 all subjects prior to vaccination at Visit 1 and at Visit 2 (approximately 1 month after Visit 1).

LLOQ values for each serotype and rules for imputing values below LLOQ will be followed as specified in Section 3.1.2.

3.2.3. Secondary Endpoints – All Cohorts

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

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3.4. 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.

The following variables will be summarized as part of the baseline characteristics:

- Demographics
- Medical history
- CCI
- CCI

Other variables to be summarized include the following:

- E-diary transmission
- Nonstudy vaccines
- Concomitant medications at enrollment
- Concomitant medications to treat SAEs or NDCMCs

3.4.1. Demographics, CCI and Medical History

The demographic variables are age at vaccination at Visit 1 (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 in years 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 date of vaccination at Visit 1 for age calculation. If the randomization date is also missing, then the informed consent date will be used for age calculation.

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Underlying medical conditions or risk factors that increase risk of serious pneumococcal infection will be recorded on the CRF.

Demographic and disposition tables will be categorized by cohort and vaccine group. In addition, separate demographic tables for subjects 60 through 64 years of age, 65 through 69 years of age, 70 through 79 years of age, and 80 years of age and above from Cohort 1 will be provided.

Medical history will be categorized according to 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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3.4.3. Nonstudy Vaccines and Concomitant Medications

The name and date of administration for any nonstudy vaccinations received 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 will be recorded in the CRF. Medications taken to treat SAEs or NDCMCs from the time of signing of the ICD to the final visit will also be collected. Nonstudy vaccines and concomitant

[redacted]

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medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODD).

4. ANALYSIS SETS

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

4.1. Safety Analysis Population

The safety population will include any subject who:

1. receives 1 dose of any of the following: 20vPnC, 13vPnC, PPSV23, or saline; and

2. has safety follow-up after any 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

Three evaluable immunogenicity populations are defined for the analyses of the immunogenicity results: the evaluable 13-matched immunogenicity population (Cohort 1), the evaluable 7-additional immunogenicity population (Cohort 1), and the evaluable-20 immunogenicity population. Subjects will be included in the vaccine group as randomized in the analyses of evaluable subjects.

4.2.1. Evaluable 13-Matched Immunogenicity Population – Cohort 1

The evaluable 13-matched immunogenicity population will be the primary analysis population for immunogenicity results of the 13 matched serotypes in Cohort 1. This population will generally include any subject who

1. receives the assigned Vaccination 1 as randomized,

2. is enrolled in the appropriate cohort based on age on the day of first vaccination (ie, 60 years of age or older in Cohort 1),

3. has the Visit 2 blood collection within 27 to 49 days after Vaccination 1,

4. has at least 1 valid OPA titer for any of the 13 matched serotypes at Visit 2, and

5. has no other major protocol deviations as determined by the clinician.

4.2.2. Evaluable 7-Additional Immunogenicity Population – Cohort 1

The evaluable 7-additional immunogenicity population will be the primary analysis population for immunogenicity results of the 7 additional serotypes in Cohort 1. This population will generally include any subject who:

1. receives Vaccination 1 (20vPnC) if randomized to the 20vPnC/saline group or receives both vaccinations as randomized if randomized to the 13vPnC/PPSV23 group,

2. is enrolled in the appropriate cohort based on age on the day of first vaccination (ie, 60 years of age and older in Cohort 1),

3. has either Visit 2 blood collection within 27 to 49 days after Vaccination 1 for the 20vPnC/saline group or Visit 3 blood collection within 27 to 49 days after Vaccination 2 for the 13vPnC/PPSV23 group,

4. has at least 1 valid and determinate OPA titer for any of the 7 additional serotypes at either Visit 2 for the 20vPnC/saline group or Visit 3 for the 13vPnC/PPSV23 group, and

5. has no other major protocol deviations as determined by the clinician.

4.2.3. Evaluable Immunogenicity Population for Comparison of Cohorts 2 and 3 to Cohort 1

A third evaluable immunogenicity population, the evaluable-20 immunogenicity population, is defined for the comparisons of subjects 60 through 64 years of age from Cohort 1 to the other 2 younger age cohorts (Cohort 2: 50 through 59 years of age; and Cohort 3: 18 through 49 years of age). This population will generally include any subject who:

1. receives the assigned vaccination at Visit 1 as randomized,

2. is enrolled in the appropriate cohort based on age on the day of first vaccination (ie, adults 60 through 64 years of age for Cohort 1, 50 through 59 years of age for Cohort 2, and 18 through 49 years of age for Cohort 3),

3. has the Visit 2 blood collection within 27 to 49 days after vaccination,

4. has at least 1 valid and determinate OPA titer for any of the 20 serotypes for Visit 2, and

5. has no 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 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 sponsor's clinician will identify those subjects with major protocol deviations before any unblinded analysis is carried out.

The evaluable-20 immunogenicity population will also be the primary analysis population for additional descriptive statistical analyses of immunogenicity results from Cohort 2 and Cohort 3.

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5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Hypothesis testing will be performed to assess noninferiority comparing the 20vPnC/saline vaccine group against the 13vPnC/PPSV23 vaccine group in Cohort 1 for each of the 20 serotype-specific OPA titers.

Hypothesis testing will also be performed to assess noninferiority comparing the 20 serotype-specific OPA titers 1 month after vaccination in each of the 20vPnC groups in the younger cohorts (subjects 50 through 59 years of age in Cohort 2 and subjects 18 through 49 years of age in Cohort 3) against subjects 60 through 64 years of age from Cohort 1 one month after vaccination in the 20vPnC/saline group.

A 2-fold margin will be used for each of the noninferiority hypothesis tests.

5.1.1. Hypothesis Testing in Cohort 1

Hypothesis testing will be performed to assess noninferiority by comparing the serotype-specific OPA titers of the 20vPnC/saline group to those from the 13vPnC/PPSV23 group in Cohort 1. The null hypothesis for each serotype-specific OPA titer is:

$$H_0: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.5)$$

[redacted]

[redacted]

where

- $\ln(0.5)$ corresponds to a 2-fold margin for noninferiority.
- $\ln(\mu_A)$ is the natural log of the geometric mean OPA titer 1 month after 20vPnC administration for the 20vPnC/saline group.
- $\ln(\mu_B)$ is the natural log of the geometric mean OPA titer 1 month after 13vPnC administration for the 13vPnC/PPSV23 group when the endpoint is the geometric mean OPA titer from 1 of the shared 13 serotypes in 13vPnC, or,
- $\ln(\mu_B)$ is the natural log of the geometric mean OPA titer 1 month after PPSV23 administration for the 13vPnC/PPSV23 group when the endpoint is the geometric mean OPA titer from 1 of the 7 additional serotypes.

Noninferiority for serotype-specific OPA titers will be formally evaluated by a 2-sided 95% confidence interval (CI) for the ratio of serotype-specific OPA geometric mean titers (GMTs) (the 20vPnC/saline group to the 13vPnC/PPSV23 group) with results from 1 month after vaccination with 20vPnC (Visit 2) and 1 month after 13vPnC (Visit 2) for the 13 matched serotypes. For the 7 additional serotypes, the CI will be calculated for the ratio of serotype-specific OPA GMTs from the 20vPnC/saline group at Visit 2 to that from the 13vPnC/PPSV23 group at Visit 3. Noninferiority for a serotype will be declared if the lower bound of the 2-sided 95% CI for the geometric mean ratio (GMR) of GMTA/GMTB for that serotype is greater than 0.5 (2-fold criterion). CCI [redacted]

5.1.2. Hypothesis Testing Comparing Cohorts 2 and 3 to Subjects 60 Through 64 Years of Age in Cohort 1

Hypothesis testing will be performed to assess noninferiority between each of the younger cohorts (subjects 50 through 59 years of age in Cohort 2 and subjects 18 through 49 years of age in Cohort 3) and subjects 60 through 64 years of age from Cohort 1 for each of the 20 serotype-specific OPA titers. Testing will be performed only for subjects receiving 20vPnC. OPA GMRs will be calculated with respect to the younger cohorts compared to the older cohort. "Younger" refers to either Cohort 3 or Cohort 2. "Older" refers to subjects 60 through 64 years of age from Cohort 1. The null hypothesis for each serotype-specific OPA titer is

$$H_0: \ln(\mu_C) - \ln(\mu_A) \leq \ln(0.5)$$

[redacted]

[redacted]

where

- $\ln(0.5)$ corresponds to a 2-fold margin for noninferiority.
- $\ln(\mu_C)$ is the natural log of the geometric mean OPA titer 1 month after 20vPnC administration for the younger group, subjects 50 through 59 years of age (Cohort 2) or subjects 18 through 49 years of age (Cohort 3).
- $\ln(\mu_A)$ is the natural log of the geometric mean OPA titer 1 month after 20vPnC administration for subjects 60 through 64 years of age from Cohort 1.

Noninferiority for serotype-specific OPA GMTs will be evaluated by a 2-sided 95% CI for the ratio of serotype-specific OPA GMTs (younger/older) with results 1 month after vaccination (Visit 2) from all subjects receiving 20vPnC. Noninferiority will be declared for a serotype if the lower bound of the 2-sided 95% CI for the GMR of GMTC/GMTA for that serotype is greater than 0.5 (2-fold criterion).

5.2. General Methods

Time points for local reactions and systemic events refer to data within 10 and 7 days after vaccination at Visit 1, respectively.

Safety and immunogenicity analysis will be summarized separately for each cohort, except for the immunogenicity bridging analysis comparing 20vPnC groups from different cohorts for noninferiority.

AEs within 1 month (Visit 2 for all cohorts) and SAEs and NDCMCs through 6 months (Visit 4 for Cohort 1 and Visit 3 for Cohorts 2 and 3) after vaccination at Visit 1 will be summarized. In Cohort 1, the AEs from Visit 2 to Visit 3 will also be summarized.

Descriptive immunogenicity results from the 20vPnC or 20vPnC/saline and 13vPnC or 13vPnC/PPSV23 groups will be summarized separately for each cohort, except in cases where pooled analysis is specified.

Descriptive summaries will be displayed by cohort with vaccine groups defined below:

Cohort 1

- 20vPnC/saline
- 13vPnC/PPSV23

Cohorts 2 and 3

- 20vPnC
- 13vPnC

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% significance level unless specified otherwise.

5.2.1. Analyses for Binary Data

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

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen[2] 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, a 95% CI 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 will be provided. No Tier 1 events have been identified at this stage 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, and the results will be reported on the original scale after back transformation.

5.2.2.1. Geometric Mean Titers and Geometric Mean Ratios

For immunogenicity results of serotype-specific OPA titers, geometric means will be computed along with associated 95% CIs. The GMTs 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% CIs based on the t-distribution, then exponentiating the confidence limits.

The OPA serotype-specific antibody titer ratios (GMRs) will be calculated for each of the noninferiority assessments as:

1. The GMT ratio of 20vPnC/saline to 13vPnC/PPSV23 in Cohort 1:

   - ratio of the GMT from the 20vPnC/saline group to that from the 13vPnC/PPSV23 group at Visit 2 for the 13 matched serotypes.

   - ratio of the GMT from the 20vPnC/saline group at Visit 2 to that from the 13vPnC/PPSV23 group at Visit 3 for the 7 additional serotypes.

2. The GMT ratio of each of the younger cohorts (Cohort 2 or 3) to subjects 60 through 64 years of age in Cohort 1:

   - ratio of the GMT from the 20vPnC group in Cohort 2 at Visit 2 to that from subjects 60 through 64 years of age in the 20vPnC/saline group in Cohort 1 at Visit 2 for all 20 serotypes.

   - ratio of the GMT from the 20vPnC group in Cohort 3 at Visit 2 to that from subjects 60 through 64 years of age in the 20vPnC/saline group in Cohort 1 at Visit 2 for all 20 serotypes.

Details regarding the derivation of GMRs are provided below in Table 7.

Table 7. Derivation of Serotype-Specific OPA GMRs at 1 Month After Vaccination

Comparison	Analysis Population	Serotypes	Numerator	Denominator
Between–vaccine group comparison within Cohort 1	Evaluable 13-matched immunogenicity population	13 Matching serotypes	Cohort 1, 20vPnC/saline group at Visit 2	Cohort 1, 13vPnC/PPSV23 group at Visit 2
	Evaluable 7-additional immunogenicity population	7 Additional serotypes	Cohort 1, 20vPnC/saline group at Visit 2	Cohort 1, 13vPnC/PPSV23 group at Visit 3
Comparison of Cohort 2 to subjects 60 through 64 years of age from Cohort 1	Evaluable-20 immunogenicity population	All 20 serotypes	Cohort 2, 20vPnC at Visit 2	Cohort 1, subjects 60 through 64 years of age in the 20vPnC/saline group at Visit 2
Comparison of Cohort 3 to subjects 60 through 64 years of age from Cohort 1	Evaluable-20 immunogenicity population	All 20 serotypes	Cohort 3, 20vPnC at Visit 2	Cohort 1, subjects 60 through 64 years of age in the 20vPnC/saline group at Visit 2

Abbreviations: GMR = geometric mean ratio; OPA = opsonophagocytic activity.

CCI [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

CCI [redacted] OPA GMR and CI will CCI [redacted] be calculated for each of the serotypes by calculating differences in means and CIs on the natural log scale based on the t-distribution, then exponentiating the results.

A 2-sided 95% CI will be used for the noninferiority comparison of the 20vPnC/saline group to the 13vPnC/PPSV23 group in Cohort 1 and for the bridging noninferiority comparison of the 20vPnC group from Cohort 2/Cohort 3 to the 20vPnC/saline group from subjects 60 through 64 years of age in Cohort 1.

5.2.2.2. Geometric Mean Fold Rises

For immunogenicity results of serotype-specific OPA titers, fold rise from before vaccination to 1 month after vaccination will be calculated. The geometric mean fold rises (GMFRs) will be calculated using the fold rises from Visit 1 to Visit 2 for each vaccine group in each cohort for all serotypes, except for the GMFRs of the 7 additional serotypes from the 13vPnC/PPSV23 group in Cohort 1, which will be calculated using the fold rises from Visit 1 to Visit 3. Serotype-specific GMFRs will be limited to subjects with nonmissing values at both time points, before and after vaccination.

The GMFRs will be calculated as the mean of the difference of logarithmically transformed antibody levels (1 month after vaccination minus before vaccination) and transformed back to the original units. The associated 2-sided 95% CIs are computed by back transformation

[redacted]

of the CIs using Student's t-distribution for the mean difference in the OPA titers on the natural log scale.

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

[redacted]

CCI [redacted]

5.4. Methods to Manage Missing Data

Missing data handling rules are described in the corresponding endpoint sections.

6. ANALYSES AND SUMMARIES

6.1. Primary Safety Endpoints (All Cohorts)

6.1.1. Local Reactions – All Cohorts

6.1.1.1. Primary Analysis

Endpoint: Proportion of subjects reporting prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination at Visit 1 – all cohorts.

- Analysis time point: Within 10 days after vaccination at Visit 1.
- 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 numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 95% Clopper-Pearson CI will be presented by vaccine group for each cohort.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

[redacted]

6.1.2. Systemic Events – All Cohorts

6.1.2.1. Primary Analysis

Endpoint: Proportion of subjects reporting prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination at Visit 1 – all cohorts.

- Analysis time point: Within 7 days after vaccination at Visit 1.
- Analysis population: Safety population.

[redacted]

[redacted]

- Analysis methodology: Descriptive statistics.
- Supporting objective: Primary objective.

Reporting results:

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

CCI

CCI

CCI

[redacted]

6.1.3. Adverse Events – All Cohorts

6.1.3.1. Primary Analysis

Endpoint: Proportion of subjects reporting AEs within 1 month after vaccination.

- Analysis time point: Within 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 numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), 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, the differences in percentages and associated 2-sided 95% CIs for between-group comparisons (20vPnC – 13vPnC) will be provided using the Miettinen and Nurminen method. Further, for Tier 1 events, 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.

[redacted]

[redacted]

Figures:

A plot of the risk differences with 95% CIs of Tier 2 events will be presented if the number of Tier 2 events is greater than 5.

CCI

[redacted]

[redacted]

6.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions – All Cohorts

6.1.4.1. Primary Analyses

Endpoint: Proportion of subjects reporting SAEs and NDCMCs – all cohorts.

- Analysis time point: Within 6 months after vaccination at Visit 1 (Visit 4 for Cohort 1 and Visit 3 for Cohort 2 and Cohort 3).
- Analysis population: Safety population.
- Analysis methodology: Descriptive statistics.
- Supporting objective: Primary objective.

Reporting results:

The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%) and the corresponding 95% Clopper-Pearson CI for subjects reporting any SAE or NDCMC, each system organ class, and each preferred term within system organ class will be presented for each cohort by vaccine group. SAEs and NDCMCs will be presented separately.

[redacted]

[redacted]

[redacted]

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
- Additional 7 serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F.

6.2.1. Serotype-Specific OPA Titers – Cohort 1 (60 Years of Age and Older)

6.2.1.1. Primary Analysis

Endpoint: Pneumococcal serotype-specific OPA titers 1 month after vaccination.

- Time points: 1 Month after administration of 20vPnC (Visit 2), 1 month after administration of 13vPnC (Visit 2), or 1 month after administration of PPSV23 (Visit 3, in Cohort 1).
- Analysis population: Evaluable 13-matched immunogenicity (13vPnC serotypes), evaluable 7-additional immunogenicity population (7 additional serotypes), [redacted] (Section 4.2 [redacted]) for Cohort 1.
- [redacted]
- Supporting objective: Primary objective.

Reporting results:

The [redacted] OPA GMRs with their associated 95% CIs, will be summarized separately for the 13 matching pneumococcal serotypes and for the 7 additional serotypes (Table 7; Section 5.2.2.1).

Figures:

A forest plot of GMRs with 95% CIs for all 20 serotypes, with a vertical reference line corresponding to GMR=0.5, will be presented.

[redacted]

[redacted]

CCI

CCI

6.3. Secondary Endpoints

6.3.1. Secondary Endpoint – Cohort 2

6.3.1.1. Serotype-Specific OPA Titers – Cohort 2 (50 Through 59 Years of Age)

6.3.1.1.1. Primary Analysis

Endpoint: Serotype-specific OPA titers 1 month after vaccination.

- Time point: 1 Month after vaccination with 20vPnC or 13vPnC at Visit 1 (Visit 2).
- Analysis population: Evaluable-20 immunogenicity, CCI [redacted] (Section 4.2 CCI [redacted]) for Cohort 2 and subjects 60 through 64 years of age in Cohort 1, restricted to results from the 20vPnC/saline group in Cohort 1 or from the 20vPnC group in Cohort 2 only.
- CCI [redacted]
- Supporting objective: Secondary objective.

Reporting results:

The CCI [redacted] OPA GMRs with their associated 95% CIs will be summarized for the comparison between Cohort 2 and Cohort 1 (subjects 60 through 64 years of age) for each serotype.

Figures:

A forest plot of GMRs with 95% CIs for all 20 serotypes, with a vertical reference line corresponding to GMR=0.5, will be presented.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

6.3.2. Secondary Endpoint – Cohort 3

6.3.2.1. Serotype-Specific OPA Titers – Cohort 3 (18 Through 49 Years of Age)

6.3.2.1.1. Primary Analysis

Endpoint: Serotype-specific OPA titers 1 month after vaccination.

- Time point: 1 Month after vaccination with 20vPnC or 13vPnC at Visit 1 (Visit 2).
- Analysis population: Evaluable-20 immunogenicity, [redacted] (Section 4.2 [redacted]) for Cohort 3 and subjects 60 through 64 years of age in Cohort 1, restricted to results from the 20vPnC/saline group in Cohort 1 or from the 20vPnC group in Cohort 3 only.

[redacted]

- Supporting objective: Secondary objective.

[redacted]

[redacted]

Reporting results:

The [redacted]
OPA GMRs with their associated 95% CIs will be summarized for the comparison between Cohort 3 and Cohort 1 (subjects 60 through 64 years of age) for each serotype.

Figures:

A forest plot of GMRs with 95% CIs for all 20 serotypes, with a vertical reference line corresponding to GMR=0.5, will be presented.

[redacted]

[redacted]

CCI [redacted]

[redacted]

6.3.3. Secondary Endpoints – All Cohorts

The following endpoints will be summarized by vaccine group (20vPnC/saline group vs 13vPnC/PPSV23 group) for Cohort 1, for 20vPnC groups by cohort (Cohort 2 and Cohort 3 vs subjects 60 through 64 years of age from Cohort 1), and by vaccine group (20vPnC group vs 13vPnC group) for Cohort 2 and Cohort 3.

6.3.3.1. Fold Rise in Serotype-Specific OPA Titers From Before to 1 Month After Vaccination – All Cohorts

Endpoint: Fold rise in serotype-specific OPA titers.

- Time points: 1 Month after vaccination with 20vPnC or 13vPnC (Visit 2), and 1 month after vaccination with PPSV23 (Visit 3) in Cohort 1 only.
- Analysis population: Evaluable 13-matched immunogenicity for OPA results of the 13vPnC serotypes in Cohort 1, evaluable 7-additional immunogenicity population for OPA results from the 7 additional serotypes in Cohort 1, evaluable-20 immunogenicity for all OPA results in Cohort 2 and Cohort 3, CCI [redacted] (Section 4.2 CCI [redacted]) for Cohort 1, Cohort 2, and Cohort 3.
- Analysis methodology: Descriptive statistics.
- Supporting objective: Secondary objective.

Reporting results:

The number of subjects (n), OPA GMFRs, and associated 95% CIs from before vaccination to 1 month after vaccination will be summarized by vaccine group for each cohort. For the 13 matching serotypes, the GMFR will be the ratio of GMTs at Visit 2 to Visit 1 for each vaccine group in each cohort. The GMFRs for the 7 additional serotypes will be the ratio of GMTs at Visit 2 to Visit 1 for both vaccine groups in Cohorts 2 and 3. In Cohort 1, the GMFRs for the 7 additional serotypes will be the ratio of GMTs at Visit 2 to Visit 1 for the 20vPnC/saline group, and the ratio of GMTs at Visit 3 to Visit 1 for the 13vPnC/PPSV23 group.

[redacted]

[redacted]

6.3.3.2. ≥4-Fold Rise in Serotype-Specific OPA Titers From Before to 1 Month After Vaccination – All Cohorts

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

- Time point: 1 Month after vaccination with 20vPnC or 13vPnC (Visit 2), and 1 month after vaccination with PPSV23 (Visit 3) for Cohort 1 only.
- Analysis population: Evaluable 13-matched immunogenicity for OPA results of the 13vPnC serotypes in Cohort 1, evaluable 7-additional immunogenicity for OPA results from the 7 additional serotypes in Cohort 1, evaluable-20 immunogenicity for all OPA results in Cohorts 2 and 3, CCI [redacted] (Section 4.2 CCI [redacted]) for Cohort 1, Cohort 2, and Cohort 3.
- Analysis methodology: Descriptive statistics.
- Supporting objective: Secondary objective.

Reporting results:

The proportion of subjects with a ≥4-fold rise and associated 95% CI from Visit 1 to Visit 2 for the 13 matching serotypes for each cohort by vaccine group will be summarized. The proportion of subjects with a ≥4-fold rise for the 7 additional serotypes will be summarized from Visit 1 to Visit 2 for both vaccine groups in Cohorts 2 and 3. In Cohort 1, the proportion of subjects for the 7 additional serotypes will be the proportion of subjects with a ≥4-fold rise from Visit 1 to Visit 2 for the 20vPnC/saline group and from Visit 1 to Visit 3 for the 13vPnC/PPSV23 group. The number of subjects (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 95% Clopper-Pearson CI will be presented for each cohort by vaccine group as well.

6.3.3.3. Serotype-Specific OPA Titers ≥ LLOQ 1 Month After Vaccination – All Cohorts

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

- Time point: Visit 1 (baseline) before vaccination, 1 month after vaccination with 20vPnC or 13vPnC (Visit 2), or 1 month after vaccination with PPSV23 (Visit 3) for Cohort 1 only.
- Analysis population: Evaluable 13-matched immunogenicity for OPA results of the 13vPnC serotypes in Cohort 1, evaluable 7-additional immunogenicity for OPA results from the 7 additional serotypes in Cohort 1, evaluable-20 immunogenicity for all OPA results in Cohort 2 and Cohort 3, CCI [redacted] (Section 4.2 CCI [redacted]) for Cohort 1, Cohort 2, and Cohort 3.
- Analysis methodology: Descriptive statistics.

[redacted]

[redacted]

- Supporting objective: Secondary objective.

Reporting results:

The proportions of subjects with serotype-specific OPA titers ≥ LLOQ and associated 95% CIs will be calculated for the time point before vaccination (Visit 1) and 1 month after vaccination with 20vPnC or 13vPnC (Visit 2), by vaccine group for each cohort, and 1 month after vaccination with PPSV23 (Visit 3) (Cohort 1, 13vPnC/PPSV23 group only). For the 13 matching serotypes, the proportion of subjects with OPA titers ≥ LLOQ will be calculated for Visit 1 and Visit 2 for all groups and all cohorts. For the 7 additional serotypes, the proportion of subjects with OPA titers ≥ LLOQ will be calculated for Visits 1 and 2 for both groups in Cohorts 2 and 3, and for the 20vPnC/saline group in Cohort 1, and Visits 1 and 3 for the 13vPnC/PPSV23 group in Cohort 1. The number of subjects (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 95% Clopper-Pearson CI will be presented for each cohort by vaccine group.

CCI [redacted]

CCI

[redacted]

[redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

CCI

[redacted]

6.6. Baseline and Other Summaries and Analyses – All Cohorts

6.6.1. Study Conduct and Subject Disposition

6.6.1.1. Subject Disposition

The number and percentage of randomized subjects will be included in the subject disposition summary. In addition, the number and percentage of subjects who received vaccination(s), who completed the vaccination phase (Visit 1 to Visit 3 for Cohort 1, or Visit 1 to Visit 2 for Cohorts 2 and 3), who completed the study, and who withdrew from the study along with the reasons for withdrawal will be tabulated by vaccine group (according to randomized group assignment) and overall by each cohort. The reasons for withdrawal will be those as specified in the database.

CCI

[redacted]

[redacted]

6.6.1.2. Demographic Characteristics

Demographic characteristics including age, sex, race, and ethnicity will be summarized for all subjects in the safety population for each vaccine group and overall by cohort. Subgroup demographic tables will also be provided for Cohort 1 subjects in age categories 60 through 64 years, 65 through 69 years, 70 through 79 years, and 80 years and above from the safety population. Descriptive statistics (n and %) will be provided for overall and subgroup tables.

CCI [redacted]

CCI [redacted]

6.6.1.3. 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 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized by vaccine group and overall by cohort for the safety population.

CCI [redacted]

6.6.2. Study Vaccine Exposure

6.6.2.1. Vaccination Timing and Administration

A listing of subjects showing the randomized vaccine and the vaccine actually received (20vPnC or 13vPnC) or the randomized vaccine group and the vaccines actually received (20vPnC/saline, 13vPnC/PPSV23) will be presented for each vaccine group.

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

Nonstudy vaccines received, and medications taken to treat SAEs and NDCMCs during the study, and medications taken at the time of enrollment will be listed.

Medications taken at the time of enrollment will be summarized for the subjects in the safety population.

[redacted]

[redacted]

CCI

[redacted]

[redacted]

8. REFERENCES

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

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

3. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75(4):800-2.