Protocol B7471002

A PHASE 2, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A MULTIVALENT PNEUMOCOCCAL CONJUGATE VACCINE IN ADULTS 60 THROUGH 64 YEARS OF AGE

Statistical Analysis Plan (SAP)

Version: 2.0

Author: PPD (Pfizer)

Date: 31-Jan-2018

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LIST OF TABLES

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1. VERSION HISTORY

This statistical analysis plan (SAP) for Study B7471002 is based on the protocol dated 20 July 2017.

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	13-Oct-2017	PPD	Version 1
Version 2.0	31-Jan-2018	PPD	Section 3.3.1: Redness or swelling <2.5 cm (5 measuring device units) will not be considered a reaction. Such reactions will be scored as "none," but will still be reported in the listings. Section 3.3.1: For calculations of duration and onset of local reactions, only reactions reported as "mild," "moderate," or "severe" will be included. Section 3.3.1: Duration of local reactions ≥21 measuring device units will also be compiled. Section 3.4: Added text "Racial designation will be summarized by categories recorded in the database. Subjects with white race or who do not have a recorded racial designation will be assigned to 'other.'" CCI [redacted] Section 3.6: Added text noting that concomitant medications for the treatments of SAEs or NDCMCs will be summarized. CCI [redacted] Section 6.1.1: Text added noting that local reaction and systemic event tables and figures will be produced after removal of e-diary data known to be data entry error. However, the maximum severity table will be regenerated with the erroneous data included. Section 6.1.1: Definition of total duration revised to count total days with the event. Section 6.1.1: Tables describing the presence of local reactions and systemic events will be repeated but limited to events graded as severe. Section 6.1.2: Compilation of mild or moderate AEs deleted.

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
			Section 6.1.2: Analysis intervals for SAEs and NDCMCs moved to a separate paragraph from the paragraph describing AEs. Various: "Study vaccination" changed to "vaccination."

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

2. INTRODUCTION

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The purpose of the proposed Phase 2 study in older adults is to assess the safety, tolerability, and immunogenicity of 20vPnC and to generate a safety and immunogenicity data set with 20vPnC to support and inform the design of the Phase 3 clinical development program for adults.

2.1. Study Objectives

The primary objective of this study is to describe the safety profile of 20vPnC in the study population.

The secondary objective of this study is to describe the immunogenicity of 20vPnC in the study population. CCI [redacted]

2.2. Study Design

This is a Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design. A total of 440 adults 60 through 64 years of age with no history of pneumococcal vaccination will be enrolled and randomized equally to receive either

- a single dose of 20vPnC followed 1 month later by saline (placebo) administration (20vPnC/saline group), or

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- a single dose of 13vPnC followed 1 month later by a dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) (13vPnC/PPSV23 group). This is the control group.

13vPnC will serve as a control for safety, as well as immunogenicity of the 13 serotypes in common with 20vPnC. PPSV23 will serve as a control for immunogenicity of the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) in 20vPnC.

Table 1. Time Points for Key Safety and Immunogenicity Objectives by Investigational Product

	20vPnC	Control – 13vPnC[a]	Control – PPSV23[b]
Prompted local reactions	X (10 days after Visit 1)	X (10 days after Visit 1)	
Prompted systemic events	X (7 days after Visit 1)	X (7 days after Visit 1)	
Adverse events[c]	X (1 month after Visits 1 and 2)	X (1 month after Visit 1)	X (1 month after Visit 2)
Immune responses to serotypes in common with 13vPnC: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	X (1 month after Visit 1)	X (1 month after Visit 1)	
Immune responses to additional 7 serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F	X (1 month after Visit 1)		X (1 month after Visit 2)

a. Control group from enrollment and vaccination with 13vPnC at Visit 1 until vaccination with PPSV23 at Visit 2.
b. Control group after vaccination with PPSV23 at Visit 2.
c. SAEs and newly diagnosed chronic medical conditions (NDCMCs) will be collected through Visit 5 (12 months after Visit 1).

Blood samples will be collected on the day of investigational product administration prior to each vaccination (Vaccination 1 and Vaccination 2), 1 month after Vaccination 2, and 12 months after Vaccination 1 CCI . Prompted local reactions at the injection site and prompted systemic events will be collected daily for 10 and 7 days, respectively, after Vaccination 1. Adverse events (AEs) occurring from signed informed consent through 1 month after Vaccination 2 will be collected and serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) will be collected through 12 months after Vaccination 1.

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary and secondary endpoints pertain to the 20vPnC vaccination (Vaccination 1), as described in the objectives, along with the applicable control group and time point (see Table 1).

- Proportions of subjects reporting prompted local reactions within 10 days after Vaccination 1 (redness, swelling, and pain at the injection site).
- Proportions of subjects reporting prompted systemic events within 7 days after Vaccination 1 (fever, headache, fatigue, muscle pain, and joint pain).
- Proportions of subjects reporting AEs within 1 month after Vaccination 1.
- Proportions of subjects reporting SAEs and NDCMCs within 6 months and 12 months after Vaccination 1.

3.2. Secondary Endpoint(s)

- Pneumococcal serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) 1 month after Vaccination 1. See Table 1 for the applicable control group and time point for each serotype.
- Pneumococcal serotype-specific OPA geometric mean fold rises (GMFRs) from before Vaccination 1 to 1 month after Vaccination 1. See Table 1 for the applicable control group and time point for each serotype.

3.3. Other Endpoints

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3.3.1. Local Reactions

The local reactions assessed and reported in the electronic diary (e-diary) are redness, swelling, and pain at the injection site, from Day 1 through Day 10, where Day 1 is the day of Vaccination 1.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21+), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 2 below. Measuring device units will be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Reactions smaller than 5 measuring device units (<2.5 cm) will be scored as "none," but such values will still be reported in the listings. Pain at the vaccine injection site will be assessed by the subject as mild, moderate, or severe according to the grading scale in Table 2.

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

= missing, if all values are missing for Day 1 to Day 10;

= 0, if the subject reports all reactions as "no" or a combination of missing and "no" for all Days 1 to 10;

= highest grade (maximum severity) within 10 days of Vaccination 1 (Day 1 to Day 10) among severity grades where the answers are neither "no" nor missing for at least 1 day during Days 1 to 10.

Note that Grade 4 severity will not be collected in the e-diary but will be collected as an AE on the case report form (CRF).

Table 2. Grading Scales for Local Reactions

	Mild Grade 1	**Moderate Grade 2**	**Severe Grade 3**	**Grade 4**
Redness (erythema)	5 to 10 measuring device units = 2.5 to 5.0 cm	11 to 20 measuring device units = 5.5 to 10.0 cm	≥21 measuring device units = ≥10.5 cm	Necrosis or exfoliative dermatitis
Swelling (edema)	5 to 10 measuring device units = 2.5 to 5.0 cm	11 to 20 measuring device units = 5.5 to 10.0 cm	≥21 measuring device units = ≥10.5 cm	Necrosis
Pain at injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization

Abbreviations: 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.

Presence or Absence

For the data summary of the presence (yes or no) of a local reaction during Day 1 to Day 10, where Day 1 is the day of Vaccination 1, the following variables are required:

- Maximum severity of each local reaction on any day (Day 1 to Day 10);
- Presence (yes or no) of each local reaction on each day (Day 1 to Day 10);
- Presence (yes or no) of each local reaction on any day (Day 1 to Day 10);
- Presence (yes or no) of any local reaction on each day (Day 1 to Day 10);

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- Presence (yes or no) of any local reaction on any day (Day 1 to Day 10);
- Presence (yes or no) of each severe (Grade 3, as defined in Table 2) local reaction on each day and any day (Day 1 to Day 10);
- Duration of each local reaction (duration will be calculated both from first to last day and also as total days with the indicated event);
- Onset day of each local reaction;
- CCI [redacted]

For each local reaction on any day, Table 3 below explains the algorithm to derive the presence of a reaction (yes or no) during Day 1 to Day 10, where Day 1 is the day of Vaccination 1.

Table 3. Derived Variables for Each Local Reaction Within the Time Interval

Variable[a]	Yes (1)	No (0)	Missing (.)
Any Day 1 to 10	Subject reports the reaction as "yes" on any Day 1 to 10.	Subject reports the reaction as "no" on all 10 Days (1 to 10) or as a combination of "no" and missing on all 10 Days (1 to 10).	Subject reports the reaction as missing on all 10 Days (1 to 10).

a. The variable will be derived for each of the local reactions (redness, swelling, and pain at the injection site) and for each of the severe or greater local reactions within Day 1 to Day 10 following Vaccination 1.

For any local reaction on any day, a similar rule applies as specified below in Table 4.

Table 4. Derived Variables for Any Local Reaction Within the Time Interval

Variable[a]	Yes (1)	No (0)	Missing (.)
Any Day 1 to 10	Subject reports any local reaction as "yes" on any Day 1 to 10.	Subject reports "no" on all 10 Days (1 to 10) or as a combination of "no" and missing on all 10 Days (1 to 10) on all 3 local reactions.	Subject reports all 3 local reactions as missing on all 10 Days (1 to 10).

a. The variable will be derived for any local reaction (any of redness, swelling, and pain at the injection site) and for any severe or greater local reaction within Day 1 to Day 10 following Vaccination 1.

Duration (From First Day to Last Day Reported)

The duration of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive. Resolution is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasted 10 days or less, or the day the reaction ended if it continued beyond Day 10 (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will

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be missing (unknown). Subjects with no reported reaction have no duration because it is not applicable. Only reactions reported as "mild," "moderate," or "severe," as defined in Table 2, will be included.

Duration of reactions ≥21 measuring device units will also be compiled.

Duration (Total Days Reported)

The duration of each local reaction (total days) will be calculated as the number of days with the reported reaction. Resolution is defined as the last day on which the reaction is recorded in the e-diary if the reaction lasted 10 days or less, or the date the reaction ended if it continued beyond Day 10 (the latter will be collected on the CRF). If there is no known resolution day, then duration will be missing (unknown). Subjects with no reported reaction have no duration because it is not applicable. Only reactions reported as "mild," "moderate," or "severe" will be included.

Total days of reactions ≥21 measuring device units will also be compiled.

Onset

The onset day of each local reaction and any local reaction will be derived. Onset is defined as the first day of reporting any severity of "mild," "moderate," or "severe."

For the onset day of each local reaction, if subjects report severity change of the local reaction, only the first day of reporting that specific local reaction will be counted.

For the onset day of any local reaction, the first day of reporting any severity of any local reaction will be counted.

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3.3.2. Systemic Events and Fever

The systemic events assessed and recorded in the e-diary are headache, fatigue, muscle pain, and joint pain, from Day 1 through Day 7, where Day 1 is the day of Vaccination 1.

For each systemic event, the maximum severity grade of the event based on the severity grading scale in Table 5 will be derived for the e-diary collection period (Day 1 to Day 7, where Day 1 is the day of Vaccination 1) as follows:

[redacted]

[redacted]

= missing, if all values are missing for Day 1 to Day 7;

= 0, if the subject reports all reactions as "no" or a combination of missing and "no" for all Days 1 to 7;

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

The symptoms of systemic events will be assessed by the subject as mild, moderate, or severe according to the severity grading scales of each systemic event in Table 5 below.

Grade 4 severity will not be collected in the e-diary but will be collected as an AE on the CRF.

Table 5. Grading Scales for Systemic Events

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

a. Prevents daily routine activity, ie, results in missed days of work or school or is otherwise incapacitating.

Oral temperature will be collected in the evening daily for 7 days following Vaccination 1 (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 ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 100.4°F [38.0°C]) in order to collect a stop date in the CRF. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 6 below:

Table 6. Ranges for Fever

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

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

Onset, duration, CCI [redacted] will be calculated in the same way as for local reactions.

For each systemic event (each systemic event or fever), from Day 1 through Day 7, where Day 1 is the day of Vaccination 1, the following endpoints and variables will be derived for analyses following the same rules as for local reactions in Section 3.3.1, where applicable:

- Maximum severity of each systemic event on any day (Day 1 to Day 7);
- Presence (yes or no) of each systemic event or fever on each day (Day 1 to Day 7);
- Presence (yes or no) of each systemic event or fever on any day (Day 1 to Day 7);
- Presence (yes or no) of any systemic event or fever on any day (Day 1 to Day 7);
- Presence (yes or no) of each severe (Grade 3, as defined in Table 5) systemic event on each day and on any day (Day 1 to Day 7);
- Duration of each systemic event or fever;
- Duration (total days) of each systemic event or fever;
- Onset day of each systemic event or fever;

[redacted]

CCI [redacted]

For the purposes of deriving the variable "any systemic event" on any day (Day 1 to Day 7) or each day, the systemic events headache, fatigue, muscle pain, and joint pain will be included, and fever will be also included as one of the possible systemic events.

3.3.3. Use of Antipyretic/Pain Medication

The use of antipyretic/pain medication is also recorded in the e-diary from Day 1 to Day 7, where Day 1 is the day of Vaccination 1.

For use of antipyretic/pain medication from Day 1 to Day 7, the following endpoints and variables will be derived for analyses following the same rules as for local reactions in Section 3.3.1, where applicable:

- Presence (yes or no) of use of antipyretic/pain medication on each day (Day 1 to Day 7);

[redacted]

[redacted]

- Presence (yes or no) of use of antipyretic/pain medication on any day (Day 1 to Day 7);
- Duration of use of antipyretic/pain medication (Day 1 to Day 7);
- Onset day of use of antipyretic/pain medication (Day 1 to Day 7).

The uses of antipyretic/pain medication will be summarized and included in the systemic event summary tables, but will not be considered as a systemic event.

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3.3.4. Adverse Events

AEs will be captured and reported in accordance with Pfizer reporting standards.

AEs will be assessed from the time of informed consent through 1 month after Vaccination 2 (Visit 3). SAEs and NDCMCs will be assessed throughout the study and collected by telephone call at 6 months after Vaccination 1 (Visit 4) and during a clinic visit at 12 months after Vaccination 1 (Visit 5).

3.4. Demographic, Medical History, and Baseline Characteristics

The descriptive statistics of demographic characteristics will be summarized by sex, race, and age at the time of enrollment and the time of vaccination.

Age at randomization in years will be derived as (randomization date – date of birth + 1) / 365.25 and truncated to the nearest integer.

For sex and race, the summary statistics will be the number and percentage of subjects within each vaccine group, and for the total. The categories for race will be those recorded in the database. Racial designation will be summarized by categories recorded in the database. Subjects with white race or who do not have a recorded racial designation will be assigned to "other." For age at the time of randomization, the mean, median, minimum, maximum, and standard deviation will be provided for each vaccine group. These tabulations will be performed for all subjects and the safety, evaluable immunogenicity, and all-available populations.

Body mass index (BMI) will be calculated as weight (kg) / (height $(m)^2$). Descriptive statistics will be calculated separately for each sex.

Subjects will report smoking use as "never smoked," "current smoker," and "ex-smoker." The proportions of subjects reporting "never smoked," "ex-smoker," and "current smoker" will be compiled.

Ex-smokers will quantify duration since last use in years, months, or days. All durations since last use in ex-smokers will be converted to years (months will be divided by 12 and

[redacted]

[redacted]

days divided by 365.25), then rounded to the nearest tenth. Descriptive statistics (mean, median, minimum, maximum, and standard deviation) will be compiled.

Current smokers will quantify duration of use in years, months, or days. These durations will be listed. All durations in current smokers will be converted to years (months will be divided by 12 and days divided by 365.25), then rounded to the nearest tenth.

Baseline medical history information will be summarized and categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects randomized with at least 1 diagnosis of each preferred term, arranged by system organ class, will be tabulated for each vaccine group and for the total.

3.5. Study Conduct and Subject Disposition

The number and percentage of subjects randomized, completing the study, and withdrawing from the study will be summarized for each vaccine group and for the total sample. The reasons for withdrawal from the study will also be summarized.

Listings of noncompliant vaccine administration and subjects who do not receive the vaccine as randomized will be provided.

The number and percentage of subjects providing blood samples within the window described in Section 4.2, as well as before and after the specified blood sample window, will be tabulated for each vaccine group and for the total.

The number and percentage of subjects providing a 12-month blood sample within the protocol-specified window of 350 to 378 days after Visit 1 (protocol Schedule of Activities), as well as outside this window, will be tabulated for each vaccine group and for the total.

All of the summary tables will be presented for each vaccine group and for the total for randomized subjects.

3.6. Concomitant Medications and Nonstudy Vaccines

Nonstudy vaccines and concomitant medications for the treatment of SAEs or NDCMCs taken from after signing the informed consent document (ICD) until conclusion of the study will be categorized according to the World Health Organization (WHO) Drug Dictionary (WHODD) and summarized.

4. ANALYSIS SETS

4.1. Safety Analysis Population

The safety population will include all subjects who receive 1 dose of 20vPnC or 13vPnC. Subjects will be assigned to vaccine group corresponding to the vaccine actually received. Subjects who lack any safety data for an indicated analysis may be excluded from that analysis.

All safety analyses will be performed on an "as-received" basis and will not include data from subjects who are randomized but do not receive investigational product.

4.2. Evaluable Immunogenicity Population

The evaluable immunogenicity population will include any subject who:

1. does not meet any exclusion criteria and who meets all inclusion criteria.
2. has no major protocol deviations as determined by the clinician.
3. receives the assigned vaccine, as randomized.
4. has blood drawn within 27 to 49 days after Vaccination 1 or after Vaccination 2.
5. has CCI OPA titers CCI for at least 1 serotype either 1 month after Vaccination 1 or 1 month after Vaccination 2.

The blood draw window has been expanded by 1 extra day before and 14 days after the protocol-specified blood draw window of 28 to 35 days as that has been established by precedent in the Prevnar 13 development program.

A subject may be included in the evaluable population even if one of the post–Vaccination 1 and post–Vaccination 2 blood collections is outside the relevant window. The intention is maximizing the number of subjects in the evaluable population, even if some subjects miss window criteria for exactly 1 blood collection. However, a subject will only be included in analysis at a given time point if that subject meets the applicable window criterion.

Individual samples may be excluded from specified immunogenicity analyses for reasons including, but not limited to, improper handling (eg, insufficient volume, sample allowed to thaw); however, such a subject may still otherwise be included in the evaluable immunogenicity population, provided all other criteria are met.

The evaluable immunogenicity population will be the primary analysis population for immunogenicity.

4.3. All-Available Immunogenicity Population

The all-available immunogenicity population will include all subjects who receive 20vPnC or 13vPnC and have at least 1 valid and determinate OPA titer CCI after either Vaccination 1 or Vaccination 2. Subjects will be assigned to their randomized vaccine. Subjects correctly receiving 20vPnC or 13vPnC at first dose, but receiving incorrect product at second dose, will be assigned to their randomized regimen.

The all-available immunogenicity population will be the secondary analysis population for immunogenicity results.

See Appendix 9.2 for an outline of handling protocol deviations.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal statistical hypothesis testing will be performed. A descriptive estimation approach will be used to assess the safety and immunogenicity objectives in the study.

Statistical decision rules will not be utilized in this study. All analyses are considered descriptive.

5.2. General Methods

All analyses will be descriptive. Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the percentage (%) and the numerator (n) and the denominator (N) used in the percentage calculation.

No formal hypothesis testing will be performed.

5.2.1. Analyses for Immunogenicity Endpoints

This study's immunogenicity variables are the results of assays performed on the blood samples collected. CCI [redacted]

OPA Titer

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 in each subject for each blood sample at each protocol-specified blood draw visit. Results will be reported as OPA titers.

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

The LLOQ titer for each serotype is presented in Table 7.

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Geometric Mean

The secondary CCI [redacted] immunogenicity endpoints, which include OPA titers CCI [redacted], will be summarized as GMTs for OPA antibody titers CCI [redacted], for each pneumococcal serotype by each vaccine group at each blood sampling time point. GMTs CCI [redacted] and the associated 95% CIs will be provided for each pneumococcal serotype by each vaccine group at each blood sampling time point.

The GMT CCI [redacted] will be calculated as the mean of the assay results after making the logarithm transformation and then back transformation to its original scale. Two (2)-sided 95% CIs will be constructed by back transformation of the CI for the mean of the logarithmically transformed assay results computed based on the Student t distribution.

The secondary CCI [redacted] immunogenicity endpoints include GMFRs. The ratio of the later assay value divided by the earlier assay value forms a ratio. Ratios will be log transformed, then applying the same geometric mean calculations and the associated 95% CI calculations as described above. The anti-log of the calculations in ln scale will form the GMFR and its 95% CI.

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Reverse Cumulative Distribution Curve

Reverse cumulative distribution curves (RCDCs) plot proportion of subjects with value equal to or exceeding specified assay value versus indicated assay value, for all observed assay values.

5.2.2. Analyses for Binary Safety Endpoints

The exact 95% confidence interval (CI) for binary endpoints confidence intervals will be computed using the F distribution (Clopper-Pearson). 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_U should be set equal to 1.0 so p_U equals 1.

The Clopper-Pearson method is described in Collett (1991) and implemented in SAS PROC FREQ. For a 95% CI, the quantiles, F_L and F_U, are from the F distribution for α=0.025 and α=0.975, respectively.

5.3. Methods to Manage Missing Data

Methods for handling missing local reactions and systemic events are described in Section 3.3.1 and Section 3.3.2.

Missing immunogenicity values will be retained as missing.

[redacted]

[redacted]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

All safety summaries will be provided by vaccine group. No statistical comparisons are planned for safety data. The safety endpoints detailed in Section 3.1 will be summarized as described below. The analyses will consist of subjects from the safety analysis population.

6.1.1. Local Reactions, Systemic Events, and Fever

The proportions of subjects with

1. presence of each local reaction each day,
2. any local reaction on each day,
3. any local reaction on any day of Day 1 to Day 10,
4. presence of each systemic event each day,
5. any systemic event on each day,
6. any systemic event on any day of Day 1 to Day 7

after Vaccination 1 will also be provided for each vaccine group as well as the associated 95% Clopper-Pearson CIs. A similar set of tables will be produced for local reactions and systemic events that are severe in grade.

Figures of the bar charts plotting the proportions of subjects for each derived reaction or systemic event will be plotted by day for each vaccine group. The bar charts will be divided into severity subgroups to highlight the proportions of subjects by severity.

For redness and swelling, the maximum reported diameters in centimeters (cm) will be summarized by each severity category specified in Table 2, for each vaccine group.

For each local reaction and systemic event, including fever, the maximum duration of each event will be summarized using descriptive statistics for each vaccine group. The maximum duration of each event for each subject will be calculated as the last day with the event minus the first day with the event + 1, ignoring any intervening days without the indicated event.

For each local reaction and systemic event, including fever, the total duration of each event will be summarized using descriptive statistics for each vaccine group. Total duration will be calculated as the number of days with the reported reaction, including days after the e-diary data collection period ends. If there is no known date when the reaction ended, then total duration will be missing (unknown). Only subjects reporting the event will be included in the summary statistics.

The onset day of each local reaction and systemic event, including fever, will be summarized using descriptive statistics for each vaccine group.

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A listing will be provided for the subjects with unscheduled visits for severe (Grade 3 and above) local reactions or systemic events.

Local reaction and systemic event tables will be generated without e-diary data that have been confirmed by the subject to have been entered in error. However, the maximum severity table will be regenerated with the erroneous data included.

6.1.2. Adverse Events

Descriptive summaries and listings of AEs will be provided. The descriptive statistics for AEs will be summarized as the number and percentage of subjects reporting at least 1 event of each preferred term with the associated Clopper-Pearson 95% CI (Section 5.2.2), arranged by system organ class, and will also be summarized as the number of occurrences of the event.

[redacted]

AEs will be summarized for each vaccine group from Vaccination 1 until Visit 2, which is 1 month later. AEs will also be summarized from Vaccination 2 until Visit 3, which is 2 months after administration of 20vPnC (Vaccination 1) and 1 month after administration of PPSV23. In addition, tables with the same descriptive statistics for related AEs and AEs characterized as severe will also be compiled for the time intervals described above. Subjects in the safety population will be summarized according to the vaccine actually received.

SAEs and NDCMCs (defined in Section 8 of the protocol) will be summarized for each vaccine group by intervals from Vaccination 1 until Visit 2, from Vaccination 1 until Visit 3, from Visit 3 to Visit 4 (6 months after 20vPnC administration), and from Visit 4 until Visit 5 (12 months after 20vPnC administration). SAEs and NDCMCs will also be summarized for each vaccine group by intervals from Vaccination 1 until Visit 4 (6 months after 20vPnC administration) and from Vaccination 1 until Visit 5 (12 months after 20vPnC administration).

6.2. Secondary Endpoints

6.2.1. Immunogenicity Analysis

All analyses for the immunogenicity data, which are the secondary CCI [redacted] endpoints, will be descriptive. Statistics for the 13 serotypes in 13vPnC 1 month after Vaccination 1 (20vPnC/saline group and 13vPnC/PPSV23 control group) will appear on the same table. Statistics for the 7 additional serotypes 1 month after Vaccination 1 (in the 20vPnC/saline group) and 1 month after Vaccination 2 (in the 13vPnC/PPSV23 group) will appear on the same table.

[redacted]

[redacted]

For completeness, statistics will be obtained for every serotype for each blood sampling time point.

The number and percentage of subjects randomized and included in each immunogenicity population (defined in Section 4.2 and Section 4.3) will be tabulated for each vaccine group and for the total. Reasons for exclusions from the immunogenicity population will be summarized using the number and percentage of subjects. Listings of subjects excluded from the evaluable immunogenicity population and the all-available immunogenicity population will be provided.

OPA GMTs CCI [redacted] with their associated 95% CIs will be summarized separately at each blood draw sampling time point for each pneumococcal serotype by each vaccine group. Geometric means will be compiled in both the evaluable immunogenicity population and the all-available immunogenicity population using the detailed statistical method of geometric mean described in Section 5.2.1.

Similarly OPA CCI [redacted] GMFRs, with their 95% CIs, will be calculated

1. from before Vaccination 1 until 1 month after Vaccination 1,
2. from before Vaccination 1 until 1 month after Vaccination 2,
3. CCI [redacted],
4. CCI [redacted],
5. CCI [redacted]

for each pneumococcal serotype by each vaccine group. Only subjects with valid assay results from both sampling time points will be included. GMFRs will be obtained for both the evaluable immunogenicity population and the all-available immunogenicity population using the detailed statistical method of geometric mean described in Section 5.2.1.

CCI [redacted] CCI [redacted]

The proportion of subjects with assay values ≥ LLOQ with the associated 95% Clopper-Pearson CIs (Section 5.2.2) for each pneumococcal serotype by each vaccine group will be summarized separately at each blood draw sampling time point, in both the evaluable immunogenicity population and the all-available immunogenicity population. CCI [redacted]

RCDCs will be plotted for each pneumococcal serotype. All time points will be included in each figure. CCI [redacted] RCDCs may be generated after

[redacted]

[redacted]

data from 2 months are available. [redacted]

Kinetic curves of geometric means will be compiled for [redacted] OPA. All time points will be included in each figure. The abscissa values will be 0, 1, 2, [redacted] months. [redacted]

[redacted]

6.3. Other Endpoints

6.3.1. Use of Antipyretic/Pain Medication

The derived endpoints for use of antipyretic/pain medication (Section 3.3.3) will be summarized as the proportions of subjects with the associated 95% Clopper-Pearson CIs (Section 5.2.2) for each vaccine group. Supportive bar charts and descriptive statistics for the duration and day of onset day will also be compiled.

6.4. Subset Analyses

None planned.

6.5. Demographic, Medical History, and Baseline Summaries and Analyses

Summaries for baseline variables are described in Section 3.4. Summaries for study conduct and subject disposition are described in Section 3.5.

Nonstudy vaccines will be summarized by WHODD categories.

7. INTERIM ANALYSES

There are no interim analyses in this study. However, when data become available analyses will be generated.

Sponsor personnel directly involved in evaluating subject data will be blinded to vaccine assignment until the analysis of all available data through Visit 2 (1 month after Vaccination 2) is available. Laboratory personnel directly conducting the immunogenicity assays will remain blinded until the complete study database is locked and unblinded.

The following analysis timings are planned for this study:

1. Unblinded safety and immunogenicity data from Visit 1 through Visit 2 (1 month after Vaccination 1) will be analyzed when available. The analyses will be descriptive. This analysis will inform internal program development decisions and potentially support regulatory interactions.

2. Unblinded safety and immunogenicity data from Visit 2 through Visit 3 (1 month after Vaccination 2) will be analyzed when available. The analyses will be descriptive. This analysis will also inform internal program development decisions and potentially support regulatory interactions.

3. Unblinded safety data from Visit 3 (1 month after Vaccination 2) through Visit 4 (6-month telephone call) will be analyzed when available.

4. Unblinded safety CCI [redacted] data from Visit 4 through Visit 5 will be analyzed when available. These will be the final analyses.

Later analyses will include results from earlier analyses, eg, immunogenicity tables from Visit 3 (1 month after Vaccination 2) will include results from earlier time points.

8. REFERENCES

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

[redacted]

[redacted]

9. APPENDICES

9.1. List of Abbreviations

Abbreviation	Term
13vPnC	13-valent pneumococcal conjugate vaccine
20vPnC	20-valent pneumococcal conjugate vaccine
AE	adverse event
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CRF	case report form
e-diary	electronic diary
E-DMC	external data monitoring committee
CCI	[redacted]
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
CCI	[redacted]
IRC	internal review committee
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NDCMC	newly diagnosed chronic medical condition
OPA	opsonophagocytic activity
PPSV23	23-valent pneumococcal polysaccharide vaccine
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

9.2. Protocol Deviations That Affect Membership in Statistical Populations

9.2.1. Deviations Assessed Prior to Randomization

At screening, the investigator will assess subjects against the inclusion and exclusion criteria described in protocol Sections 4.1 and 4.2.

9.2.2. Deviations Assessed After Randomization

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