Protocol B7471008

A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF 3 LOTS OF 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN PNEUMOCOCCAL VACCINE–NAÏVE ADULTS 18 THROUGH 49 YEARS OF AGE

Statistical Analysis Plan (SAP)

Version: 2

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Date: 11 FEB 2020

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1. VERSION HISTORY

This statistical analysis plan (SAP) for Study B7471008 is based on the protocol dated 22 Oct 2018.

Table 1. Summary of Major Changes in SAP Amendments

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

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471008. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

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 demonstrate that the immune responses to the 20 serotypes induced by 20vPnC are equivalent across 3 lots.

2.1.3. Secondary Objective

- To describe the immune response to 20vPnC.

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[redacted]

2.2. Study Design

This Phase 3, multicenter, randomized, double-blind study with a 4-arm parallel design will be conducted at investigator sites in the United States. The purpose of this study is to evaluate the safety and consistency of immune response elicited across 3 different lots of 20vPnC.

A total of ~1610 adults 18 through 49 years of age with no history of pneumococcal vaccination will be enrolled and randomized to receive 20vPnC or 13-valent pneumococcal conjugate vaccine (13vPnC). This population was selected as it is an age group that will be targeted in the planned indication and has lower variability in immune response than older or potentially prevaccinated populations, helping with interpretation of lot-consistency immunogenicity results. The 13vPnC arm is only a safety control, but sera will be assayed to maintain blinding and for descriptive purposes. Subjects will be randomized into 1 of 4 groups in a 2:2:2:1 ratio (20vPnC Lot 1: 20vPnC Lot 2: 20vPnC Lot 3: 13vPnC) by site-based randomization. CCI [redacted]

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, 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 20vPnC or 13vPnC 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 an e-diary for 7 days after vaccination.

At Visit 2 (28 to 42 days after Visit 1), subjects will return to the investigator site 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.

At Visit 3 (approximately 6 months [168 to 196 days] after Visit 1), the sites will contact the subject 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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[redacted]

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 3 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 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

[redacted]

Table 3. 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 injection site pain

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.

[redacted]

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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 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.

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 ≥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. 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.

[redacted]

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 (pooled 20vPnC lots and 13vPnC): 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 (pooled 20vPnC lots and 13vPnC): 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 if the event rate is greater than 1% either in the pooled 20vPnC lots or in the 13vPnC group.

- Tier 3 events (individual 20vPnC lots, pooled 20vPnC lots, and 13vPnC): These are events that are neither Tier 1 nor Tier 2 events.

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3.2. Primary Immunogenicity Endpoint

- Serotype-specific opsonophagocytic activity (OPA) titers 1 month after vaccination.

OPA titers for the 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.

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 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.

CCI [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.

3.5.1. Demographics CCI [redacted] and Medical History

The demographic variables will include sex (male or female), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white), ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported), and age at the time of vaccination (in years). In cases where more than 1 category is selected for race, the subject would be counted under the category "multiracial" for analysis.

Age at the time of vaccination (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 first vaccination for age calculation.

CCI [redacted]

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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[redacted]

3.5.3. Nonstudy Vaccinations and Concomitant Medications

Any nonstudy vaccinations received from the time of signing of the ICD to Visit 3 and medications taken to treat SAEs or NDCMCs from the time of signing of the ICD to Visit 3 will be recorded. Nonstudy vaccinations and concomitant medications will be categorized according to the World Health Organization (WHO) Drug Dictionary (WHODD).

4. ANALYSIS SETS

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

4.1. Safety Population

The safety population will include all subjects who receive 1 dose of any 20vPnC lot or 13vPnC and have safety follow-up after the vaccination. Subjects will be included in the vaccine group corresponding to the vaccine actually received. The safety population will be the only analysis population for safety evaluation.

4.2. Evaluable Immunogenicity Population

The evaluable immunogenicity population will generally include any subject who

1. receives randomized vaccine,

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

3. has at least 1 valid and determinate OPA titer for any serotype at Visit 2, and

4. 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 study medical monitor, 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 protocol deviations before any unblinded analysis is carried out.

The evaluable immunogenicity population will be the primary analysis population for the immunogenicity endpoints. Subjects will be included in the vaccine group as randomized in the analysis, which, by the population definition, is equivalent to the vaccine group corresponding to the vaccine actually received.

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5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The primary immunogenicity objective of the study is to demonstrate that the immune responses to the 20 serotypes induced by 20vPnC are equivalent across 3 lots. The lot-to-lot consistency will be evaluated by each primary immunogenicity endpoint, serotype-specific OPA titer 1 month after vaccination, using a 2-fold equivalence margin for each between-lot comparison of OPA titers. The null hypothesis for each of the 20 serotypes is:

$$H_0: |\ln(\mu_1)-\ln(\mu_2)| \geq \ln(2) \text{ or } |\ln(\mu_1)-\ln(\mu_3)| \geq \ln(2) \text{ or } |\ln(\mu_2)-\ln(\mu_3)| \geq \ln(2)$$

where $\ln(\mu_1)$, $\ln(\mu_2)$, and $\ln(\mu_3)$ are the natural log-transformed OPA geometric mean titers (GMTs) 1 month after vaccination from subjects receiving 20vPnC Lot 1, Lot 2, and Lot 3, respectively. The 3 lots will be considered equivalent if each of the pairwise 2-sided 95% confidence intervals (CIs) for the geometric mean ratios (GMRs) of OPA titers is contained in the interval (0.5, 2.0). Note that this requires a total of 60 comparisons (3 pairwise between-lot comparisons for each of 20 serotypes).

5.2. General Methods

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Between-lot comparison will be performed on serotype-specific OPA titers to test the hypotheses of lot-to-lot consistency for the three 20vPnC lots. In addition, between-vaccine-group differences (pooled 20vPnC lots vs 13vPnC) and the associated 95% CIs for Tier 2 AEs CCI [redacted] will be provided. Other analyses will be descriptive in nature. Unless otherwise stated, "95% CI" refers to 2-sided 95% CI in this document.

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 will be computed using the Clopper-Pearson method.[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) 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 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 performed on the natural log scale, and the results will be reported in the original scale after back transformation.

5.2.2.1. Geometric Mean Ratio

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

[redacted]

5.2.2.2. Geometric Mean Titer

Serotype-specific OPA GMT will be calculated before study vaccination and 1 month after vaccination for each vaccine group [redacted]. Geometric means and their 2-sided 95% CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, then exponentiating the results.

5.2.2.3. Geometric Mean Fold Rise

Serotype-specific OPA geometric mean fold rises (GMFRs) will be summarized for each vaccine serotype from before to 1 month after vaccination for each vaccine group [redacted]. GMFRs will be limited to subjects with nonmissing values both before vaccination and after vaccination. The GMFRs will be calculated as the mean difference of individual subject logarithmically transformed antibody levels (postvaccination minus prevaccination) and then transformed back to the original units. Two (2)-sided 95% CIs are also computed by back transformation of the CIs based on Student's t-distribution for the mean difference of measures on the logarithmically transformed assay results.

[redacted]

5.3. 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

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 vaccine group and for the pooled 20vPnC group.

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[redacted]

6.1.2. Systemic Events

6.1.2.1. Primary Analysis

Endpoint: 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 systemic events 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 vaccine group as well as for the pooled 20vPnC group.

[redacted]

CCI

[redacted]

6.1.3. Adverse Events

6.1.3.1. Primary Analysis

Endpoint: Proportions of subjects reporting AEs

- 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, 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 vaccine group as well as for the pooled 20vPnC group.

In addition, for AEs classified as Tier 2 events, differences in percentages and the associated 2-sided 95% CIs for between-group comparisons (pooled 20vPnC lots – 13vPnC group) will be provided using the Miettinen and Nurminen method.

Figures:

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

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[redacted]

[redacted]

[redacted]

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, the denominator (N) used in the percentage calculation, and the corresponding 95% Clopper-Pearson CI will be presented for each vaccine group as well as for the pooled 20vPnC group, along with corresponding listings.

CCI [redacted]

6.2. Primary Immunogenicity Endpoints

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

6.2.1. Serotype-Specific OPA Titers 1 Month After Vaccination

6.2.1.1. Primary Analysis

Endpoint: Pneumococcal serotype-specific OPA titers

- Time point: 1 Month after vaccination
- Analysis population: Evaluable immunogenicity population, CCI [redacted] limited to 20vPnC lots only
- CCI [redacted]
- Supporting objective: Primary objective

[redacted]

Reporting results:

The [redacted] estimate of the serotype-specific OPA GMR and the associated 95% CI for each pair of lot comparisons (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) will be presented for each serotype.

Figures:

A forest plot of GMRs with 95% CIs for each pair of lot comparisons for each serotype will be presented.

[redacted]

[redacted]

6.3. Secondary Endpoints

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

Endpoint: Fold rise in serotype-specific OPA titers

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

Reporting results:

Serotype-specific OPA GMFRs and associated 95% CIs will be summarized for each vaccine serotype from before vaccination to 1 month after vaccination for each vaccine group [redacted].

6.3.2. ≥4-Fold Rise in Serotype-Specific OPA Titers From Before 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 population, [redacted]
- Analysis methodology: Descriptive statistics
- Supporting objective: Secondary objective

Reporting results:

The proportion of subjects with a ≥4-fold rise in OPA titer from before vaccination to 1 month after vaccination and associated 95% CI will be provided for each serotype for each vaccine group[redacted].

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

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

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

Reporting results:

The proportion of subjects with OPA titers ≥ LLOQ and associated 95% CI will be calculated for each serotype before vaccination and 1 month after vaccination for each vaccine group [redacted].

[redacted]

[redacted]

6.6. Baseline and Other Summaries and Analyses

6.6.1. Study Conduct and 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 by vaccine group and for the pooled 20vPnC group. The specific reasons for withdrawal (lost to follow-up, AE, protocol deviation, etc) will also be presented.

[redacted]

6.6.2. Baseline Summaries

6.6.2.1. Demographics [redacted]

The demographic characteristics, which will include sex, race, ethnicity, and age at the time of vaccination, will be summarized using descriptive statistics for each vaccine group and for the pooled 20vPnC group. The summary will be provided for the safety population and the evaluable immunogenicity population.

CCI [redacted]

6.6.2.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to the current version (at the time of reporting) of MedDRA. The number and percentage of subjects with at least 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized by vaccine group and for the pooled 20vPnC group for the safety population.

CCI [redacted]

6.6.4. Nonstudy Vaccinations and Concomitant Medications

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

6.7. Safety Summaries and Analyses

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

CCI [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.

[redacted]