Protocol B1851172

A PHASE 3, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SINGLE DOSE OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN JAPANESE SUBJECTS AGED 6 TO 64 YEARS WHO ARE CONSIDERED TO BE AT INCREASED RISK OF PNEUMOCOCCAL DISEASE AND WHO ARE NAIVE TO PNEUMOCOCCAL VACCINES

Statistical Analysis Plan
(SAP)

Version: 2.0

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1. VERSION HISTORY

This statistical analysis plan (SAP) for Study B1851172 is based on the protocol dated 20 Mar 2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Author(s)	Change	Rationale
1.0	PPD		
2.0	PPD	Table 2 OPA LLOQs for serotype 7F and 9V were modified.	For update to most current version
		Section 6.1.1.5. Adverse Events, Endpoints Added description of subgroups	Omission
		Section 6.1.1.5, Adverse Events, Reporting summaries Deleted "Number(%) of Subjects With Adverse Events"	Erroneous description
		Section 6.1.1.5. Adverse Events, Reporting summaries Summary table for "Severe and Life-Threatening AE" was divided into for "Severe AE" and "Life-Threatening AE".	To clarify summarized results
		Section 6.1.1.5, Adverse Events, Reporting summaries Added the following items: ✓ Adverse Event Leading to Discontinuation ✓ Related Adverse Event Leading to Discontinuation ✓ Immediate Adverse Events ✓ Related Immediate Adverse Events ✓ Deaths ✓ Related Deaths	Omission
		Section 6.5.2. Baseline Summaries (Demographic, Medical History) For medical history summary, analysis population was changed from safety population to all enrolled subjects.	Discussion with the clinician for this study.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Author(s)	Change	Rationale
		Section 6.5.6. Immunosuppressive Drug, Immune-Modifying Drugs, and/or Monoclonal Antibody Analysis population was changed from safety population to all enrolled subjects.	Discussion with the clinician for this study.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B1851172. 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

Primary Objective:	**Primary Endpoints:**
• To assess the safety and tolerability of a single dose of 13-valent pneumococcal conjugate vaccine (13vPnC) as measured by the incidence of local reactions, systemic events, adverse events (AEs), and serious adverse events (SAEs).	• Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 7-day period following study vaccination in the 6- to <18-year age group. • Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 14-day period following study vaccination in the 18- to <65-year age group. • Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 7-day period following study vaccination in the 6- to <18-year age group. • Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 14-day period following study vaccination in the 18- to <65-year age group. • Number and proportion of subjects reporting AEs and SAEs until Visit 2 categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) in all age groups.
Secondary Objective:	**Secondary Endpoints:**
• To describe the immune responses elicited by a single dose of 13vPnC.	• Serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) 1 month after vaccination in all age groups. • Geometric mean fold rises (GMFRs) in serotype-specific OPA titers from before vaccination to 1 month after vaccination in all age groups. • Serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) 1 month after vaccination in all age groups. • GMFRs in serotype-specific IgG from before vaccination to 1 month after vaccination in all age groups.

2.2. Study Design

This is a Phase 3, multicenter, single-arm, open-label study to assess the safety, tolerability, and immunogenicity of a single dose of 13vPnC in Japanese subjects aged 6 to 64 years who are considered to be at increased risk of pneumococcal disease and who are naive to pneumococcal vaccines.

This study consists of 2 age groups, 6 to <18 years old and 18 to <65 years old. Subjects will be enrolled in 1 of these age groups and will be assigned a container number of investigational product by an interactive web response (IWR) system. For the purposes of subject participation in the study, including data collection procedures, enrollment in the study is considered to occur at the time of investigational product assignment.

Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 1 month (29 to 43 days).

Approximate Duration of the Study

The study will be completed in approximately 6 months. Study duration is from first subject first visit (FSFV) to last subject last visit (LSLV).

Approximate Number of Subjects

Approximately 200 subjects will be enrolled: approximately 50 subjects in the 6- to <18-year age group and approximately 150 subjects in the 18- to <65-year age group.

For the purpose of ensuring a minimum number of subjects in each of the age categories, at least 15 subjects aged 6 to <12 years (children) and 15 subjects aged 12 to <18 years (adolescents) will be enrolled within the 6- to <18-year age group. Furthermore, at least 50 subjects aged 18 to <50 years (young adults) and 50 subjects aged 50 to <65 years (older adults) will be enrolled within the 18- to <65-year age group.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

See Section 2.1.

3.2. Secondary Endpoints

See Section 2.1.

3.3. Other Endpoints

Not applicable (N/A).

3.4. Baseline Variables

The demographic and baseline characteristics include sex, race, ethnicity, smoking status, and age at the time of vaccination. Age at the time of vaccination is the only demographic variable that needs to be derived. This variable is derived as years (vaccination date – date of birth + 1) / 365.25 and truncated to the nearest integer.

Smoking status, as either smoker, ex-smoker, or never smoked during the 6 months prior to the study participation, will be obtained from the case report form (CRF).

3.5. Safety Endpoints

Safety endpoints are the primary endpoints. See Section 2.1.

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 releasing the database, and classifications will be documented per standard operating procedures.

4.1. Safety Analysis Set

The safety population will include all subjects who receive 1 dose of study vaccine. The safety population will be the only analysis population for the primary endpoints.

For local reactions, systemic events, fever, and use of antipyretic/pain medication, the definition of the denominators for the percentage calculations will be described in Section 6.1.1.1 based on electronic diary (e-diary) record. In addition, these tables will be generated without e-diary data that have been confirmed by the subject to have been entered in error. Data-entry errors will be discussed in the clinical study report text and documented in a separate listing.

4.2. All-Available Immunogenicity Population

The all-available immunogenicity population will include all subjects who were enrolled, received the study vaccine, and had at least 1 valid and determinate assay result (OPA titer or IgG concentration) for at least 1 serotype 1 month after vaccination.

4.3. Evaluable Immunogenicity Population

The evaluable immunogenicity population will include subjects who meet the following:

1. Were eligible for the study based on the inclusion and exclusion criteria.
2. Received the study vaccine.
3. Received no prohibited vaccines.

4. Had blood drawn within the specified time frame 1 month after vaccination (28 to 42 days after Visit 1 (ie, Day 29 to Day 43 when Day 1 is vaccination visit).

5. Had at least 1 valid and determinate assay result (OPA titer or IgG concentration) for at least 1 serotype 1 month after vaccination.

6. Had no major protocol violations as determined by the sponsor's clinician, or any other protocol deviations that may materially affect assessment of immunogenicity endpoints.

4.4. Other Analysis Sets

N/A.

5. GENERAL METHODOLOGY AND CONVENTIONS

All analyses will be performed after completion of the study.

5.1. Hypotheses and Decision Rules

N/A. The study will be assessed by descriptive statistics.

5.2. General Methods

5.2.1. Analyses for Binary Data

Descriptive Summary:

The following statistics will be presented: number and percentage of subjects. The 2-sided 95% confidence interval (CI) will be also produced, if necessary.

Estimations:

Proportion

The CI for a single proportion will be computed using the F distribution. If r equals the number of responses and n equals the number of subjects, then it follows that p = r / n is the estimate of the proportion of responses. An exact 95% CI can be computed by solving the following 2 equations.

For the lower limit, p_L, use $$p_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$

and

for the upper limit, p_U, use $$p_U = \frac{rF_U}{(n - r) + (r + 1)F_U}$$

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) and 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 resulting proportions will be multiplied by 100 for presentation in tables. See Collett (1991)[1] for more details.

5.2.2. Analyses for Continuous Data

Descriptive Summary:

The following statistics will be presented: number of subjects, mean, standard deviation, median, minimum, and maximum. The 2-sided 95% CI will be also produced, if necessary.

Estimations:

Geometric Mean (GM)

For each serotype, OPA GMTs and IgG GMCs will be calculated. The serotype-specific OPA titers and IgG concentrations will be logarithmically transformed for analysis. GMTs or GMCs will be back transformations of the mean of the log-transformed measures. Two-sided 95% CIs will be constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution.

Geometric Mean Fold Rise (GMFR)

For each serotype, OPA and IgG GMFRs will be calculated. The serotype-specific OPA titers or IgG concentrations will be logarithmically transformed for analysis. GMFRs will be back transformations of the mean of the difference of the log-transformed measures (1 month after vaccination – prevaccination). Two-sided CIs for GMFRs will be back transformations of a CI based on the Student t distribution for the mean difference of the log-transformed measures.

Reverse Cumulative Distribution Curve (RCDC)

For each serotype, the empirical reverse cumulative distribution curves (RCDCs) will plot the percentage of subjects achieving a given titer or concentration.

5.3. Methods to Manage Missing Data

For the analysis of the immunogenicity endpoints, missing values will be retained as missing and will not be imputed.

Handling of missing values for local reactions and systemic events is described in Section 6.1.1.1 and Section 6.1.1.2.

5.4. Methods to Manage Data Below the Lower Limit of Quantitation (LLOQ)

OPA Titer

Pfizer's OPA lower limit of quantitation (LLOQ) was defined from the GMT of the lowest titer values established during the validation that demonstrated acceptable linearity (relative accuracy) and precision as defined in the validation protocol MVP-1020. The LLOQ titer for each serotype was set as in Table 2.

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

IgG Concentration

Pfizer's Luminex IgG LLOQs in micrograms per mL (µg/mL) for each serotype are set as in Table 2. Antibody concentrations above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis.

Table 2. Lower Limit of Quantitation of Antibody Level for Each Serotype

Antigen	OPA LLOQ	IgG LLOQ
1	18	0.002
3	12	0.004
4	21	0.005
5	29	0.002
6A	37	0.005
6B	43	0.015
7F	113	0.003
9V	141	0.013
14	35	0.005
18C	31	0.002
19A	18	0.038
19F	48	0.012
23F	13	0.009

Abbreviations: IgG = immunoglobulin G; LLOQ = lower limit of quantitation;
OPA = opsonophagocytic activity.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Safety Summaries and Analyses

- Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 7-day period following study vaccination in the 6- to <18-year age group.

- Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 14-day period following study vaccination in the 18- to <65-year age group.

- Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 7-day period following study vaccination in the 6- to <18-year age group.

- Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 14-day period following study vaccination in the 18- to <65-year age group.

- Number and proportion of subjects reporting AEs and SAEs until Visit 2 categorized according to MedDRA in all age groups.

6.1.1.1. Local Reactions

Endpoints: Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions.

- Analysis time points: The 7-day period (6- to <18-year age group) and 14-day period (18- to <65-year age group) following study vaccination.

- Analysis population: Safety population (Definitions of denominators for the summary tables are described in each reporting summary section).

- Subgroups: Each age group (6 to <18 years old and 18 to <65 years old) and each age category (6 to <12 years old, 12 to <18 years old, 18 to <50 years old, and 50 to <65 years old) in each age group.

For each local reaction, severity will be derived by the maximum severity grade of the reaction based on the severity grading scale of the local reactions in Table 3 for subjects aged 6 to <12 years, and Table 4 for subjects aged 12 to <18 years and those aged 18 to <65 years.

Table 3. Local Reaction Grading Scale (Subjects Aged 6 to <12 Years)

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe	GRADE 4[b]
Redness	1 to 4 caliper units (or measuring device units) 0.5 to 2.0 cm	>4 to 14 caliper units (or measuring device units) >2.0 to 7.0 cm	>14 caliper units (or measuring device units) >7.0 cm	Necrosis or exfoliative dermatitis[b]
Swelling	1 to 4 caliper units (or measuring device units) 0.5 to 2.0 cm	>4 to 14 caliper units (or measuring device units) >2.0 to 7.0 cm	>14 caliper units (or measuring device units) >7.0 cm	Necrosis[b]
Pain (tenderness) at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain (tenderness) 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 caliper units, the higher caliper unit number will be recorded in the e-diary.

a. When subjects experience local reactions >14 caliper units (>7.0 cm) or severe pain (tenderness) at the injection site, the subject/legally acceptable representative/parent/legal guardian will telephone the study site. In the event that the subject/legally acceptable representative/parent/legal guardian does not call, the investigator will call the subject/legally acceptable representative/parent/legal guardian.
b. Grade 4 assessment should be made by the investigator and recorded as an AE on the CRF.

Table 4. Local Reaction Grading Scale (Subjects Aged 12 to <18 Years and 18 to <65 Years)

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe	GRADE 4[b]
Redness	5 to 10 caliper units (or measuring device units) 2.5 to 5.0 cm	>10 to 20 caliper units (or measuring device units) >5.0 to 10.0 cm	>20 caliper units (or measuring device units) >10.0 cm	Necrosis or exfoliative dermatitis[b]
Swelling	5 to 10 caliper units (or measuring device units) 2.5 to 5.0 cm	>10 to 20 caliper units (or measuring device units) >5.0 to 10.0 cm	>20 caliper units (or measuring device units) >10.0 cm	Necrosis[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	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 caliper units, the higher caliper unit number will be recorded in the e-diary.

a. When subjects experience local reactions >20 caliper units (>10.0 cm) or severe pain at the injection site, the subject/legally acceptable representative/parent/legal guardian will telephone the study site. In the event that the subject/legally acceptable representative/parent/legal guardian does not call, the investigator will call the subject/legally acceptable representative/parent/legal guardian.
b. Grade 4 assessment for local reactions should be made by the investigator and recorded as an AE on the CRF.

Reporting Summaries:

- Summary of Subjects Reporting Local Reactions by Maximum Severity Grade of the Reaction

  The number of subjects reporting "yes" for at least 1 day or "no" for all days (these values are used as the denominators for the percentage calculations), number of subjects reporting at least 1 occurrence of the specified reaction or any reaction by the maximum severity grade, observed proportion of subjects, and their exact 2-sided CIs (Clopper and Pearson).

  The above is repeated for moderate or severe reactions.

Analysis Specifications

The severity (grading) scales for redness and swelling are different between subjects 6 to <12 years of age and 12 to <18 years of age. The age-appropriate grading scale will be used for each subject, and the combined data will be summarized as the 6- to <18-year age group.

For each local reaction on any day, Table 5 provides the algorithm to derive the presence of a reaction (yes or no) during Day 1 to Day 7 (6- to <18-year age group) or Day 14 (18- to <65-year age group) following vaccination, where Day 1 is the day of vaccination.

Table 5. Derived Variables for Each Local Reaction Within the Time Interval

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Day 1 to Day 7 or 14)	Subject reports the specific reaction in the required interval.	Subject reports the specific reaction as none (or absent) for all days in the required interval.	Subject reports the specific reaction as a combination of none and missing for all days in the required interval.

a. The variable will be derived for each of the local reactions and (redness, swelling, and pain at the injection site) and for each of the severe or greater local reactions within Day 1 to Day 7 or 14 following vaccination.

For any local reaction on any day, a similar rule applies as specified in Table 6:

Table 6. Derived Variables for Any Local Reaction Within the Time Interval

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Day 1 to Day 7 or 14)	Subject reports any reaction as yes (or present) on any day in the required interval.	Subject reports all reactions as none (or absent) for all days in the required interval.	Subject reports all reactions as a combination of none and missing for all days in the required interval.

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 7 or 14 following vaccination.

Other Reporting Summaries:

- Subjects Reporting the Specific Reaction or Any Local Reaction on Each Day

  The number of subjects reporting "yes" for at least 1 day or "no" for all days (these values are used as the denominators for the percentage calculations), number of subjects reporting at least 1 occurrence of the specified reaction or any reaction for that day (and any day), and observed proportion of subjects.

  The above is repeated for moderate or severe reactions.

- Duration (Days) of Local Reactions

  The number of subjects reporting "yes" for at least 1 day or "no" for all days, number of subjects reporting the specified reaction, mean, range (minimum, maximum), standard deviation, and number of unknown durations.

Analysis Specifications

The number of subjects reporting the specified reaction, mean, range (minimum, maximum), and standard deviation will be calculated from the number of subjects reporting the specified reaction.

The duration of the specified 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 the last day on which the reaction is recorded in the e-diary if the reaction lasted 7 days (6- to <18-year age group) or 14 days (18- to <65-year age group) or less, or the date on which the reaction ended if it continued beyond Day 7 or 14 (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will be missing (unknown). Subjects with no reported reaction have no duration because it is not applicable.

- Duration (Total Days) of Local Reactions

The number of subjects reporting "yes" for at least 1 day or "no" for all days, number of subjects reporting the specified reaction, mean, range (minimum, maximum), standard deviation, and number of unknown durations.

Analysis Specifications

The number of subjects reporting the specified reaction, mean, range (minimum, maximum), and standard deviation will be calculated from the number of subjects reporting the specified reaction.

The total days will be calculated as the sum total of reported days of the specified reaction. However, if the reaction continues beyond Day 7 or 14, the calculation of total days will include all days from the last e-diary day until the date of resolution collected on the CRF. If there is no known date when the reaction ended, then duration beyond Day 7 or 14 will be missing (unknown). Subjects with no reported reaction have no duration because it is not applicable.

- Summary of Day of Onset of Local Reactions

The number of subjects reporting the specified reaction or any reaction, mean, range (minimum, maximum), and standard deviation.

Analysis Specifications

For the onset day of the specified reaction, if subjects report change in severity 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.

Figures:

A bar graph showing the percent incidence for the specified reaction and for any reaction, by day. These summaries will be compiled for each age category in addition to each age group.

6.1.1.2. Systemic Events

Note: Systemic events include fever, fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain. Fever is discussed further in Section 6.1.1.3. Use of antipyretic/pain medication is discussed in Section 6.1.1.4.

Endpoints: Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events.

- Analysis time points: The 7-day period (6- to <18-year age group) and 14-day period (18- to <65-year age group) following study vaccination.
- Analysis population: Safety population (additional handling is the same as that for local reactions in Section 6.1.1.1).

For each systemic event, severity will be derived by the maximum severity grade of the event based on the severity grading scale in Table 7.

Table 7. Systemic Event Grading Scale (for All Age Groups and Categories)

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe	GRADE 4[b]
Fatigue (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
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	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

Abbreviation: CRF = case report form.

a. When subjects experience severe systemic events, the subject/legally acceptable representative/parent/legal guardian will telephone the study site. In the event that the subject/legally acceptable representative/parent/legal guardian does not call, the investigator will call the subject/legally acceptable representative/parent/legal guardian.

b. Grade 4 assessment for systemic events should be made by the investigator and recorded as an AE on the CRF.

Reporting Summaries:

For each systemic event, the below summary tables will be generated following the same rules as for local reactions in Section 6.1.1.1, where applicable:

- Summary of Subjects Reporting Systemic Events by Maximum Severity Grade of the Events
- Subjects Reporting the Specific Event or Any Systemic Event on Each Day
- Duration (Days) of Systemic Events
- Duration (Total Days) of Systemic Events
- Summary of Day of Onset of Systemic Events

6.1.1.3. Fever

Analysis time points and the analysis population will be the same as for systemic events in Section 6.1.1.2.

Axillary temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 8 below. Fever is defined as an axillary temperature of ≥37.5°C.

Table 8. Scale for Fever

37.5 to 38.4°C
38.5 to 38.9°C
39.0 to 40.0°C
>40.0°C

Reporting Summaries:

For fever, summaries will be included in tables for systemic events following the same rules as for local reactions in Section 6.1.1.1, where applicable.

6.1.1.4. Use of Antipyretic/Pain Medication

Analysis time points and the analysis population will be the same as for systemic events in Section 6.1.1.2.

Reporting Summaries:

For use of antipyretic and/or pain medication, summaries will be included in tables for systemic events following the same rules as for local reactions in Section 6.1.1.1, where applicable.

6.1.1.5. Adverse Events

Endpoints: Number and proportion of subjects reporting AEs and SAEs categorized according to MedDRA.

- Analysis time points: From the time of informed consent through and including Visit 2
- Analysis population: Safety Population
- Subgroups: For all ages and each age group (6 to <18 years old and 18 to <65 years old)

Reporting Summaries:

- Adverse Events Reported After Study Vaccination

  The sample size, number and percentage of subjects reporting at least 1 event of each preferred term, arranged by system organ class with the associated Clopper-Pearson 95% CI, and number of occurrences of the event.

The below summary tables will be generated in the same way as the summary above. For death, only number and percentage of subjects reporting death will be summarized:

- Related Adverse Events Reported After Study Vaccination
- Serious Adverse Events Reported After Study Vaccination
- Related Serious Adverse Events Reported After Study Vaccination
- Severe Adverse Events Reported After Study Vaccination
- Related Severe Adverse Events Reported After Study Vaccination
- Life-Threatening Adverse Events Reported After Study Vaccination
- Related Life-Threatening Adverse Events Reported After Study Vaccination
- Adverse Events Leading to Discontinuation Reported After Vaccination
- Related Adverse Events Leading to Discontinuation Reported After Vaccination
- Immediate Adverse Events Reported After Vaccination (Immediate adverse events stand for events occurred during 30-minutes postvaccination observation)
- Related Immediate Adverse Events Reported After Vaccination
- Deaths During the Study Period
- Related Deaths During the Study Period

6.2. Secondary Endpoints (Immunogenicity)

- Serotype-specific OPA GMTs 1 month after vaccination in all age groups.
- GMFRs in serotype-specific OPA titers from before vaccination to 1 month after vaccination in all age groups.
- Serotype-specific IgG GMCs 1 month after vaccination in all age groups.
- GMFRs in serotype-specific IgG from before vaccination to 1 month after vaccination in all age groups.

6.2.1. Serotype-Specific OPA Titers

Endpoints: Serotype-specific OPA GMTs

- Analysis time points: Baseline and 1 month after vaccination
- Analysis populations: Evaluable immunogenicity population (primary analysis population for immunogenicity) and all-available immunogenicity population
- Subgroups: For all ages and each age group (6 to <18 years old and 18 to <65 years old)

Reporting Summaries:

- Pneumococcal OPA GMTs

  Number of subjects with a determinate OPA titer to the specified serotype at the specified blood draws, GMT, and their 2-sided 95% CIs.

Endpoints: Serotype-specific OPA GMFRs

- Analysis time points: Baseline and 1 month after vaccination
- Analysis populations: Evaluable immunogenicity population and all-available immunogenicity population
- Subgroups: For all ages and each age group (6 to <18 years old and 18 to <65 years old)

Reporting Summaries:

- Pneumococcal OPA GMFRs

  Number of subjects with valid and determinate assay results for the specified serotype at both baseline and 1 month after vaccination, GMT, GMFR, and their 2-sided 95% CIs.

Other Endpoints: Serotype-specific OPA ≥4-fold Rise

- Analysis time points: Baseline and 1 month after vaccination
- Analysis populations: Evaluable immunogenicity population and all-available immunogenicity population
- Subgroups: For all ages and each age group (6 to <18 years old and 18 to <65 years old)

Reporting Summaries:

- Subjects Achieving a ≥4-Fold Rise in OPA Titers

Number of subjects with determinate fold rise to the specified serotype, number and proportion of subjects achieving a 4-fold rise in OPA titers for the specified serotype from before vaccination to 1 month after vaccination, and exact 2-sided CIs (Clopper and Pearson) based upon the observed proportion of subjects.

Other Endpoints: Serotype-specific OPA ≥ LLOQ

- Analysis time points: Baseline and 1 month after vaccination
- Analysis populations: Evaluable immunogenicity population and all-available immunogenicity population
- Subgroups: For all ages and each age group (6 to <18 years old and 18 to <65 years old)

Reporting Summaries:

- Proportions of Subjects With OPA Titers ≥ LLOQ

  Number of subjects with determinate OPA titers to the specified serotype, number and proportion of subjects with an OPA titer ≥ LLOQ to the specified serotype, and exact 2-sided CIs (Clopper and Pearson) based upon the observed proportion of subjects.

Figures:

The RCDC plot to show the percentage of subjects achieving a given OPA titer for each serotype.

6.2.2. Serotype-Specific IgG Concentrations

Endpoints: Serotype-specific IgG GMCs, serotype-specific IgG GMFRs, and serotype-specific IgG ≥4-fold Rise

The below summary tables and figures will be generated following the same rules as for OPA titers in Section 6.2.1:

Reporting Summaries and Figures:

- Pneumococcal IgG GMCs
- Pneumococcal IgG GMFRs
- Subjects Achieving a ≥4-Fold Rise in IgG Concentration
- RCDC plot

6.3. Other Endpoints

N/A.

6.4. Subset Analyses

N/A.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct and Subject Disposition

The number of subjects who were screened, who were screen failures, and the number and percentage of subjects who were enrolled, who were vaccinated, who completed the 1-month blood draw, and who were withdrawn before the 1-month blood draw and the reasons for withdrawal/discontinuation from the study will be tabulated for each age group and for all ages, and for each age category. The denominator for the percentage calculations is the total enrolled number of subjects for each group or category. In addition, the number and percentage of subjects who had a pregnancy, who had a medication error, and who completed at least 1 procedure for each visit will be tabulated. The reasons for withdrawal will be those specified in the database; no rewording/recoding of the reason for withdrawal will be performed.

6.5.2. Baseline Summaries (Demographic, Medical History)

The demographic characteristics to be summarized are sex, race, ethnicity, smoking status, and age at the time of vaccination (in years). For sex, race, smoking status, and ethnicity, the summary statistics will be the number and percentage of subjects for each age group and for all ages. For age at the time of vaccination, the mean, median, minimum, maximum, and standard deviation will be provided for each age group and for all ages. These tabulations will be performed for the analysis populations described in Section 4.

Baseline medical history information will be summarized and categorized according to 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 age group and for all ages. These tabulations will be performed for all enrolled subjects.

6.5.3. Physical Examination

Baseline physical examination information will be summarized. The number and percentage of subjects with each type of finding (subcategories: normal, abnormal, or not performed) for the physical examination will be tabulated for each age group and for all ages. This tabulation will be performed for the safety population.

6.5.4. Immunogenicity Blood Samples Drawn

The number and percentage of subjects receiving study vaccination and providing blood samples within the protocol-specified time frame will be tabulated for each age group and for all ages. This tabulation will be performed for subjects who received study vaccination.

6.5.5. Prior and Concomitant Nonstudy Vaccinations

Any nonstudy vaccines received from 6 months prior to study enrollment until completion of study participation will be categorized according to the World Health Organization (WHO) Drug Dictionary. Each vaccine will be summarized according to the Anatomic Therapeutic Chemical (ATC) 4 class. The number and percentage of subjects receiving each vaccine will be tabulated for each age group and for all ages. These tabulations will be performed for all enrolled subjects.

6.5.6. Immunosuppressive Drugs, Immune-Modifying Drugs, and/or Monoclonal Antibody

Any immunosuppressive drugs, immune-modifying drugs, and/or monoclonal antibody received from 6 months prior to study enrollment until completion of study participation will be categorized according to the WHO Drug Dictionary. Each vaccine will be summarized according to the ATC 4 class. The number and percentage of subjects receiving each treatment will be tabulated for each age group and for all ages. In addition, the total number and percentage of subjects receiving any systemic steroids and the number and percentage of subjects receiving immunosuppressive systemic steroids (a course of systemic steroids with equivalent of ≥ 10 mg/day of prednisone or equivalent for >14 days) will be summarized separately. These tabulations will be performed for all enrolled subjects.

6.5.7. Electronic Diary Transmission and Completion

The number and percentage of subjects vaccinated, transmitting e-diaries, and transmitting and completing the e-diary for each day and all days of Day 1 to Day 7 (6- to <18-year age group) or Day 14 (18- to <65-year age group) following vaccination will be summarized and tabulated for each age group and for all ages. This tabulation will be performed for the safety population.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or to support clinical development.

8. REFERENCES

1. Collett D. *Modelling Binary Data*. London: Chapman & Hall; 1991.