Protocol C4801002

A PHASE 2, RANDOMIZED, OPEN-LABEL TRIAL TO DESCRIBE THE SAFETY AND IMMUNOGENICITY OF A MONOVALENT PNEUMOCOCCAL CONJUGATE CANDIDATE ADMINISTERED AS A 2-DOSE SERIES IN HEALTHY TODDLERS 11 THROUGH 15 MONTHS OF AGE WHO PREVIOUSLY RECEIVED THE PCV10 PRIMARY SERIES

Statistical Analysis Plan
(SAP)

Version: 2

Date: 01 May 2024

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 23 Oct 2023	Protocol amendment 1 15 Sep 2023	N/A	N/A
2 01 May 2024	Protocol amendment 1 15 Sep 2023	Exploratory immunological assays may be performed after the final study results are generated. Other minor updates were incorporated for clarity on the supplementary and sensitivity analyses and on the conduct of the study analyses.	Removed the analyses based on data from the exploratory immunological assays for the following exploratory endpoints (Sections 2.2, 3.3, and 6.3): • IgG and IgM subclass concentrations. • Relative dissociation rate of total serum antibodies measuring avidity of antibodies to antigen. • Serum IgG response to carrier protein. Added language to Section 3.1.1 to specify that related AEs that are considered local reactions be included in the reactogenicity reporting if the participant has e-diary data transmitted for at least 1 day. In Section 4, clarified that the mITT population requires at least 1 dose of the study intervention. Added language in Section 6.1.1.2 to include by-day reactogenicity graphs. Added unplanned assessment data in Section 6.1.1.3. Added language to Section 6.1.2.3 to include a sensitivity analysis for AEs leading to discontinuation. Updated the language in Section 6.5.1.1 from "age at informed consent" to "age at Dose 1". Updated the ATC fourth-level classification to WHODD in Section 6.5.4. Removed analysis of immunogenicity results through Visit 2 (1 month after Dose 1) in Section 7.2.1.

2. INTRODUCTION

This SAP provides detailed methodology for summary and statistical analyses of the data collected in Study C4801002.

2.1. Modifications to the Analysis Plan Described in the Protocol

The exploratory endpoints, estimands, and corresponding analyses are specified in the SAP.

2.2. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
	Primary Objectives:	**Primary Endpoints:**	**Primary Estimands:**
Safety	To describe the safety profile of the mPnC candidate administered as a 2-dose series in children ≥11 to ≤15 months of age	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs	In participants receiving at least 1 dose of the study intervention from each group, the percentage of participants reporting: • Prompted local reactions within 7 days after each dose • Prompted systemic events within 7 days after each dose • AEs from Dose 1 through 1 month after Dose 2 • SAEs from Dose 1 through 1 month after Dose 2
	Secondary Objectives:	**Secondary Endpoints:**	**Secondary Estimands:**
Immunogenicity	To describe the immune responses elicited by the mPnC candidate	• IgG concentrations for the candidate serotype	In participants in compliance with the key protocol criteria (evaluable participants) from each group: • Pneumococcal IgG GMCs 1 month after Dose 1 and 1 month after Dose 2 • Percentages of participants with predefined IgG concentration 1 month after Dose 1 and 1 month after Dose 2 • Pneumococcal IgG GMFRs from before Dose 1 to 1 month after Dose 1 and from 1 month after Dose 1 to 1 month after Dose 2
		• OPA titers for the candidate serotype	In participants in compliance with the key protocol criteria (evaluable participants) from each group: • Pneumococcal OPA GMTs 1 month after Dose 1 and 1 month after Dose 2 • Pneumococcal OPA GMFRs from before Dose 1 to 1 month after Dose 1 and from 1 month after Dose 1 to 1 month after Dose 2

Type	Objectives	Endpoints	Estimands
	Exploratory Objectives:	**Exploratory Endpoints:**	**Exploratory Estimands:**
Immunogenicity	CCI		

The estimands corresponding to each primary and secondary objective are described in the table above. The estimands to evaluate each immunogenicity objective will be based on the evaluable immunogenicity population (Section 4). The estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedule and protocol requirements as directed.

2.3. Study Design

This is a Phase 2, multicenter, randomized, open-label study to describe the safety and immunogenicity of an mPnC candidate as a 2-dose series in healthy toddlers 11 through 15 months of age. This study will be conducted at investigator sites in the EU. Approximately 100 children between 11 and 15 months of age who previously received the 2-dose PCV10 infant primary series as part of their routine vaccines will be enrolled. Participants will be enrolled and randomized in a 1:1 ratio by site-based randomization to receive either the mPnC candidate or the control (mPnC control) as a 2-dose series at Visit 1 and Visit 3 (~2 months after Dose 1); participants will receive the same study intervention (either mPnC candidate or mPnC control) for both doses. Participants will be observed for 30 minutes after each dose. Participants will also receive their toddler (third) dose of PCV10 concomitantly at Visit 1.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose.
- Systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) within 7 days after each dose.

- AEs from Dose 1 through 1 month after Dose 2.
- SAEs from Dose 1 through 1 month after Dose 2.

3.1.1. Local Reactions and Systemic Events

The local reactions, including redness, swelling, and pain at the injection site, and the systemic events, including fever, decreased appetite, drowsiness/increased sleep, and irritability, are reported in the e-diary from Day 1 through Day 7 after each dose, where Day 1 is the day of study intervention administration at each dose. Besides the events collected in the e-diary, related AEs recorded on the AE CRF that are considered local reactions or any AEs (related or not) that are considered systemic events, starting within 7 days after study intervention will be included in the reactogenicity reporting if the participant has e-diary data transmitted for at least 1 day. This section describes derivations with details for the assessment of reactogenicity data: severity level, onset day, and duration.

Severity and Maximum Severity

The definitions for reactogenicity severity collected from the e-diary and from CRFs are described in Appendix 2.

For each local reaction or systemic event, the maximum severity grade will be derived as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after each dose (Day 1 through Day 7) among severity grades reported for that local reaction or systemic event.

If a local reaction or systemic event is captured in more than 1 data source, eg, the e-diary, unplanned assessments, and/or the AE CRF, the highest grade across all sources will be used in the summary.

Onset Day

The onset day of each local reaction or systemic event will be derived. Onset day is defined as the first day of reporting the reaction or event with any severity after each dose.

Duration (First to Last Day Reported)

The duration (days) of each local reaction or systemic event will be calculated as the number of days from the start of the first reported reaction or event to the resolution of the last reported reaction or event, inclusive, after study intervention administration. For a reaction or event collected in the e-diary, the resolution is defined as the last day on which the reaction or event is recorded in the e-diary if the reaction or event lasted 7 days or less, or defined as the day on which the reaction or event ended beyond Day 7 (the latter will be collected on the CRF). For a reaction or event collected on the AE CRF, the AE end date will be considered the resolution date.

For a reaction or event collected in multiple sources, the earliest starting date and the latest end date will be used in calculating duration. If there is no known date when a reaction or event ends, the duration will be reported as unknown or missing.

If a reaction or event after Dose 1 is ongoing at the time of Dose 2, the Dose 2 date will be used as the end date for the duration calculation for that reaction or event.

Use of Antipyretic/Pain Medication

The use of antipyretic/pain medication is also recorded in the e-diary from Day 1 through Day 7, where Day 1 is the dosing day. For the use of antipyretic/pain medication from Day 1 through Day 7, the following endpoint and variable will be derived:

- Presence (yes or no) of use of antipyretic/pain medication after each dose.

3.1.2. Adverse Events and Serious Adverse Events

AEs and SAEs will be categorized according to MedDRA terms and summarized by system organ class and preferred term at the participant level. The time period for actively eliciting and collecting AEs and SAEs for each participant begins from the time the participant provides informed consent through and including the visit occurring 1 month after the last dose. For reporting purposes, only events occurring following study intervention will be counted in the summary tables. Events occurring prior to study intervention administration will only be included in listings.

3.2. Secondary Endpoints

Blood will be collected before Dose 1 (Visit 1), approximately 1 month after Dose 1 (Visit 2), and approximately 1 month after Dose 2 (Visit 4) to assess immunogenicity. Pneumococcal IgG concentrations and OPA titers for the candidate serotype will be measured in sera collected at Visits 1, 2, and 4:

- Pneumococcal IgG concentrations 1 month after Dose 1 and 1 month after Dose 2.
- Participants with predefined IgG concentration (0.35 µg/mL) 1 month after Dose 1 and 1 month after Dose 2.
- Fold rises of pneumococcal IgG concentrations from before Dose 1 to 1 month after Dose 1 and from 1 month after Dose 1 to 1 month after Dose 2.
- Pneumococcal OPA titers 1 month after Dose 1 and 1 month after Dose 2.
- Fold rises of pneumococcal OPA titers from before Dose 1 to 1 month after Dose 1 and from 1 month after Dose 1 to 1 month after Dose 2.

IgG concentrations and OPA titers above the LLOQ are considered accurate and their quantitated values will be reported. Missing assay results will not be imputed. The handling of assay values below LLOQ is discussed in Section 5.3.

3.3. Exploratory Endpoints

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3.4. Baseline Variables

Baseline will be the measurement obtained prior to Dose 1.

3.4.1. Demographics and Medical History

The demographic variables are age at Dose 1 (in months), sex (male or female), race (Black/African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, multiracial, and not reported), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported). In cases where more than 1 category is selected for race, the participant will be counted under the category "multiracial" for analysis.

Medical history will be categorized according to MedDRA.

3.4.2. Concomitant Vaccines and Concomitant Medications

The name and date of administration for all nonstudy vaccinations received from 28 days prior to Visit 1 through Visit 4, and medications taken to treat SAEs from the time of signing of the ICD through Visit 4, will be collected and recorded on the CRF.

Concomitant vaccines and concomitant medications will be coded using the WHODD.

3.5. Other Safety Endpoints

Primary safety endpoints are described above in the Primary Endpoints — Safety section (Section 3.1). This section describes supportive safety endpoints.

Supportive AE endpoints include related AEs, severe AEs, immediate AEs, and AEs leading to discontinuation. Immediate AEs are those occurring within the first 30 minutes after each dose. The time period for collecting all supportive AE endpoints begins from the time the participant provides informed consent through 1 month following the last dose. For reporting purposes, only events occurring following Dose 1 will be counted in the summary tables. Events occurring prior to Dose 1 will only be in listings.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database for the first planned analysis, and classifications will be documented per standard operating procedures. The populations are defined below:

Participant Analysis Set	Description
Screened	All participants whose parents/legal guardian sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Dose 1 evaluable immunogenicity	All participants who: 1. are eligible and randomized, 2. receive the study intervention to which they are randomized, 3. have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 1, and 4. have no other major protocol deviations as determined by the clinician up to the 1-month post–Dose 1 visit. The Dose 1 evaluable immunogenicity population will be the primary analysis population for the immunogenicity results before Dose 1 and 1 month after Dose 1. Participants will be grouped on a randomized basis.
Dose 2 evaluable immunogenicity	All participants who: 1. are eligible and randomized, 2. receive both doses of study intervention to which they are randomly assigned, 3. have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 2, and 4. have no other major protocol deviations as determined by the clinician. The Dose 2 evaluable immunogenicity population will be the primary analysis population for the immunogenicity results at 1 month after Dose 2. Participants will be grouped as randomized.
mITT immunogenicity	All randomized participants who receive at least 1 dose of the study intervention and have at least 1 valid immunogenicity result after study intervention administration. Participants will be grouped as randomized.
Safety	All participants who receive at least 1 dose of the study intervention. Participants will be grouped as administered.

For the Dose 1 and Dose 2 evaluable immunogenicity population definitions, the blood collection window has been expanded by 1 extra day before, and 14 days after, the protocol-specified blood collection window of 28 to 42 days as defined in the protocol, for consistency with established rules in the 13vPnC and 20vPnC development programs.

For determination of the evaluable immunogenicity populations, items 1 through 3 above will be computerized checks of the data, while item 4 will be determined by clinical review. A major protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant 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 participants with major protocol deviations before any analysis specified in Section 7.2.1 is performed.

Reactogenicity results (local reactions and systemic events) after a specified dose will be reported for all participants in the safety population who have any e-diary data collected after the specified dose.

5. GENERAL METHODOLOGY AND CONVENTIONS

Methodology for summary and statistical analyses of the data collected in this study is described here. In general, the study data will be summarized by study intervention group. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level.

For all immunogenicity endpoints, the analysis will be primarily based on the evaluable immunogenicity populations. An additional analysis will be performed based on the mITT population if there is a large enough difference (>10%) in the numbers of participants included between the mITT and the evaluable immunogenicity populations. Participants will be summarized according to the study intervention group to which they were randomized.

The safety analyses are based on the safety population. Participants will be summarized according to the study interventions they received.

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study. All statistical analyses are descriptive and for estimation purpose.

5.2. General Methods

5.2.1. Analysis 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 2-sided 95% CIs where applicable.

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

5.2.2. Analysis for Continuous Data

5.2.2.1. Descriptive Statistics

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

5.2.2.2. Geometric Mean

The GM for each group will be calculated as the mean of the logarithmically transformed assay results and then exponentiating the mean. The 2-sided 95% CI will be obtained by exponentiating the limits of the CI for the mean of the logarithmically transformed assay results based on the t distribution.

5.2.2.3. Geometric Mean Fold Rise

Fold rise is the change in the assay results from an earlier time point to a later time point. The GMFR will be calculated as the mean of the difference of antibody levels (later time point - earlier time point) on the natural log scale and then exponentiating the results. The 2-sided 95% CIs will be obtained by exponentiating the limits of the CIs for the mean difference of the logarithmically transformed assay results based on the t distribution. Only data from participants with nonmissing assay results at both time points will be included in the GMFR calculation.

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs for immunogenicity results will be plotted as a step function of the proportion of participants with the assay results equal to or exceeding a specified value over the full range of the observed assay results.

5.3. Methods to Manage Missing Data

In evaluations, missing reactogenicity e-diary data will not be imputed. A partial AE start date (missing day, missing both month and day) will be imputed by assigning the earliest possible start date using all available information, such as the stop date of the AE and the administration date(s) from the same participant, following the Pfizer standard of handling incomplete AE start dates. A completely missing start date for an AE is not allowed in data collection. No other missing information will be imputed in the safety analysis.

Serology result values that are designated as serum QNS, IND, or "not done" will be set to missing. No imputation will be done for these missing values. Missing serology results will not be imputed. Assay results above the LLOQ will be reported, but results that are below the LLOQ, or BLQs, will be set to 0.5 × LLOQ.

The LLOQ and LOD (when applicable) for each assay will be provided by the laboratory performing the assays prior to any statistical analysis of assay results.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Local Reactions and Systemic Events

6.1.1.1. Main Analysis

- Estimands:
  - The percentages of participants reporting local reactions (pain at the injection site, redness, and swelling) within 7 days after each dose (Section 3.1.1).
  - The percentages of participants reporting systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) within 7 days after each dose (Section 3.1.1).
- Analysis set: Safety population with any e-diary data reported after each dose (Section 4).
- Analysis time point: Day 1 through Day 7 after each dose.
- Analysis methodology: Descriptive summary statistics (Section 5.2.1).
- Reporting results: The numerator (n) and denominator (N, defined as the number of participants who received the specific dose in the safety population and had any e-diary data reported after the specific dose) used for the calculation of the percentages. The percentages, and the associated 2-sided Clopper-Pearson 95% CI will be presented, by group and severity, for the following variable:
  - Maximum severity of each and any local reaction or systemic event on any day (Day 1 through Day 7) after each dose.

6.1.1.2. Supplementary Analyses

As supplementary analyses to support the assessment of local reactions or systemic events, the following endpoints (as defined in Section 3.1.1) may be summarized (provided data are not sparse) with the same analysis time point and analysis population:

- Duration (days) of each local reaction or systemic event after each dose.
- Onset day of each local reaction or systemic event after each dose.

These continuous endpoints will be summarized by displaying the n, mean, median, standard deviation, minimum, and maximum for each group.

Descriptive summary statistics for use of antipyretic/pain medication after each dose (see Section 3.1.1) will be provided for each group: n, N, percentage, and 2-sided 95% CI.

Figures

Bar charts with the percentages of participants for each local reaction or systemic event on each and any day (Day 1 through Day 7) after each dose will be plotted for each vaccine group, with different patterns displayed in the bar charts for different severity levels (each day) and different maximum severity levels (any day), respectively.

6.1.1.3. Sensitivity Analysis

Summary of local reactions and systemic events by maximum severity is also assessed using the e-diary and unplanned assessment data only.

6.1.2. Adverse Events

6.1.2.1. Main Analysis

- Estimand: The percentages of participants reporting AEs (excluding reactogenicity events collected on the AE CRF that are included in the local reaction or systemic event summary) from Dose 1 through 1 month after Dose 2 (Section 3.1.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 through 1 month after Dose 2.
- Analysis methodology: Descriptive summary statistics (Section 5.2.1).
- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% Clopper-Pearson CI for participants reporting any AE, by system organ class and preferred term, will be presented for each group.

6.1.2.2. Supplementary Analyses

- Estimand: The percentages of participants reporting supportive AEs (excluding reactogenicity events collected on the AE CRF that are included in the local reaction or systemic event summary): immediate AEs, related AEs, severe AEs, and AEs leading to discontinuation (Section 3.5).
- Analysis set: Safety population (Section 4).
- Analysis time points: From study intervention administration through 30 minutes after for immediate AEs; and Dose 1 through 1 month after Dose 2 for related AEs, severe AEs, and AEs leading to discontinuation.
- Analysis methodology: Descriptive summary statistics (Section 5.2.1).

- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% Clopper-Pearson CI for participants reporting any supportive AE, by system organ class and preferred term, will be presented for each group.

6.1.2.3. Sensitivity Analysis

- Sensitivity analyses on any AEs, immediate AEs, and AEs leading to discontinuation will be conducted by using all AEs collected on the AE CRF.

6.1.3. Serious Adverse Events

- Estimand: The percentages of participants reporting SAEs from Dose 1 through 1 month after Dose 2 (Section 3.1.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 through 1 month after Dose 2.
- Analysis methodology: Descriptive summary statistics (Section 5.2.1).
- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% Clopper-Pearson CI for participants reporting any SAE, by system organ class and preferred term, will be presented for each group.

6.2. Secondary Endpoints

6.2.1. Pneumococcal IgG Concentrations

- Estimand: IgG GMCs 1 month after Dose 1 and 1 month after Dose 2 (Section 3.2).
- Analysis sets: Dose 1 and Dose 2 evaluable immunogenicity populations (Section 4).
- Analysis time points: 1 Month after Dose 1 and 1 month after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.2.2).
- Reporting results: n, GMC, and the corresponding 2-sided 95% CI at each analysis time point will be presented for each group.

Figures

Empirical RCDCs will be provided for the pneumococcal IgG concentrations for each group.

6.2.2. Participants With Predefined IgG Concentrations

- Estimand: Percentage of participants with predefined IgG concentrations 1 month after Dose 1 and 1 month after Dose 2 (Section 3.2).
- Analysis sets: Dose 1 and Dose 2 evaluable immunogenicity populations (Section 4).
- Analysis time points: 1 Month after Dose 1 and 1 month after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.1).
- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% Clopper-Pearson CI for participants with predefined IgG concentrations will be presented for each group.

6.2.3. Fold Rise in IgG Concentrations

- Estimand: GMFRs in IgG concentrations from Dose 1 to 1 month after Dose 1, and from 1 month after Dose 1 to 1 month after Dose 2 (Section 3.2).
- Analysis sets: Dose 1 evaluable immunogenicity population for GMFR from before Dose 1 to 1 month after Dose 1; Dose 2 evaluable immunogenicity population for GMFR from 1 month after Dose 1 to 1 month after Dose 2 (Section 4).
- Analysis time points: From Dose 1 to 1 month after Dose 1 and from 1 month after Dose 1 to 1 month after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.2.3).
- Reporting results: n, GMFRs, and the corresponding 2-sided 95% CIs will be presented for each group.

6.2.4. Pneumococcal OPA Titers

- Estimand: Pneumococcal OPA GMTs 1 month after Dose 1 and 1 month after Dose 2 (Section 3.2).
- Analysis sets: Dose 1 and Dose 2 evaluable immunogenicity populations (Section 4).
- Analysis time point: 1 Month after Dose 1 and 1 month after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.2.2).
- Reporting results: n, GMTs, and the corresponding 2-sided 95% CIs will be presented for each group.

Figures

Empirical RCDCs will be provided for the pneumococcal OPA titers for each group.

6.2.5. Fold Rise in OPA Titers

- Estimand: GMFRs in OPA titers from Dose 1 to 1 month after Dose 1, and from 1 month after Dose 1 to 1 month after Dose 2 (Section 3.2).
- Analysis sets: Dose 1 evaluable immunogenicity population for GMFR from before Dose 1 to 1 month after Dose 1; Dose 2 evaluable immunogenicity population for GMFR from 1 month after Dose 1 to 1 month after Dose 2 (Section 4).
- Analysis time points: From Dose 1 to 1 month after Dose 1 and from 1 month after Dose 1 to 1 month after Dose 2.
- Analysis methodology: Descriptive statistics (Section 5.2.2.3).
- Reporting results: n, GMFRs, and the corresponding 2-sided 95% CIs will be presented for each group.

6.3. Exploratory Endpoints

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6.4. Subset Analyses

Not applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age at Dose 1, sex, race, and ethnicity, will be summarized using descriptive statistics for each group and overall for the safety population and evaluable immunogenicity populations.

6.5.1.2. 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 participants with at least 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized by study intervention group and overall for the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who received study intervention, who completed the study, and who withdrew from the study, along with the reasons for withdrawal, and timing will be tabulated by study intervention group (according to randomized group assignment) and overall. The reasons for withdrawal will be those as specified on the CRFs.

Randomized participants excluded from the safety or immunogenicity analysis populations will also be summarized separately, along with reasons for exclusion, by study intervention group.

6.5.2.2. E-Diaries

The numbers and percentages of participants not transmitting the e-diary, transmitting the e-diary for each day, and transmitting the e-diary for all days in the required reporting period after each dose will be summarized according to the study intervention actually received. The safety population will be used for the summary of e-diary data transmission.

6.5.3. Study Intervention Exposure (Timing and Administration)

The number and percentage of participants randomized and receiving each study intervention within the protocol-specified time frame will be tabulated for each group and overall for all randomized participants. A listing of participants who received a study intervention other than that which they were randomized to receive will be produced, if any such incorrect dosing occurs. A listing of participants showing the randomized intervention and the intervention actually received will be presented.

6.5.4. Prior/Concomitant Vaccinations and Concomitant Medications

Each prior/concomitant vaccine will be summarized according to the WHODD preferred term. The number and percentage of participants receiving each concomitant vaccine after study intervention administration will be tabulated for each group for all participants in the safety population. Similar summarization will be done separately for concomitant medications received.

6.6. Safety Summaries and Analyses

Summaries and analyses of the safety endpoints are described under Primary Endpoints (see Section 6.1).

7. INTERIM ANALYSES

7.1. Introduction

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 for supporting clinical development. In addition, immunogenicity data may be analyzed when available.

7.2. Interim Analyses

No interim analysis will be conducted for this study.

7.2.1. Analysis Timing

Statistical analyses will be carried out as specified below:

- Analysis of safety data through Visit 2 (1 month after Dose 1);
- Final analysis of safety and immunogenicity, including complete IgG and OPA results available after the completion of the study and any available exploratory endpoint data.

Immunogenicity data reviews by the sponsor may be conducted any time the data are available to aid in decision-making for the sponsor programs.

Certain analyses may be combined if the data become available around the same time.

Additional analyses may be conducted or combined if required for regulatory purposes or for further clinical evaluation of the study intervention.

8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

9. APPENDICES

Appendix 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 quantitation
CI	confidence interval
CRF	case report form
e-diary	electronic diary
EU	European Union
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
IgG	immunoglobulin G
IND	indeterminate
IRT	interactive response technology
LLOQ	lower limit of quantitation
LOD	limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
mPnC	monovalent pneumococcal conjugate
N/A	not applicable
OPA	opsonophagocytic activity
PCV10	10-valent pneumococcal conjugate vaccine
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
WHODD	World Health Organization Drug Dictionary

Appendix 2. Reactogenicity Data Consolidation

For reactogenicity collected in the e-diary, redness and swelling will be measured and recorded in measuring device (caliper) units, and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 2. The systemic events of fever, decreased appetite, drowsiness/increased sleep, and irritability will be assessed by participants as mild, moderate, or severe according to the grading scale in Table 3.

A Grade 4 local reaction or systemic event, which can only be classified by an investigator and then collected as an AE on the CRF, will be reported as a Grade 4 reactogenicity event in the data summary.

For reactogenicity collected on the AE CRF, the grading scales will be based on the AE intensity scale in Table 4.

Table 2. Grading Scales for Local Reactions Collected From the E-Diary

Local Reaction	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Redness	1 to 4 caliper units (measuring device units) = >0 to 2.0 cm	5 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
Swelling	1 to 4 caliper units (measuring device units) = >0 to 2.0 cm	5 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
Pain at injection site (tenderness)	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched, with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe injection site pain (tenderness)

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. Parents/legal guardians of participants experiencing Grade 3 local reactions are required to contact the investigator site. In the event that the participant's parent(s)/legal guardian does not call, the investigator will call the participant's parent(s)/legal guardian. An unscheduled visit may be required.
b. Grade 4 assessment should be made by the investigator; Grade 4 local reactions will not be collected in the e-diary but will be collected as AEs on the CRF. The intensity of the local reaction should be graded using the AE intensity grading scale.

Table 3. Grading Scales for Systemic Events Collected From the E-Diary

Systemic Event	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Decreased appetite (loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to feed	Emergency room visit or hospitalization for severe decreased appetite (loss of appetite)
Drowsiness (increased sleep)	Increased or prolonged sleeping bouts	Slightly subdued, interfering with daily activity	Disabling, not interested in usual daily activity	Emergency room visit or hospitalization for severe drowsiness (increased sleep)
Irritability (fussiness) (synonymous with restless sleep; decreased sleep)	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted	Emergency room visit or hospitalization for severe irritability (fussiness)

a. Grade 4 assessment should be made by the investigator; Grade 4 systemic events will not be collected in the e-diary but will be collected as AEs on the CRF. The intensity of the systemic event should be graded using the AE intensity grading scale.

Table 4. Assessment of AE Intensity Grade

Grade	Description	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.

Fever

Temperature will be collected in the evening daily for 7 days following each dose (Days 1 through 7) and at any time during the 7 days that fever is suspected. The highest temperature for each day will be recorded in the e-diary. In the event of an ongoing fever on Day 7, the temperature will be collected daily until the fever has resolved in order to collect a stop date on the CRF. A participant's parent(s)/legal guardian will be prompted to contact the study site if the participant experiences a fever >104.0°F (>40.0°C). 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. Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 5 for summary of maximum temperature. If a fever was reported on the AE CRF within 7 days and no temperature was captured on the CRF or in the e-diary, the fever will be mapped to the ranges based on the AE intensity.

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[a]
>40.0°C[a]

Note: Fever is defined as temperature ≥38.0°C based on e-diary data or indicated on the CRF within 7 days after administration.

a. Participants reporting a fever >104.0°F (>40.0°C) will be prompted to contact the study site.

If a local reaction or systemic event is captured in more than 1 data source, eg, the e-diary, unplanned assessments, and/or AE CRF, the highest grade will be used in the safety summary analysis.

Any reactogenicity events collected on the AE CRF from participants who do not have any e-diary data collected will be included in the AE/SAE summary as appropriate, not in the summary of local reactions or systemic events.

Document Approval Record

Document Name:	C4801002 Statistical Analysis Plan Clean Copy, V2, 01 May 2024
Document Title:	A PHASE 2, RANDOMIZED, OPEN-LABEL TRIAL TO DESCRIBE TH E SAFETY AND IMMUNOGENICITY OF A MONOVALENT PNEUMO COCCAL CONJUGATE CANDIDATE ADMINISTERED AS A 2-DOSE SERIES IN HEALTHY TODDLERS 11 THROUGH 15 MONTHS OF A GE WHO PREVIOUSLY RECEIVED THE PCV10 PRIMARY SERIES

Signed By:	Date(GMT)	Signing Capacity
PPD	01-May-2024 18:30:38	Final Approval