Protocol B7471010

A PHASE 3, SINGLE-ARM, MULTICENTER TRIAL TO DESCRIBE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN PNEUMOCOCCAL VACCINE–NAÏVE ADULTS ≥18 YEARS OF AGE IN INDIA

Statistical Analysis Plan (SAP)

Version: **1**

Date: **23 May 2023**

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 23 May 2023	1 22 December 2022	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471010. 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. Modifications to the Analysis Plan Described in the Protocol

There are no changes in the analysis plan from the description in the protocol.

2.2. Study Objectives, Endpoints, and Estimands

The endpoints and estimands corresponding to each primary, secondary, and exploratory objective are described in Table 2.

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:		
Safety		
To describe the safety profile of 20vPnC when administered to adults ≥18 years of age in India	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) • AEs • SAEs	In participants receiving the single dose of study intervention and having safety follow-up after vaccination, the percentage of participants reporting (by age cohort): • Prompted local reactions within 7 days after vaccination • Prompted systemic events within 7 days after vaccination • AEs within 1 month after vaccination • SAEs within 1 month after vaccination

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Secondary:		
Immunogenicity		
To describe the immune response to 20vPnC	Pneumococcal serotype-specific OPA titers	In participants in compliance with the key protocol criteria (evaluable participants) receiving 20vPnC (by age cohort): • GMFR in OPA titers from before vaccination to 1 month after vaccination
Exploratory:		
Immunogenicity		
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2.3. Study Design

This Phase 3, single-arm, multicenter study will be conducted at investigator sites in India. The purpose of this study is to assess the safety and immunogenicity of 20vPnC in adults ≥18 years of age.

Approximately 400 eligible adults ≥18 years of age will be vaccinated with 20vPnC.

Participants will be assigned to 2 cohorts by age (approximately 200 participants per cohort): 18 to 49 years of age and ≥50 years of age. The first 50 participants in each age cohort will be enrolled in the immunogenicity subset (with a study total of 100 participants). Participants in the immunogenicity subset will have blood drawn for immunogenicity assessments prior to vaccination and at approximately 1 month after vaccination (blood will be drawn in the first approximately 50 participants in each age cohort [18 to 49 years of age and ≥50 years of age] for a study total of approximately 100 participants [approximately 25% of all participants]). The 20vPnC will be prepared and administered by an appropriately qualified investigator site staff member. Participants will be observed for 30 minutes after vaccination, and any reactions occurring during that time will be recorded as AEs.

Each participant will participate in the study for approximately 1 month. Based on an estimated enrollment timing, the study duration will be approximately 4 months.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Prompted local reactions (redness, swelling, and pain at the injection site).
- Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain).
- AEs.
- SAEs.

3.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 through Day 7, where Day 1 is the day of vaccination. This section describes derivations with details for the assessment of local reactions: severity level, duration, and onset day.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device (caliper) units (range: 1 to 21), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 3. 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 participant as mild, moderate, or severe according to the grading scale in Table 3.

Table 3. Grading Scales for Local Reactions in Study Participants

Local Reaction	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3[a] Severe	GRADE 4[b]
Redness	5 to 10 measuring device units = >2.0 to 5.0 cm	11 to 20 measuring device units = >5.0 to 10.0 cm	>20 measuring device units = >10.0 cm	Necrosis or exfoliative dermatitis
Swelling	5 to 10 measuring device units = >2.0 to 5.0 cm	11 to 20 measuring device units = >5.0 to 10.0 cm	>20 measuring device units = >10.0 cm	Necrosis
Pain at injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity[c]	Emergency room visit or hospitalization for severe pain at injection site

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. Participants experiencing Grade 3 local reactions are required to contact the investigator site. In the event that the participant does not call, the investigator will call the participant.
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, and intensity should be graded using the AE intensity grading scale in Section 10.2.3 of the protocol.
c. Prevents daily activity, eg, results in missed days of work 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 7, where Day 1 is the day of vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades reported for that local reaction in the e-diary.

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3.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fever, fatigue (tiredness), headache, muscle pain, and joint pain from Day 1 through Day 7, where Day 1 is the day of vaccination. The derivations for systemic events will be handled similarly to the way local reactions are handled: severity level, duration, and onset day.

The systemic events of fatigue, headache, muscle pain, and joint pain will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 4. Grade 4 systemic events will not be collected in the e-diary but will be collected as an AE on the CRF. The event will be graded using the AE severity grading scale.

Table 4. Grading Scales for Systemic Events

Systemic Event	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe[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

a. Prevents daily routine activity, eg, results in missed days of work or is otherwise incapacitating; includes use of narcotics for analgesia.
b. 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 in the CRF. The severity of the systemic event should be graded using the AE severity grading scale as per the protocol Section 10.2.

Fever

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.

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

Note: Fever is defined as a temperature of ≥38.0°C.

a. Participants reporting a fever >39.0°C will be prompted to contact the study site.

3.1.3. Adverse Events

AEs will be categorized according to MedDRA terms. AEs will be assessed from the time of informed consent through 1 month after vaccination.

AE reporting will be based on the specific reporting period. Missing AE start dates will be imputed following the Pfizer data standard rules as described in Section 5.3.

3.1.4. Serious Adverse Events

SAEs will be categorized according to MedDRA terms. SAEs will be collected from the time of informed consent through the end of the study (1 month after vaccination).

3.2. Secondary Endpoint

- Pneumococcal serotype-specific OPA titers before and 1 month after vaccination.

OPA titers for each pneumococcal serotype will be determined for each participant in the immunogenicity subset (approximately 50 participants in each age cohort) using the Luminex assay and Pfizer's OPA assay, both before vaccination and 1 month after vaccination. Fold changes in OPA titers will be calculated for each participant by taking the ratio of OPA titers 1 month after vaccination to before vaccination.

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3.4. Baseline Variables

Measurements or samples collected before vaccination are considered the baseline data for the assessments.

3.4.1. Demographics and Medical History

The demographic variables are age at vaccination (in years), sex (male or female), race (Black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, White, not reported, and unknown), ethnicity (Hispanic/Latino or of Spanish origin and non-Hispanic/non-Latino), height, weight, and racial designation (Indian Subcontinent Asian, Southeast Asian, Far East Asian, Japanese, Korean, Chinese, Taiwanese, and others).

Age at vaccination will be derived in years based on the participant's birthday. For example, if the vaccination date is 1 day before the participant's 18th birthday, the participant will be considered 17 years old. For participants who completed Visit 1 but did not receive the vaccine, the enrollment date will be used in place of the date of vaccination for the age calculation. If the Visit 1 date is also missing, then the informed consent date will be used for age calculation.

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. E-Diary Transmission

An e-diary will be considered transmitted if any data for the local reactions and systemic events are present for any day.

3.4.3. Concomitant Vaccines and Medications

Specific concomitant vaccines will be collected as indicated in the protocol and recorded in the CRF. Concomitant medications will be recorded only if they are used to treat SAEs. Concomitant vaccines and medications will be coded using the WHO DDE.

3.5. Safety Endpoints

Local reactions, systemic events, AEs, and SAEs have been described above in the primary endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety results in the table below.

Population	Description
Enrolled in the study	All participants who signed an ICD.
Assigned to study intervention	All participants who are assigned an enrollment number in the IWR system.
Safety	All participants who receive any study intervention and have safety data assessed after vaccination.
Evaluable immunogenicity	All eligible participants in the immunogenicity subset who receive 1 dose of the study intervention with at least 1 valid immunogenicity result from the blood sample collection within 27 to 49 days after vaccination and have no other major protocol deviations as determined by the clinician.
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E-diary data will be summarized among those in the safety population who report any e-diary data.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal statistical hypothesis test will be performed as this is a descriptive study. A descriptive estimation approach will be used to assess all study objectives regarding safety in the study.

Point estimates and nominal 95% CIs will be provided for all safety endpoints at each planned analysis.

5.2. General Methods

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

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

For both of the immunogenicity endpoints, the analysis will be primarily based on the evaluable immunogenicity population. CCI [redacted]

All safety and immunogenicity results will also be summarized separately for each age cohort and all participants.

5.2.1. Analyses for Binary Endpoints

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 CIs (Clopper-Pearson)[1] for the various proportions of individual groups will be computed using the F distribution.

5.2.2. Analyses for Continuous Endpoints

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

5.2.3. Geometric Mean

For immunogenicity results of serotype-specific OPA titers, the geometric mean 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 Student's t-distribution.

5.2.4. Geometric Mean Fold Rises

The OPA GMFR from before to 1 month after 20vPnC for each age cohort is defined as the geometric mean of the fold rise in the assay results. Only data from participants with nonmissing assay results at both time points will be included in the GMFR calculation.

GMFR will be calculated as the mean difference of the logarithmically transformed assay results (time point after vaccination - before vaccination) and exponentiating the mean difference. The 2-sided 95% CI will be obtained by exponentiating the limits of the CI for the mean difference of the logarithmically transformed assay results based on Student's t-distribution.

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5.3. Methods to Manage Missing Data

A partial AE start date (missing day or 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 vaccination date from the same participant, following the Pfizer standard of handling an incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection. The LLOQ for each assay will be provided by Vaccine Research and Development as part of the electronic data transfer or within the Clinical Testing Completion Memo prior to statistical analysis. Assay results above the LLOQ will be reported, and values below the LLOQ, denoted as BLQ, will be imputed as 0.5 × LLOQ for analysis.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Local Reactions

6.1.1.1. Main Analysis

- Estimands: The percentage of participants reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days after vaccination (Section 2.2).
- Analysis set: Safety population among those who report any e-diary data (Section 4).
- Analysis time point: Within 7 days after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: Count and percentage of participants with the indicated endpoint and the associated 2-sided 95% CI for each and any local reaction after vaccination will be presented by maximum severity across severity levels.

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In addition, the proportions of participants reporting prompted local reactions by maximum severity level, with e-diary errors included, will be provided as a sensitivity analysis.

Figures:

Bar charts with the proportions of participants for each local reaction on each day (Day 1 through Day 7) and any day (Day 1 through Day 7) will be plotted, with different patterns displayed in the bar charts for different severity levels for each day and different maximum severity levels for any day.

6.1.2. Systemic Events

6.1.2.1. Main Analysis

- Estimands: The percentage of participants reporting prompted systemic events (fever, fatigue, headache, muscle pain, and joint pain) within 7 days after vaccination (Section 2.2).
- Analysis set: Safety population among those who report any e-diary data (Section 4).
- Analysis time point: Within 7 days after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: Count and percentage of participants with the indicated endpoint and the associated 2-sided 95% CI for each and any systemic event after vaccination will be presented by maximum severity across severity levels.

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6.1.3. Adverse Events

6.1.3.1. Main Analysis

- Estimands: The percentage of participants reporting AEs from vaccination to 1 month after vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time points: Vaccination to 1 month after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI for participants reporting any AE, by system organ class and each preferred term within system organ class, will be presented.

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6.1.4. Serious Adverse Events

6.1.4.1. Main Analysis

- Estimands: The percentage of participants reporting SAEs from vaccination to 1 month after vaccination (Section 2.2).
- Analysis set: Safety population (Section 4).
- Analysis time point: Vaccination to 1 month after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI for participants reporting any SAEs, by system organ class and each preferred term within system organ class, will be presented.

6.1.4.2. Supplementary Analyses

All SAEs will be noted in the AE listings. SAEs will also be displayed in a separate listing.

6.2. Secondary Endpoint

6.2.1. OPA Titers

6.2.1.1. Main Analysis

- Estimand: GMFRs of pneumococcal serotype-specific OPA titers from before to 1 month after vaccination (by age cohort) (Section 2.2).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Before vaccination and 1 month after vaccination.
- Analysis methodology: The GMFR and corresponding 2-sided 95% CI will be calculated as described in Section 5.2.4.
- Reporting results: For each of the serotypes, the GMFRs and the corresponding 2-sided 95% CIs will be presented at the specified time points.

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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 vaccination, sex, race, ethnicity, height, weight, and racial designation, will be summarized for the evaluable immunogenicity population and safety population.

6.5.1.2. Medical History

Each reported medical history term will be mapped to a system organ class and preferred term according to MedDRA. The number and percentage of participants with an assigned vaccine having at least 1 diagnosis, overall and at each system organ class and preferred term level, will be summarized for the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

Disposition of participants relative to vaccination will be summarized for all participants as follows: The number and percentage of participants who receive vaccination, complete the 1-month postvaccination visit, and withdraw between vaccination and the 1-month post vaccination visit with specific reasons (participant request, lost to follow-up, AE, protocol violation, other) will be summarized by cohort and overall.

Participants excluded from the safety population will also be summarized along with the reasons for exclusion.

6.5.2.2. Blood Samples for Assay

The number and percentage of enrolled participants providing blood samples within and outside of protocol-specified time frames will be tabulated.

6.5.2.3. E-Diaries

The participants who were vaccinated and who transmitted e-diaries will be summarized. The summary will also include the number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary, and transmitting the e-diary for any day in the required reporting period, by cohort and overall.

The safety population will be used.

6.5.3. Study Intervention Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants enrolled and receiving the vaccine (20vPnC) within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each cohort for all participants. The denominator for the percentage is the total number of participants in the given cohort.

6.5.4. Concomitant Medications and Nondrug Treatments

Each concomitant vaccine will be summarized according to the ATC fourth-level classification. The number and percentage of enrolled participants receiving concomitant vaccines will be summarized by cohort and overall.

Concomitant medications used to treat SAEs will be summarized for the time of vaccination to 1 month after vaccination by cohort (safety population) and overall.

6.6. Safety Summaries and Analyses

Summaries and analyses of the safety measures, including local reactions, systemic events, AEs, and SAEs, are described in the section for the primary endpoints (see Section 6.1).

7. INTERIM ANALYSES

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCE

[1] Collett D. Statistical inference for binary data. Chapter 2. In: Modelling binary data. London, England: Chapman & Hall; 1991:17-42.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
20vPnC	20-valent pneumococcal conjugate vaccine
AE	adverse event
ATC	Anatomic Therapeutic Chemical
BLQ	below limit of quantitation
CI	confidence interval
CRF	case report form
e-diary	electronic diary
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
IWR	interactive web-based response
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
OPA	opsonophagocytic activity
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
WHO DDE	World Health Organization Drug Dictionary Enhanced

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