Protocol B1851214

A PHASE 4, OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY TO DESCRIBE THE SAFETY OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN ADULTS 18 TO 49 YEARS OF AGE IN INDIA

Statistical Analysis Plan (SAP)

Version: 1

Date: 08 Apr 2022

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 08 Apr 2022	Original	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B1851214. 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. The impacts of COVID-19 will be assessed before the first planned analysis, and the SAP will be amended accordingly to account for these impacts, if needed.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary objective are described in Table 2.

Table 2. List of Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary Safety	**Primary Safety**	**Primary Safety**
To describe the safety profile of 13vPnC when administered to adults 18 to 49 years of age	• 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: • 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

2.2. Study Design

This is a Phase 4, open-label, single-arm, multicenter study in which participants 18 to 49 years of age will receive a single intramuscular administration of 13vPnC. This study will be conducted in India.

Approximately 200 participants will be vaccinated.

Each participant will participate in the study for approximately 1 month. Based on an estimated enrollment timing, the study duration will be approximately 5 months.

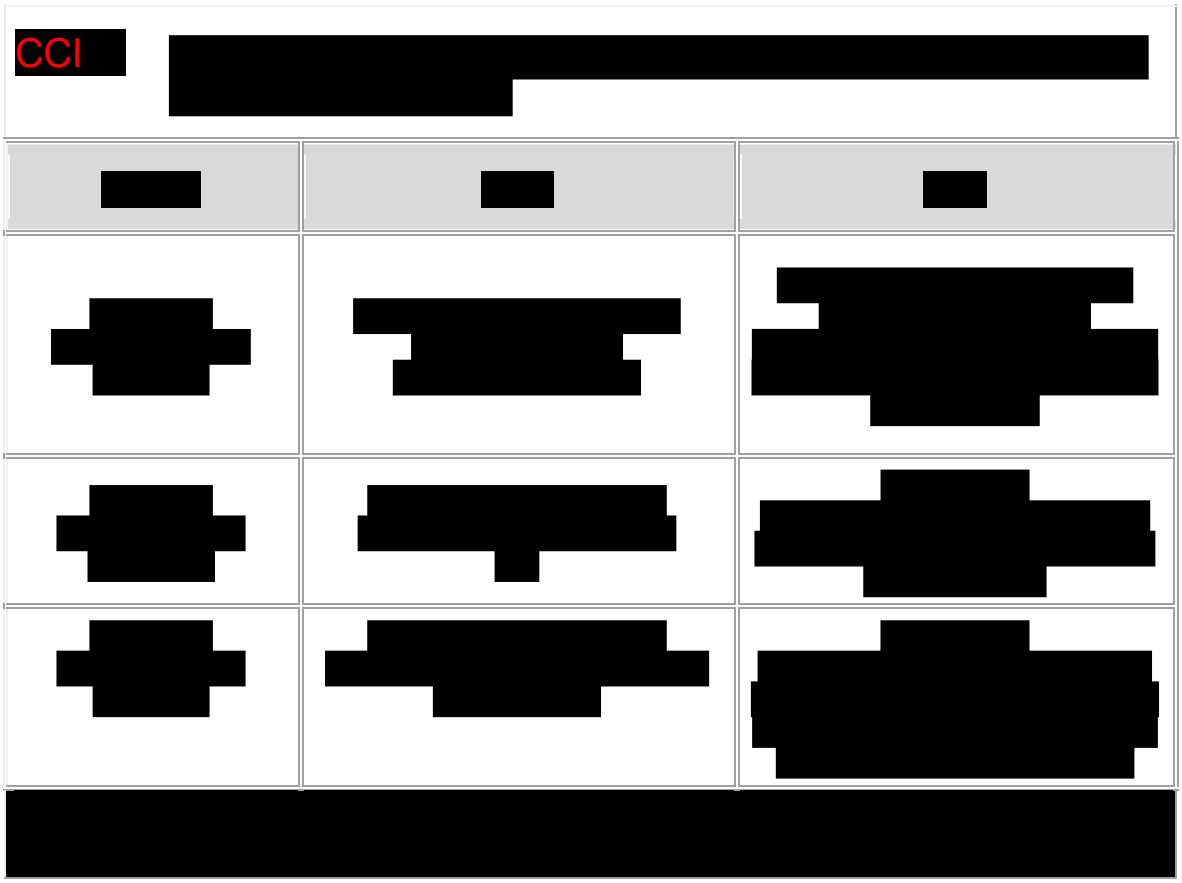
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- 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. CCI



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 4. 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 4.

Table 4. 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

Abbreviation: CRF = case report form.
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 10.3 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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[redacted]

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[redacted]

[redacted]

3.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fatigue (tiredness), headache, muscle pain, and joint pain. CCI [redacted]

The systemic events of fatigue, headache, muscle pain, and joint pain will be assessed by participant as mild, moderate, or severe according to the grading scale in Table 5. 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 5. Grading Scales for Systemic Events

Systemic Event	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4[a]
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

Abbreviation: CRF = case report form.

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 in the CRF. The severity of the systemic event should be graded using the AE severity grading scale.

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 6.

Table 6. Ranges for Fever

≥38.0°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C

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

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 end of the study.

3.2. Secondary Endpoint(s)

Not applicable.

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[redacted]

3.4. Baseline Variables

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

3.4.1. Demographics, Medical History, and Physical Examination

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), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and of Spanish origin). 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.

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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.
Safety	All participants who receive any study intervention and have safety data assessed after vaccination.

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.

Time points for local reactions and systemic events refer to data within 7 days after vaccination.

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level.

5.2.1. Analyses for Binary Endpoints

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.

5.3. 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(s) from the same participant, following the Pfizer standard of handling incomplete AE start date. A complete missing start date for an AE is not allowed in the data collection.

Methods for handling missing local reactions and systemic events are described in Section 3.1.1 and Section 3.1.2, respectively.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Local Reactions

6.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days after vaccination (Section 2.1).
- 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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6.1.2. Systemic Events

6.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting prompted systemic events (fatigue, headache, muscle pain, and joint pain) within 7 days after vaccination (Section 2.1).
- 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 percentages of participants reporting AEs from vaccination to 1 month after vaccination (Section 2.1).
- 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 each system organ class and each preferred term within system organ class.

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[redacted]

[redacted]

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 2.1).
- 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 each system organ class and each preferred term within system organ class, will be presented.

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6.2. Secondary Endpoint(s)

Not applicable.

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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, and ethnicity will be summarized for the 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 after vaccination visit, and withdraw between vaccination and the 1 month after vaccination visit with specific reasons (participant request, lost to follow-up, failed to return, AE, protocol violation, other) will be summarized.

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

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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 (13vPnC) within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for all participants. The denominator for the percentages is the total number of participants.

6.5.4. Concomitant Medications and Nondrug Treatments

Each concomitant vaccine will be summarized according to the ATC 4th level classification. The number and percentage of enrolled participants receiving concomitant vaccines will be summarized.

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

6.6. Safety Summaries and Analyses

Summaries and analyses of the safety measures, local reactions, systemic events, AEs, and SAEs, are described under the Primary Endpoints (see Section 6.1).

7. INTERIM ANALYSES

No interim analysis is planned in this study. Statistical analyses will be carried out at the completion of the study.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

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
13vPnC	13-valent pneumococcal conjugate vaccine
AE	adverse event
ATC	Anatomic Therapeutic Chemical
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
ICD	informed consent document
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
SAE	serious adverse event
SAP	statistical analysis plan
WHO DDE	World Health Organization Drug Dictionary Enhanced