Protocol B7471013

A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY INFANTS

Statistical Analysis Plan (SAP)

Version: 1

Date: 30 Oct 2020

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

[redacted]

[redacted]

CCI

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 30 Oct 2020	Original protocol 19 Feb 2020	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471013. 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 prior to 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 CCI objective are described in Table 2. The estimands to evaluate the safety objectives are based on the safety population (see Section 4 for definition). These estimands estimate the safety profile of 20vPnC from participants in the study who receive at least 1 dose of 20vPnC with safety data.

In the safety objective evaluations, missing AE start dates will be imputed according to Pfizer safety rules (Section 5.3). No other missing information will be imputed in the safety analysis.

Table 2. List of Primary, Secondary, CCI Objectives, Endpoints, and Estimands

Primary Safety Objective	Primary Safety Estimands	Primary Safety Endpoints
• To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product with safety follow-up after any vaccination: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after each vaccination in each group • The percentage of participants reporting AEs from Dose 1 through 1 month after Dose 3 in each group	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs

[redacted]

[redacted]

Table 2. List of Primary, Secondary, CCI Objectives, Endpoints, and Estimands

Primary Safety Objective	Primary Safety Estimands	Primary Safety Endpoints
	• The percentage of participants reporting AEs from Dose 4 through 1 month after Dose 4 in each group • The percentages of participants reporting SAEs up to 6 months after Dose 4 in each group • The percentages of participants reporting NDCMCs up to 6 months after Dose 4 in each group	

CCI

2.2. Study Design

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in the United States and potentially other countries to be determined.

Approximately 1500 infants ≥42 to ≤98 days of age at the time of consent, by their parent(s)/legal guardian(s), will be enrolled. Participants will be randomized in a 2:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at 2, 4, 6, and 12 to 15 months of age (Doses 1, 2, 3, and 4, respectively) by center-based randomization. Participants will receive the same vaccine (20vPnC or 13vPnC) for all 4 doses.

Participants will be observed for 30 minutes after each vaccination and any reactions occurring during that time will be recorded as AEs. Prompted local reactions (redness, swelling, and pain at the 20vPnC or 13vPnC injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and use of antipyretic/pain medications occurring within 7 days after each vaccination will be collected via a provided e-diary (or e-diary application). AEs, including nonserious AEs, will be collected from the signing of informed consent through 1 month after Dose 3 and from Dose 4 through 1 month after Dose 4. SAEs and NDCMCs will be collected for the entire duration of the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

- Prompted local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose
- Prompted 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 3 and from Dose 4 through 1 month after Dose 4
- SAEs during the study (from Dose 1 through 6 months after Dose 4)
- NDCMCs during the study (from Dose 1 through 6 months after Dose 4)

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the 20vPnC or 13vPnC injection site, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. CCI [redacted]

CCI [redacted]

[redacted]

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device (caliper) units (range: 1 to >14; an entry in the e-diary of 15 will denote >14), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 4. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF. 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's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scale in Table 4.

Table 4. Grading Scales for Local Reactions

Local Reaction	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3[a] Severe	GRADE 4[b]
Redness	1 to 4 caliper units (or 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 (or 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 pain (tenderness) 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. Parents/legal guardians of the participants experiencing local reactions >14 caliper units (>7.0 cm) are to be contacted by the study site. An unscheduled visit may be required.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

For each local reaction after each dose, 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 each dose) 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.

[redacted]

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary are fever, decreased appetite, drowsiness/increased sleep, and irritability from Day 1 through Day 7, where Day 1 is the day of each dose. [redacted] Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 6 for summary of maximum temperature.

The systemic events of decreased appetite, irritability, and drowsiness/increased sleep will be assessed by participants' parents/legal guardians as mild, moderate, or severe according to the grading scale in Table 5. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

Table 5. Grading Scales for Systemic Events

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)

Table 5. Grading Scales for Systemic Events

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

Abbreviation: CRF = case report form.

a. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

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.

CCI

[redacted]

3.1.1.4. Adverse Events

AEs will be categorized according to MedDRA terms. AEs will be assessed from the time of informed consent through 1 month after Dose 3 and from Dose 4 through 1 month after Dose 4.

The primary endpoint "AEs from Dose 1 through 1 month after Dose 3" and "from Dose 4 through 1 month after Dose 4" and other supportive AE endpoints will be summarized by system organ class and preferred term on a participant level.

This primary endpoint will be supported by summaries and listings of related AEs, severe AEs, and immediate AEs (within the first 30 minutes after each dose).

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.

A 3-tier approach will be used to summarize AEs from Dose 1 through 1 month after Dose 3 and, separately, from Dose 4 through 1 month after Dose 4. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.1.1.3.1).

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's Safety Review Plan. No Tier 1 events have been identified to date for 20vPnC.

- Tier 2 events: These are events that are not Tier 1, but are "relatively common." A MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants with the AE term in at least 1 vaccine group.

- Tier 3 events: These are events that are neither Tier 1 nor Tier 2.

3.1.1.5. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

SAEs and NDCMCs will be categorized according to MedDRA terms. NDCMCs and SAEs will be collected from the signing of the ICD through the end of the study.

3.2. Secondary Endpoints

Not applicable.

CCI

[redacted]

3.4. Baseline and Other Variables

Measurements or samples collected prior to Dose 1 are considered the baseline data for the assessments.

3.4.1. Demographics and Medical History

The demographic variables are age at Dose 1 (in days), sex (male or female), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white, multiracial, and not reported), country/region, gestational age, ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported), and racial designation (Indian subcontinent Asian, Southeast Asian, Japanese, Korean, Chinese, African, African-Caribbean, Australian aboriginal, Torres Strait Islander, other). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis. Age at Dose 1 in days will be derived as (Dose 1 date – date of birth + 1).

For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of Dose 1 for age calculation. If the randomization date is also missing, then the informed consent date will be used for age calculation.

Medical history will be categorized according to MedDRA.

CCI [redacted]

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

The name, date of administration, and site of administration for all vaccinations given on the same day as investigational product administration (Visits 1, 2, 3, and 5) will be summarized. At Visit 1, information on prior vaccinations received by the participant will be summarized.

Concomitant medications will be recorded only if they were used to treat SAEs and NDCMCs. Concomitant and prior vaccines and concomitant medications will be coded using the WHO Drug Dictionary.

3.5. Safety Endpoints

Local reactions, systemic events, AEs, SAEs, and NDCMCs have been described above (Section 3.1.1) in the primary safety endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Analysis populations are defined for the statistical analysis of safety results in the table below. Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database for analysis, and the classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Safety	All participants who receive at least 1 dose of the investigational product with safety follow-up after any dose. Participants will be grouped according to the vaccine as administered in the safety analysis. Safety data after Dose 4 will be summarized for the subset of the safety population who also receive Dose 4 with safety follow-up after Dose 4.

5. GENERAL METHODOLOGY AND CONVENTIONS

Analysis of safety data through 1 month after Dose 4 (see Section 7.2) may be carried out for all participants when data are available and released. For this reason, the study team will be unblinded after the last participant completes Visit 6 (1 month after Dose 4) and the database snapshot has been taken. The investigator site staff will remain blinded to participant vaccine group until the last participant completes the final visit (Visit 7) and the database has been locked for final analysis.

5.1. Hypotheses and Decision Rules

There is no formal hypothesis test and all statistical analyses will be descriptive.

5.2. General Methods

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

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

5.2.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CI where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[1] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen[2] method.

The 3-tier approach will be used to summarize AEs. For both Tier 1 (if any are identified during the study) and Tier 2 events, a 95% CI for the between-group difference in proportions will be calculated based on the Miettinen and Nurminen method. In addition, for Tier 1 events (if any), the asymptotic p-values will also be presented for the difference in proportions, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. For Tier 3 events, counts and percentages for each vaccine group will be provided.

5.2.2. Analyses for Continuous Data

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, 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. An AE with a completely missing start date is not allowed in the data collection.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

Results from local reactions after each dose (Dose 1, Dose 2, Dose 3, and Dose 4) will be summarized separately.

6.1.1.1.1. Main Analysis

- Estimand: The percentage of participants reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after each dose.
- Analysis methodology: The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1) for each reaction.
- Intercurrent events and missing data: Missing values will not be imputed. CCI [redacted]

[redacted]

[redacted]

- 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 each dose in each vaccine group will be presented by maximum severity across severity levels. Between-group differences (20vPnC – 13vPnC) in these percentages and their 2-sided 95% CIs will also be provided.

CCI

[redacted]

6.1.1.2. Systemic Events

Results from systemic events after each dose (Dose 1, Dose 2, Dose 3, and Dose 4) will be summarized separately.

6.1.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting prompted systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep) within 7 days after each dose (Section 2.1).

- Analysis set: Safety population (Section 4).

- Analysis time point: Within 7 days after each dose.

- Analysis methodology: The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1) for each event.

- Intercurrent events and missing data: Missing values will not be imputed. CCI [redacted]

- 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 each dose in each vaccine group will be presented by maximum severity across severity levels. Between-group differences (20vPnC – 13vPnC) in these percentages and their 2-sided 95% CIs will also be provided.

CCI [redacted]

6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimands:

  - The percentages of participants reporting AEs from Dose 1 through 1 month after Dose 3 (Section 2.1).

  - The percentages of participants reporting AEs from Dose 4 through 1 month after Dose 4 (Section 2.1).

- Analysis set: Safety population (Section 4).
- Analysis time points: Dose 1 through 1 month after Dose 3, Dose 4 through 1 month after Dose 4.
- Analysis methodology: 3-Tiered approach as described in Section 5.2.1.
- Intercurrent events and missing data: No missing values will be imputed except for partial AE start dates (Section 5.3).
- Reporting results: For all 3 tiers, 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, each system organ class, and each preferred term within system organ class will be presented by vaccine group.

  In addition, for AEs classified as Tier 2 events, the differences in percentages (20vPnC – 13vPnC) and associated 2-sided 95% CIs will be provided.

  Further, for Tier 1 events, if any are identified, the difference in percentages, the associated 2-sided 95% CI for the risk difference, and the asymptotic p-values will also be provided.

CCI

[redacted]

[redacted]

6.1.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

6.1.1.4.1. Main Analyses

- Estimands:
  - The percentage of participants reporting SAEs from Dose 1 through 6 months after Dose 4 (Section 2.1).
  - The percentage of participants reporting NDCMCs from Dose 1 through 6 months after Dose 4 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 through 6 months after Dose 4.
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: No missing values will be imputed except for partial SAE/NDCMC start dates (see Section 5.3).
- 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/NDCMCs, each system organ class, and each preferred term within system organ class will be presented by vaccine group. SAEs and NDCMCs will be presented separately. There will be a listing of all AEs, including SAEs and NDCMCs, and a separate listing of SAEs only.

CCI

[redacted]

6.2. Secondary Endpoints

Not applicable.

CCI

[redacted]

[redacted]

CCI

[redacted]

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

6.4.1.1. Demographic Characteristics

Demographic characteristics, including age at each dose, sex, race, ethnicity, racial designation, country/region, and gestational age, will be summarized for the safety population for each vaccine group and overall. Similar summaries will be done for the randomized population.

6.4.1.2. 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 by vaccine group for the safety population.

6.4.2. Study Conduct and Participant Disposition

6.4.2.1. 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 each vaccination (Dose 1, 2, 3, or 4), who completed the follow-up visits (1 month after Dose 3, 1 month after Dose 4), who completed the 6-month telephone contact, who completed all visits, who withdrew before the visit 1 month after Dose 3, who withdrew after the visit 1 month after Dose 3 but prior to Dose 4, who withdrew after Dose 4 but before the visit 1 month after Dose 4, and who withdrew after the visit 1 month after Dose 4, along with the reasons for withdrawal, will be tabulated by vaccine group (according to randomized group assignment). The reasons for withdrawal will be those as specified in the database.

Randomized participants excluded from the safety analysis population will also be summarized separately, along with the reasons for exclusion, by vaccine group.

CCI

[redacted]

[redacted]

6.4.3. Study Vaccination Exposure

6.4.3.1. Vaccination Timing and Administration

For each dose, the number and percentage of participants randomized and receiving each investigational product (20vPnC or 13vPnC), as well as the corresponding concomitant vaccines, will be tabulated for each vaccine group and overall for all randomized participants. The denominator for the percentage calculations is the total number of randomized participants in the given vaccine group or overall. A listing of participants who received a vaccine other than what they were randomized to receive will be produced, if any such incorrect dosing occurs.

A listing of participants showing the randomized vaccine and the vaccine actually received (20vPnC or 13vPnC) at each dose will be presented.

6.4.4. Prior/Concomitant Vaccination and Concomitant Medications Used to Treat SAEs and NDCMCs

Each prior/concomitant vaccine will be summarized according to the ATC fourth-level classification. The prior/concomitant vaccine received before Dose 1 will be listed. The number and percentage of randomized participants receiving each vaccine after Dose 1 will be tabulated according to vaccine group for all randomized participants. Summarization will be done separately for concomitant vaccines received:

- with Dose 1, Dose 2, Dose 3, or Dose 4, separately
- between Dose 1 and 1 month after Dose 3
- between 1 month after Dose 3 and Dose 4
- between Dose 4 and 1 month after Dose 4

Concomitant medications used to treat SAEs and NDCMCs will be summarized from Dose 1 through the 6-month follow-up telephone contact. The safety population will be used.

6.5. Safety Summaries and Analyses

Summaries and analyses of the safety measures local reactions, systemic events, AEs, SAEs, and NDCMCs are described under Primary Safety Endpoints (see Section 6.1.1).

7. INTERIM ANALYSES

No interim analysis is planned in this study. Statistical analyses will be carried out when the final data for the specified analyses are available.

CCI

[redacted]

[redacted]

7.1. Introduction

Not applicable.

7.2. Analysis Timings

Statistical analyses are planned to be carried out when the final data for the specified analyses are available:

- Primary Analysis 1: Safety data through the visit occurring 1 month after Dose 4 from all participants may be analyzed by the study team when available (at which time the study team will be unblinded).

- Final Analysis: Safety data from 1 month after Dose 4 through the visit occurring 6 months after Dose 4 from all participants.

The study team will remain blinded up to Primary Analysis 1, if it is undertaken; otherwise, they will be blinded until the last participant completes the study. The investigator site staff will remain blinded to participant vaccine group until the last participant completes the final visit telephone call.

8. REFERENCES

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

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
13vPnC	13-valent pneumococcal conjugate vaccine
20vPnC	20-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
CCI	[redacted]
ICD	informed consent document
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
SAE	serious adverse event
SAP	statistical analysis plan
WHO	World Health Organization