Protocol B7471014

A PHASE 3, SINGLE-ARM TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY CHILDREN 15 MONTHS THROUGH 17 YEARS OF AGE

Statistical Analysis Plan
(SAP)

Version: 1

Date: 03 Nov 2021

PFIZER GENERAL BUSINESS

[redacted]

TABLE OF CONTENTS

LIST OF TABLES 5
APPENDICES 5
1. VERSION HISTORY 6
2. INTRODUCTION 6
2.1. Study Objectives, Endpoints, and Estimands 6
2.2. Study Design 10
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 10
3.1. Primary Endpoint(s) 10
3.1.1. Primary Safety Endpoint(s) 10
3.1.1.1. Local Reactions 11
3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever) 12
CCI [redacted]
3.1.1.4. Adverse Events 14
3.1.1.5. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions 14
3.1.2. Primary Immunogenicity Endpoint(s) 15
3.2. Secondary Endpoint(s) 15
CCI [redacted]
3.4. Baseline Variables 17
3.4.1. Demographics, Medical History and Physical Exam 17
CCI [redacted]
3.4.3. Prior/Concomitant Vaccines and Concomitant Medications 18
3.5. Safety Endpoints 18
4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS) 18
5. GENERAL METHODOLOGY AND CONVENTIONS 19
5.1. Hypotheses and Decision Rules 19
5.1.1. Cohort 1 and Cohort 2 19
5.1.2. Cohort 3 and Cohort 4 20
5.2. General Methods 20

5.2.1. Analyses for Binary Endpoints 20
5.2.2. Analyses for Continuous Endpoints 20
5.2.2.1. Geometric Mean 21
5.2.2.2. Geometric Mean Fold Rises 21
CCI [redacted]
5.3. Methods to Manage Missing Data 21
6. ANALYSES AND SUMMARIES 22
6.1. Primary Endpoint(s) 22
6.1.1. Primary Safety Endpoint(s) 22
6.1.1.1. Local Reactions 22
6.1.1.2. Systemic Events 23
6.1.1.3. Adverse Events 24
6.1.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions 25
6.1.2. Primary Immunogenicity Endpoint(s) 25
6.1.2.1. IgG Concentration 26
6.1.2.2. OPA Titers 26
6.2. Secondary Endpoint(s) 27
6.2.1. Participants With Predefined Pneumococcal Serotype-Specific IgG Concentrations at 1 Month After 20vPnC 27
6.2.2. Participants With a ≥4-Fold Rise in Serotype-Specific OPA Titers From Before to 1 Month After 20vPnC 27
6.2.3. Pneumococcal Serotype-Specific IgG Concentrations 28
6.2.4. Fold Changes in Pneumococcal Serotype-Specific IgG Concentrations From Before to 1 Month After 20vPnC 28
6.2.5. Pneumococcal Serotype-Specific OPA Titers Before and 1 Month After 20vPnC 29
6.2.6. Fold Changes in Pneumococcal Serotype-Specific OPA Titers From Before to 1 Month After 20vPnC 29
CCI [redacted]
CCI [redacted]

CCI
[redacted]
CCI
[redacted]
6.5. Baseline and Other Summaries and Analyses 32
6.5.1. Baseline Summaries....32
6.5.1.1. Demographic Characteristics 32
6.5.1.2. Medical History....32
6.5.2. Study Conduct and Participant Disposition....33
6.5.2.1. Participant Disposition 33
6.5.2.2. Blood Samples for Assay 33
CCI
[redacted]
6.5.3. Study Vaccine Exposure....33
6.5.3.1. Vaccination Timing and Administration....33
6.5.4. Concomitant Medications and Nondrug Treatments....33
6.6. Safety Summaries and Analyses 34
7. INTERIM ANALYSES....34
7.1. Introduction....34
7.2. Interim Analyses and Summaries....34
8. REFERENCES 34
9. APPENDICES 35

LIST OF TABLES

Table 1. Summary of Changes....6
Table 2. List of Primary, Secondary [redacted] Objectives, Endpoints, and Estimands....7
Table 3. Grading Scales for Local Reactions in Study Participants....11
Table 4. Grading Scales for Systemic Events - Participants Who Are ≥15 Months to <2 Years of Age (Cohort 1)....13
Table 5. Grading Scales for Systemic Events - Participants Who Are ≥2 to <18 Years of Age (Cohorts 2-4)....13
Table 6. Ranges for Fever....14
Table 7. Predefined Pneumococcal Serotype-Specific IgG Concentrations....15

APPENDICES

Appendix 1. List of Abbreviations....35

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 03 Nov 2021	1/ 18 Oct 2021	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471014. 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, secondary CCI [redacted] objective are described in Table 2. The estimands to evaluate the immunogenicity objectives for superiority are based on the evaluable population (see Section 4 for definition). These estimands estimate vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. The estimand addresses the objective of estimating the true difference between the 2 time points within each cohort, since noncompliance may obscure the true difference in immune response between the 2 time points in each cohort. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ in the analysis.

In the primary 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.

CCI [redacted]

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

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**

• To describe the safety profile of 20vPnC	In participants from each cohort receiving 20vPnC and having safety data reported after vaccination:
	• The percentage of participants reporting prompted local reactions within 7 days after vaccination
	• The percentage of participants reporting prompted systemic events within 7 days after vaccination
	• The percentage of participants reporting AEs up to 1 month after vaccination
	• The percentage of participants reporting SAEs up to 6 months after vaccination
	• The percentage of participants reporting NDCMCs up to 6 months after vaccination
		• Prompted local reactions (redness, swelling, and pain at the injection site)
		• Prompted systemic events:
		  • **Cohort 1**: Fever, decreased appetite, drowsiness/increased sleep, and irritability
		  • **Cohorts 2 through 4**: Fever, fatigue, headache, muscle pain, and joint pain
		• AEs
		• SAEs
		• NDCMCs

Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
Cohort 1 and Cohort 2: To demonstrate that the serotype-specific IgG concentrations for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding IgG concentrations before 20vPnC	In participants in compliance with the key protocol criteria (evaluable participants): • GMFRs of serotype-specific IgG concentrations for the 7 additional serotypes from before to 1 month after vaccination	• Pneumococcal serotype-specific IgG concentrations
Cohort 3 and Cohort 4: To demonstrate that the serotype-specific OPA titers for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding OPA titers before 20vPnC	In participants in compliance with the key protocol criteria (evaluable participants): • GMFRs of serotype-specific OPA titers for the 7 additional serotypes from before to 1 month after vaccination	• Pneumococcal serotype-specific OPA titers

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

Objectives	Estimands	Endpoints
Secondary Immunogenicity	**Secondary Immunogenicity**	**Secondary Immunogenicity**
• To further describe the immune responses to 20vPnC in Cohorts 1, 2, 3, and 4	In evaluable participants: • Percentage of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes at 1 month after vaccination in Cohort 1 only • Percentage of participants with a ≥4-fold rise in serotype-specific OPA titers for the 7 additional serotypes from before to 1 month after vaccination in Cohorts 2, 3, and 4 only • Serotype-specific IgG GMCs for the 20vPnC serotypes before and 1 month after vaccination • GMFRs of serotype-specific IgG concentrations for the 13vPnC serotypes from before to 1 month after vaccination (in Cohorts 1 and 2) • GMFRs of serotype-specific IgG concentrations for the 20vPnC serotypes from before to 1 month after vaccination (in Cohorts 3 and 4) • Serotype-specific OPA GMTs for the 20vPnC serotypes before and 1 month after vaccination • GMFRs of serotype-specific OPA titers for the 20vPnC serotypes from before to 1 month after vaccination (in Cohorts 1 and 2) • GMFRs of serotype-specific OPA titers for the 13vPnC serotypes from before to 1 month after vaccination (in Cohorts 3 and 4)	• Pneumococcal serotype-specific IgG concentrations • Pneumococcal serotype-specific OPA titers

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

Objectives	Estimands	Endpoints
CCI		

Abbreviations: GMC = geometric mean concentration, GMFR = geometric mean fold rise, GMT = geometric mean titer. CCI ; NDCMC = newly diagnosed chronic medical condition.

2.2. Study Design

This Phase 3, multicenter, single-arm study will be conducted at investigator sites in the United States.

Approximately 800 children ≥15 months to <18 years of age at the time consent (and assent, if applicable) is obtained will be enrolled into 4 cohorts based on age (Cohort 1: ≥15 to <24 months, Cohort 2: ≥2 to <5 years, Cohort 3: ≥5 to <10 years, and Cohort 4: ≥10 to <18 years) and will receive a single dose of 20vPnC.

Blood will be collected prior to and 1 month after vaccination for immunogenicity assessments. Participants will be observed for 30 minutes after vaccination and any reactions occurring during that time will be recorded as AEs. Prompted local reactions (redness, swelling, and pain at the injection site), age-applicable systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability in Cohort 1; and fever, fatigue, headache, muscle pain, and joint pain in Cohorts 2-4), and use of antipyretic/pain medications will be collected via a provided e-diary (or e-diary application) daily for 7 days after vaccination. AEs will be collected from the time informed consent is obtained to 1 month after vaccination. SAEs and NDCMCs will be collected through the 6 months after vaccination.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

The primary, secondary[CCI] endpoints pertain to the vaccination with 20vPnC, as described in the objectives. Any reference to participants reporting an event in this SAP should be understood to mean parent(s)/legal guardian(s) or participant, as age appropriate, reporting the event for the participant.

3.1. Primary Endpoint(s)

3.1.1. Primary Safety Endpoint(s)

- Prompted local reactions (redness, swelling, and pain at the injection site) within 7 days of vaccination.
- Prompted systemic events within 7 days of vaccination:
  - **Cohort 1**: Fever, decreased appetite, irritability, and drowsiness/increased sleep
  - **Cohorts 2 through 4**: Fever, fatigue, headache, muscle pain, and joint pain.
- AEs from vaccination to 1 month after vaccination.
- SAEs from vaccination to 6 months after vaccination.

- NDCMCs from vaccination to 6 months after vaccination.

3.1.1.1. 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: presence, 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 >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 3 below. 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	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 cm	Necrosis or exfoliative dermatitis[b]
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 cm	Necrosis[b]
Pain at injection site (tenderness)	Cohort 1: Hurts if gently touched (eg, whimpers, winces, protests, or withdraws) Cohorts 2-4: Does not interfere with activity	Cohort 1: Hurts if gently touched with crying Cohorts 2-4: Interferes with activity	Cohort 1: Causes limitation of limb movement Cohorts 2-4: Prevents daily activity[c]	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. Parent(s)/legal guardian(s) 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 in the CRF. The severity of the local reaction should be graded using the AE grading scale in Protocol Section 10.3.4.
c. Prevents daily activity, eg, results in missed days of work or school or is otherwise incapacitating.

For each local reaction, the maximum severity grade will be derived for the e-diary collection period (Day 1 to 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.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

3.1.1.2. Systemic Events (Systemic Event Symptoms and Fever)

The systemic events assessed and recorded in the e-diary for Cohort 1 are fever, decreased appetite, drowsiness/increased sleep, and irritability from Day 1 through Day 7, where Day 1 is the day of vaccination. For Cohorts 2 through 4, the systemic events are fever, fatigue, headache, muscle pain, and joint pain. The derivations for systemic events will be handled similar to the way local reactions are handled: presence, severity level, duration, and onset day. 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 for Cohort 1 and fatigue, headache, muscle pain, and joint pain for Cohorts 2 through 4 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 or Table 5, respectively. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

Table 4. Grading Scales for Systemic Events - Participants Who Are ≥15 Months to <2 Years of Age (Cohort 1)

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

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

Table 5. Grading Scales for Systemic Events - Participants Who Are ≥2 to <18 Years of Age (Cohorts 2-4)

Systemic Event	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe[a]	GRADE 4[b]
Fatigue (= tiredness in e-diaries)	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. Prevents daily routine activity, eg, results in missed days of work or school or is otherwise incapacitating; includes use of narcotics for analgesia.

b. Grade 4 assessment should be made by the investigator. Grade 4 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.

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 a 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 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.

3.1.1.5. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

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

3.1.2. Primary Immunogenicity Endpoint(s)

- Cohorts 1 and 2: Pneumococcal serotype-specific IgG concentrations for the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) before and 1 month after 20vPnC
- Cohorts 3 and 4: Pneumococcal serotype-specific OPA titers for the 7 additional serotypes before and 1 month after 20vPnC

Concentrations of anticapsular IgG and OPA titers for each pneumococcal serotype will be determined for each participant using the Luminex assay and Pfizer's OPA assay, respectively, both before vaccination and 1 month after vaccination.

Fold changes will be calculated for each participant by taking the ratio of assay results from the later visit to the earlier visit.

3.2. Secondary Endpoint(s)

- Pneumococcal serotype-specific IgG concentrations before and 1 month after 20vPnC

To support the secondary pneumococcal immunogenicity estimands, IgG concentrations will be classified based on serotype-specific IgG reference concentrations as defined below in Table 7 for the 7 additional serotypes in Cohort 1.

Table 7. Predefined Pneumococcal Serotype-Specific IgG Concentrations

Serotypes	Reference Concentration (µg/mL)
1, 3, 4, 6A, 7F, 9V, 14, 18C, 19F, 23F	≥0.35
5	≥0.23
6B	≥0.10
19A	≥0.12
8, 10A, 11A, 12F, 15B, 22F, 33F	≥0.35
CCI [redacted]	[redacted]

Abbreviation: TBD = to be determined.

CCI [redacted]

Fold changes in IgG concentrations will be calculated for each participant by taking the ratio of assay results from the later visit to the earlier visit for the 13vPnC serotypes in Cohorts 1 and 2 and for all 20 serotypes in Cohorts 3 and 4.

- Pneumococcal serotype-specific OPA titers before and 1 month after 20vPnC
  - Fold changes in OPA titers for all 20 serotypes in Cohorts 1 and 2 and for the 13vPnC serotypes in Cohorts 3 and 4 (see Section 3.1.2 for calculations)
  - Classification of fold changes as a ≥4-fold rise for the 7 additional serotypes in Cohorts 2, 3, and 4. The 4-fold rise in OPA titers is being performed on children traditionally considered to have a more mature immune response to polysaccharide antigens (≥2 years of age)[1]

OPA titers will be determined on serum from randomly selected subsets of participants provided by the study statistician, with the exception of the 7 additional serotypes in Cohorts 3 and 4, which will be assayed for all subjects in those cohorts. Further details of the subsetting will be described in a memo.

CCI

CCI [redacted]

[redacted]

3.4. Baseline Variables

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

3.4.1. Demographics, Medical History and Physical Exam

The demographic variables are age at vaccination (in months for Cohort 1 and in years for Cohorts 2, 3, and 4), 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), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported). Age at vaccination for Cohort 1 will be derived in months as 12 × (vaccination date - date of birth + 1) / 365.25 rounded to 1 decimal place. Age at vaccination for Cohorts 2-4 will be derived in years based on the subject's birthday. For example, if the vaccination date is 1 day before the subject's 11th birthday, the subject will be considered 10 years old. For participants who did not receive a vaccine at Visit 1, 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.

CCI [redacted]

3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

Specific prior and 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 and NDCMCs. Concomitant and prior vaccines and concomitant medications will be coded using WHO DDE.

Participants' age at the time of their last 13vPnC or 7vPnC vaccination will be categorized as <1 year of age or ≥1 year of age. Additionally, time since the last 13vPnC or 7vPnC vaccination will be categorized in the following intervals: 2 to <6 months, 6 to <12 months, 1 to <5 years, 5 to <10 years, and 10 years or more.

3.5. Safety Endpoints

Local reactions, systemic events, antipyretic/pain medication, AEs, SAEs, and NDCMCs have been described above in the primary endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Population	Description
Enrolled	All participants who have a signed ICD.
Evaluable immunogenicity	All participants who: 1. Are eligible, 2. Receive 20vPnC, 3. Have at least 1 valid immunogenicity result from 1 month after vaccination collected within 27 to 56 days after vaccination for Cohorts 1-2 or within 27 to 49 days after vaccination for Cohorts 3-4, and 4. Have no other major protocol deviations as determined by the clinician The evaluable immunogenicity population will be used as the primary analysis population for the pneumococcal immunogenicity results.
CCI [redacted]	[redacted]
Safety	All participants who receive 20vPnC and have safety follow-up after vaccination.

For the evaluable immunogenicity population definition, 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, for consistency with established rules in the Prevnar 13® development program for Cohorts 1 and 2. For Cohorts 3 and 4, the window was expanded by 1 day before and 7 days after the protocol-specified blood collection window consistent with the 20vPnC adult program. A major protocol deviation is a protocol deviation that, in the opinion of the Pfizer clinician or medical monitor, 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.

CCI [redacted]

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

5.1.1. Cohort 1 and Cohort 2

For the primary immunogenicity objective, hypothesis testing will be used to assess superiority of the IgG concentrations for the 7 additional pneumococcal serotypes 1 month after 20vPnC to the IgG concentrations before 20vPnC within each cohort. The null hypothesis (H_0) for a serotype is

$$H_0: \mu_{\text{fold rise}} \leq 1.0$$

where

- $\mu_{\text{fold rise}}$ is the geometric mean of the fold rise in IgG concentration from before to 1 month after vaccination;

The null hypothesis (H_0) will be rejected for a serotype if the lower bound of the 2-sided 95% CI calculated based on the Student's t-distribution (Section 5.2.2.2) for the IgG GMFR is greater than 1.0.

5.1.2. Cohort 3 and Cohort 4

For the primary immunogenicity objective, hypothesis testing will be used to assess superiority of the OPA titers for the 7 additional pneumococcal serotypes 1 month after 20vPnC to the OPA titers before 20vPnC within each cohort. The null hypothesis (H_0) for a serotype is

$$H_0: \mu_{\text{fold rise}} \leq 1.0$$

where

- $\mu_{\text{fold rise}}$ is the geometric mean of the fold change in OPA titer from before to 1 month after vaccination;

The null hypothesis (H_0) will be rejected for a serotype if the lower bound of the 2-sided 95% CI calculated based on the Student's t-distribution (Section 5.2.2.2) for the OPA GMFR is greater than 1.0.

5.2. General Methods

Safety and immunogenicity results will be summarized separately for each cohort.

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

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

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).[2]

5.2.2. Analyses for Continuous Endpoints

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

5.2.2.1. Geometric Mean

For immunogenicity results of serotype-specific IgG concentrations and OPA titers, the GM will be computed along with associated 95% CIs. The GM and associated 2-sided 95% CI will be calculated as the mean of the assay results on the natural logarithmic scale based on the Student's t-distribution, and then exponentiating the results.

5.2.2.2. Geometric Mean Fold Rises

The GMFRs will be calculated by exponentiating the mean of the difference of logarithmically transformed assay results (later minus earlier). The associated 2-sided 95% CIs are computed by exponentiating the limits of CIs obtained using the Student's t-distribution for the mean difference on the natural log scale.

CCI [redacted]

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 data are described in Section 3.1.1.1 and Section 3.1.1.2, respectively.

The LLOQ for each assay will be provided by Vaccines 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.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Safety Endpoint(s)

6.1.1.1. Local Reactions

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 vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after vaccination.
- Analysis methodology: Descriptive statistics.
- 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 local reaction after vaccination in each cohort will be presented by maximum severity across severity levels.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

6.1.1.2. Systemic Events

6.1.1.2.1. Main Analysis

- Estimand: The percentage of participants reporting prompted systemic events (Cohort 1: fever, decreased appetite, irritability, and drowsiness/increased sleep; Cohorts 2-4: fever, fatigue, headache, muscle pain, and joint pain) within 7 days after vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Within 7 days after vaccination.
- Analysis methodology: Descriptive statistics.
- 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 vaccination in each cohort will be presented by maximum severity across severity levels.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

6.1.1.3. Adverse Events

6.1.1.3.1. 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.
- Intercurrent events and missing data: No missing values will be imputed except for partial AE start dates (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 AE, by each system organ class and each preferred term within system organ class, will be presented by cohort.

CCI [redacted]

[redacted]

[redacted]

6.1.1.4. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

6.1.1.4.1. Main Analysis

- Estimands:
  - The percentage of participants reporting SAEs from vaccination to 6 months after vaccination (Section 2.1).
  - The percentage of participants reporting NDCMCs from vaccination to 6 months after vaccination (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time points: Vaccination to 6 months 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/NDCMCs, by each system organ class and each preferred term within system organ class, will be presented by cohort. SAEs and NDCMCs will be presented separately.

CCI [redacted]

6.1.2. Primary Immunogenicity Endpoint(s)

The ordering of the pneumococcal serotypes in summaries displaying only the 7 additional serotypes will be as follows:

- 8, 10A, 11A, 12F, 15B, 22F, and 33F.

6.1.2.1. IgG Concentration

6.1.2.1.1. Main Analysis

- Estimands: For Cohorts 1 and 2, GMFRs of pneumococcal serotype-specific IgG concentrations for the 7 additional serotypes from before to 1 month after vaccination (Section 2.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Before and 1 month after vaccination.
- Analysis methodology: The GMFR and corresponding 2-sided 95% CI will be calculated as described in Section 5.2.2.2. Superiority will be declared if the lower bound of the 95% CI is greater than 1.0.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.
- Reporting results: For each of the 7 additional vaccine serotypes, the GMCs, the GMFRs, and the corresponding 2-sided 95% CIs will be presented for each cohort at the specified time points.

6.1.2.2. OPA Titers

6.1.2.2.1. Main Analysis

- Estimands: For Cohorts 3 and 4, GMFRs of pneumococcal serotype-specific OPA titers for the 7 additional serotypes from before to 1 month after vaccination (Section 2.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Before and 1 month after vaccination.
- Analysis methodology: The GMFR and corresponding 2-sided 95% CI will be calculated as described in Section 5.2.2.2. Superiority will be declared if the lower bound of the 95% CI is greater than 1.0.
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Missing data will not be imputed.
- Reporting results: For each of the 7 additional vaccine serotypes, the GMTs, the GMFRs, and the corresponding 2-sided 95% CIs will be presented for each cohort at the specified time points.

6.2. Secondary Endpoint(s)

The ordering of the pneumococcal serotypes in summaries displaying all 20 serotypes will be as follows:

- 13vPnC serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; and
- 7 Additional serotypes: 8, 10A, 11A, 12F, 15B, 22F, and 33F.

6.2.1. Participants With Predefined Pneumococcal Serotype-Specific IgG Concentrations at 1 Month After 20vPnC

- Estimands: For Cohort 1, percentages of participants with predefined serotype-specific IgG concentrations (Section 2.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time point: 1 Month after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each of the 7 additional serotypes, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI for participants with predefined IgG concentrations from each vaccine group.

6.2.2. Participants With a ≥4-Fold Rise in Serotype-Specific OPA Titers From Before to 1 Month After 20vPnC

- Estimand: In Cohorts 2, 3, and 4, percentage of participants with a ≥4-fold rise in serotype-specific OPA titers from before to 1 month after 20vPnC (Section 2.1).
- Analysis set: Evaluable immunogenicity population (Section 4) restricted to the subsets of subjects who are selected for serotype-specific OPA titers.
- Analysis time points: Before and 1 month after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each of the 7 additional serotypes, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI for participants with a ≥4-fold rise in OPA titers from each vaccine group will be presented.

6.2.3. Pneumococcal Serotype-Specific IgG Concentrations

- Estimands: For all cohorts, GMCs of pneumococcal serotype-specific IgG concentrations for the 20vPnC serotypes before and 1 month after vaccination (Section 2.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Before and 1 month after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: For the 20vPnC serotypes, the GMC and the corresponding 2-sided 95% CIs will be presented for each cohort at the specified time points.

CCI [redacted]

[redacted]

6.2.4. Fold Changes in Pneumococcal Serotype-Specific IgG Concentrations From Before to 1 Month After 20vPnC

- Estimands:
  - For Cohorts 1 and 2, GMFRs of pneumococcal serotype-specific IgG concentrations for the 13vPnC serotypes from before to 1 month after vaccination (Section 2.1).
  - For Cohorts 3 and 4, GMFRs of pneumococcal serotype-specific IgG concentrations for the 20vPnC serotypes from before to 1 month after vaccination (Section 2.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Before and 1 month after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: For each of the 13vPnC serotypes in Cohorts 1 and 2 or for each of the 20vPnC serotypes in Cohorts 3 and 4, the GMCs, the GMFRs, and the corresponding 2-sided 95% CIs will be presented for each cohort at the specified time points.

6.2.5. Pneumococcal Serotype-Specific OPA Titers Before and 1 Month After 20vPnC

- Estimands: For all cohorts, GMTs of pneumococcal serotype-specific OPA titers before and 1 month after vaccination (Section 2.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Before and 1 month after vaccination.
- Analysis methodology: Descriptive statistics.
- Reporting results: For the 20vPnC serotypes, the GMT and the corresponding 2-sided 95% CIs for serotype-specific OPA titers will be presented for each cohort at the specified time points.

CCI [redacted]

6.2.6. Fold Changes in Pneumococcal Serotype-Specific OPA Titers From Before to 1 Month After 20vPnC

- Estimands:
  - For Cohorts 1 and 2, GMFRs of pneumococcal serotype-specific OPA titers for the 20vPnC serotypes from before to 1 month after vaccination (Section 2.1).
  - For Cohorts 3 and 4, GMFRs of pneumococcal serotype-specific OPA titers for the 13vPnC serotypes from before to 1 month after vaccination (Section 2.1).
- Analysis set: Evaluable immunogenicity population (Section 4).
- Analysis time points: Before and 1 month after vaccination.
- Analysis methodology: Descriptive statistics.

Reporting results: For each of the 20vPnC serotypes in Cohorts 1 and 2 and for each of the 13vPnC serotypes in Cohorts 3 and 4, the GMTs, the GMFRs, and the corresponding 2-sided 95% CIs will be presented for each cohort at the specified time points.

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

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 and the evaluable immunogenicity population, by cohort.

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 by cohort 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 Visit 2 (1 month after vaccination), complete Visit 3 (6 months after vaccination), withdraw between vaccination and the 1 month after vaccination visit or withdraw after the 1-month vaccination visit and before Visit 3 (6 months after vaccination), and the specific reasons (parent/legal guardian request, lost to follow-up, failed to return, AE, protocol violation, other) will be summarized by cohort.

CCI [redacted]

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.

CCI [redacted]

6.5.3. Study Vaccine Exposure

6.5.3.1. Vaccination Timing and Administration

The number and percentage of participants enrolled and receiving 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 percentages is the total number of participants in the given cohort.

6.5.4. Concomitant Medications and Nondrug Treatments

Each prior/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 according to cohort.

Concomitant medications used to treat SAEs and NDCMCs will be summarized for the time of vaccination to 6 months after vaccination (safety population).

A categorical summary of participants' age at the time of their last 13vPnC or 7vPnC vaccination will be done. Participants will be categorized as <1 year of age or ≥1 year of age. Additionally, time since the last 13vPnC or 7vPnC vaccination will be summarized in the categories shown in Section 3.4.3.

6.6. Safety Summaries and Analyses

The safety measures for local reactions, systemic events, AEs, SAEs, and NDCMCs summaries and analyses are described under the Primary Endpoint(s) section (see Section 6.1).

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]

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1 Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1997;46(No. RR-8):1-24.

2 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
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
CCI	[redacted]
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
IgG	immunoglobulin G
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
OPA	opsonophagocytic activity
C	[redacted]
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
WHO DDE	World Health Organization Drug Dictionary Enhanced