Protocol B7471016

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, THIRD PARTY UNBLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY JAPANESE INFANTS

Statistical Analysis Plan
(SAP)

Version: 2

Date: 09 Jun 2022

[redacted]

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 17 Sep 2020	Original protocol 09 Jun 2020	N/A	N/A
2 09 Jun 2022	Final protocol 09 Jun 2020	Made updates for consistency across the 20vPnC pediatric program, as well as to increase clarity and correct minor errors in the original version	[redacted]

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471016. 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 any unblinded analysis, and the SAP may 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] objective are described in Table 2. The estimands to evaluate the immunogenicity objectives for NI of 20vPnC SC relative to 13vPnC SC are based on the evaluable populations (see Section 4 for definitions). These estimands estimate the 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 maximum potential difference between 2 groups, since the impact of noncompliance is likely to diminish the observed difference between the 2 groups. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ 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.

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

Primary Safety Objective	Estimands	Primary Safety Endpoints
• To describe the safety profile of 20vPnC by both SC injection and IM injection	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination: • The percentage of participants reporting prompted local reactions at injection site of investigational product 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 to 1 month after Dose 3 in each group • The percentage of participants reporting AEs from Dose 4 to 1 month after Dose 4 in each group • The percentage of participants reporting SAEs up to 1 month after Dose 4 in each group • The percentage of participants reporting NDCMCs up to 1 month after Dose 4 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

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

Primary Immunogenicity Objectives	Estimands	Primary Immunogenicity Endpoints
For 20vPnC SC group:		
• To demonstrate the percentage of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC SC group are noninferior to the percentage of the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC SC group and the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate the percentage of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest percentage among the 13 serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations, between the 20vPnC SC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
For 20vPnC IM group:		
• To describe the immune responses to 20 serotypes induced by 20vPnC given by IM injection at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC IM group and the 20vPnC SC group	• Pneumococcal serotype-specific IgG concentration

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

Secondary Immunogenicity Objectives	Estimands	Secondary Immunogenicity Endpoints
• To demonstrate the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC SC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC SC group to the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
• To demonstrate the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest IgG GMC among the 13 serotypes induced by the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC SC group to the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
• To further describe the immunogenicity of 20vPnC by both SC and IM injection	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: GMR of serotype-specific IgG concentrations from the 20vPnC IM group to the 20vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
	In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: serotype-specific IgG GMCs at 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations
	In evaluable participants at 1 month after Dose 3 and 1 month after Dose 4: • Serotype-specific OPA GMTs at 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4 in each group	• Pneumococcal serotype-specific OPA titers
	In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: percentage of participants with the predefined serotype-specific IgG concentration in each group	• Pneumococcal serotype-specific IgG concentrations

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

Secondary Immunogenicity Objectives	Estimands	Secondary Immunogenicity Endpoints
	In evaluable participants: • GMFRs in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations
CCI		

2.2. Study Design

This Phase 3, multicenter, randomized, double-blind, third-party-unblind study will be conducted at investigator sites in Japan. CCI [redacted] The purpose of this study is to describe safety and conduct the pivotal immunogenicity comparison of 20vPnC administered by SC injection to the licensed pneumococcal conjugate vaccine, 13vPnC (ie, Prevenar 13®), administered by the currently indicated SC injection in infants CCI [redacted] Data will also be generated on 20vPnC administered by IM injection, with the 20vPnC administered by SC injection as a control.

Approximately 666 infants 2 through 6 months of age at the time of consent, by their parent(s)/legal guardian(s), will be enrolled into the study. Participants will be randomized equally to one of the following vaccine groups: (1) 20vPnC SC group, (2) 13vPnC SC group (control vaccine), or (3) 20vPnC IM group. Participants will receive the same vaccine (20vPnC or 13vPnC) by the same injection method (SC or IM injection) for all 4 doses at Visits 1, 2 (4 to 8 weeks after Visit 1), 3 (4 to 8 weeks after Visit 2), and 5 (12 to 15 months of age with ≥60 days after Dose 3). All vaccine groups will be blinded to all members of the site involved in the study except unblinded site staff who will administer 20vPnC or 13vPnC.

As this study is the first study where 20vPnC is administered subcutaneously and the study participants are infants, a daily enrollment limit of ≤5 participants will be in place from study start until the study has accumulated safety data from 45 participants through 7 days of follow-up after Dose 1. These data will be carefully monitored and reviewed by the study team. If there are no safety signals in the first 45 participants after Dose 1, the daily enrollment limit will be removed.

Specific vaccines containing Hib, HBV, rotavirus, diphtheria, tetanus, acellular pertussis, and poliovirus antigens will also be administered concomitantly with Doses 1 to 3 (Visit 1, Visit 2, and Visit 3) in the upper arm or orally (in the case of rotavirus vaccine) consistent with the vaccination schedule recommended by the Japan Pediatric Society.[1] Specific vaccines containing Hib, diphtheria, tetanus, acellular pertussis, poliovirus, measles, rubella, and varicella antigens will be administered concomitantly with Dose 4 (Visit 5) in the upper arm(s) consistent with the vaccination schedule recommended by the Japan Pediatric Society. Prompted local reactions (redness, swelling, and pain at the 20vPnC SC and IM or 13vPnC SC 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 to 1 month after Dose 3 (Visit 4) and from Dose 4 (Visit 5) to 1 month after Dose 4 (Visit 6). SAEs and NDCMCs will be collected for the entire duration of the study.

Blood will be collected 1 month after Dose 3 (Visit 4), immediately prior to Dose 4 (Visit 5), and 1 month after Dose 4 (Visit 6) to assess immunogenicity.

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 to 1 month after Dose 3
- AEs from Dose 4 to 1 month after Dose 4
- SAEs during the study (from Dose 1 to 1 month after Dose 4)
- NDCMCs during the study (from Dose 1 to 1 month 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 (SC and IM) or 13vPnC (SC) injection site, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. CCI [redacted]

Severity and Maximum Severity

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

Table 3. 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. The severity of the local reaction should be graded using the AE grading scale.

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.

CCI

[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 are fever, decreased appetite, drowsiness/increased sleep, and irritability from Day 1 through Day 7, where Day 1 is the day of each dose. CCI [redacted] Maximum temperature range over the period from Day 1 through Day 7 will be mapped into the ranges described in Table 5 for summary of maximum temperature.

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 4. 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

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

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

Temperatures (axillary) will be recorded in degrees for reporting. Fever will be grouped into ranges for the analysis according to Table 5.

Table 5. Ranges for Fever

≥37.5°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C

N**ote**: Fever is defined as temperature ≥37.5°C.

[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 (Visit 4) and from Dose 4 (Visit 5) through 1 month after Dose 4 (Visit 6).

The AE endpoints will be summarized by system organ class and preferred term on a participant level.

This safety 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 "common." A MedDRA preferred term is defined as a Tier 2 event if there are at least 4 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.

3.1.2. Primary Immunogenicity Endpoints

- Pneumococcal serotype-specific IgG concentration 1 month after Dose 3

Concentrations of anticapsular IgG for the 20 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 8, 10A, 11A, 12F, 15B, 22F, and 33F) will be determined and classified based on predefined serotype-specific IgG concentrations in all participants at 1 month after Dose 3 using the Luminex assay. The Luminex assay has been validated for the 13vPnC serotypes and the reference concentrations have been bridged to the WHO ELISA,[2] and the predefined IgG concentrations are defined below.

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

[redacted]

3.2. Secondary Endpoints

3.2.1. Secondary Immunogenicity Endpoints

- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 3
- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4
- Pneumococcal serotype-specific OPA titers 1 month after Dose 3, before Dose 4, and 1 month after Dose 4
- Fold changes in pneumococcal serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4

3.2.1.1. OPA Titers

OPA titers will be determined on serum from randomly selected subsets of participants provided by an unblinded statistician. The random selection will ensure that each subset has equal representation of both vaccine series. Further details of the subsetting will be described in a memo to the unblinded statistician before any testing proceeds.

3.2.1.2. IgG Concentrations

IgG concentrations 1 month after Dose 4 will be classified using the same reference concentrations as described in Section 3.1.2. Fold changes will be calculated for each participant by taking the ratio of IgG concentrations from the later visit to the earlier visit.

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[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 each dose (in months), sex (male or female), race (Asian), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino).

This variable is derived in the database as days: (visit date – date of birth) + 1. For analysis, age at the time of vaccination in months will be derived as follows:

12 × (vaccination date – date of birth +1) / 365.25, rounded to 1 decimal place.

This formula provides age of the participant in months for each vaccination separately.

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 participant will receive investigational product with the specific concomitant vaccines as shown in Table 6.

Table 6. Vaccination Schedule for Investigational Product and Specified Concomitant Vaccines

Visit Number	Visit 1	Visit 2	Visit 3	Visit 5
Study Vaccination[a]	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**
Visit Window	**2 Through 6 Months of Age**	**4 to 8 Weeks After Visit 1**	**4 to 8 Weeks After Visit 2 (Completed by 12 Months of Age)**	**12 to 15 Months of Age (≥60 Days After Dose 3)**
Investigational product (20vPnC or 13vPnC)	X	X	X	X
Specified concomitant vaccines				
Hib vaccine	X (Vax 1)	X (Vax 2)	X (Vax 3)	X (Vax 4)
HBV vaccine[b]	X (Vax 1)	X (Vax 2)		
Rotavirus vaccine	X (Vax 1)	X (Vax 2)	X[c] (Vax 3)	
DTaP-IPV[b]		X (Vax 1)	X (Vax 2)	X (Vax 4)
MR combination vaccine[d]				X (Vax 1)
Varicella vaccine[d]				X (Vax 1)

Abbreviations: DTaP-IPV = diphtheria, tetanus, and acellular pertussis; and inactivated polio combination vaccine; HBV = hepatitis B virus; Hib = *Haemophilus influenzae* type b; MR = measles and rubella; Vax = vaccination.

a. Doses of vaccines to be administrated at Visits 1 to 3 will be preferred to be administered at 2, 3, and 4 months of age consistent with the recommended vaccination schedule.
b. Dose 3 of DTaP-IPV and HBV vaccine will be administered according to the vaccination schedule defined in the labeling. These vaccines will be administered between the blood sample collection 1 month after Dose 3 (Visit 4) and 14 days before Dose 4 (Visit 5).
c. Dose 3 for pentavalent rotavirus vaccine only.
d. Dose 2 of MR combination vaccine and varicella vaccine will be administered according to the vaccination schedule defined in the labeling.

Other vaccines licensed for this age group may be administered as specified in the protocol. 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 and immunogenicity results in the table below. For the specified criteria in each population definition that are not associated with unblinded information (vaccination as randomized or as actually received), 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 the specified analysis and 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.
Dose 3 evaluable immunogenicity	All participants who 1. are eligible and randomized 2. are 2 to 6 months of age (defined as the first day the participant is 2 months of age to the last day the participant is 6 months of age) at the first vaccination 3. receive the first 3 vaccinations to which they are randomized 4. have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 3 5. have no other major protocol deviations as determined by the clinician The Dose 3 evaluable immunogenicity population will be the primary analysis population for the immunogenicity results from the blood collected up to before Dose 4. Participants will be grouped as randomized in the immunogenicity analysis.
Dose 4 evaluable immunogenicity	All participants who 1. are eligible and randomized 2. are 2 to 6 months of age (defined as the first day the participant is 2 months of age to the last day the participant is 6 months of age) at the first vaccination 3. receive all 4 vaccinations as randomized, and are 12 to 15 months of age (also at least 60 days after Dose 3) 4. have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 4

Population	Description
	5. have no other major protocol deviations as determined by the clinician The Dose 4 evaluable immunogenicity population will be the primary analysis population for the pneumococcal immunogenicity results 1 month after Dose 4. Participants will be grouped as randomized in the immunogenicity analysis
[redacted]	CCI [redacted]
Safety	All participants who receive at least 1 dose of the investigational product with safety follow-up after any dose. Safety data after Dose 4 will be summarized on the subset of the safety population who also receive Dose 4 with safety follow-up after Dose 4. The statistical analysis of e-diary results will be based on the safety population among those with any e-diary data collected after the specified vaccination. Participants will be grouped according to the vaccine (route) as administered in the safety analysis with safety population.

For the Dose 3 and Dose 4 evaluable immunogenicity population definitions, the blood collection window has been expanded by 1 extra day before and 14 days after the protocol-specified blood collection window of 28 to 42 days defined in the protocol, for consistency with established rules in the Prevenar 13 development program. A major protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with major protocol deviations before any unblinded analysis.

For data from participants who receive the incorrect vaccine (route) by mistake, the results will be included in the summary up to the last correct vaccine (route) received in specified reporting time frame and/or dose. Data from all participants will be listed in the listing including those who receive the incorrect vaccine (route) due to errors.

CCI [redacted]

[redacted]

[redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS

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

5.1. Hypotheses and Decision Rules

5.1.1. Immunogenicity Hypotheses

5.1.1.1. Percentage of Participants With Predefined Pneumococcal Serotype-Specific IgG Concentration 1 Month After Dose 3 (Primary Immunogenicity Objectives)

Hypothesis testing will be used to assess the NI of 20vPnC SC to 13vPnC SC for percentages of participants with predefined pneumococcal serotype-specific IgG concentrations 1 month after Dose 3 (see Section 3.1.2 for predefined concentrations). The null hypothesis (H_{0A}) for a serotype is

$$H_{0A}: \pi_{20vPnC\ SC} - \pi_{13vPnC\ SC} \leq -10\%,$$

with a 10% margin for NI, where

- $\pi_{20vPnC\ SC}$ is the percentage of participants achieving the IgG concentration of predefined level in the 20vPnC SC group for the serotype 1 month after Dose 3.
- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) in 13vPnC, $\pi_{13vPnC\ SC}$ is the percentage of participants achieving the predefined IgG concentration level for the serotype from the 13vPnC SC group 1 month after Dose 3.
- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\pi_{13vPnC\ SC}$ is the percentage of participants achieving a predefined IgG concentration level from the serotype with the lowest percentage 1 month after Dose 3 among the 13 serotypes from the 13vPnC SC group, provided that the lowest percentage is not from serotype 3. If the lowest percentage in the 13vPnC SC group is from serotype 3, the next lowest percentage in the 13vPnC SC group will be used in the comparison. Historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes.

The null hypothesis (H_{0A}) will be rejected and NI of the 20vPnC SC group to the 13vPnC SC group for the percentage of participants with the predefined IgG concentration level will be declared for a serotype if the lower bound of the 2-sided 95% CI for the difference (20vPnC SC group – 13vPnC SC group) in percentages, based on the Miettinen and Nurminen method,[3] is greater than –10% (10% NI margin).

5.1.1.2. Pneumococcal Serotype-Specific IgG GMCs 1 Month After Dose 3 (Secondary Immunogenicity Objectives)

Hypothesis testing will be used to assess NI of 20vPnC SC to 13vPnC SC for pneumococcal serotype-specific IgG GMCs 1 month after Dose 3. The null hypothesis (H_{0B}) for a serotype is

$$H_{0B}: \ln(\mu_{20vPnC\ SC}) - \ln(\mu_{13vPnC\ SC}) \leq \ln(0.5)$$

where ln(0.5) corresponds to a 2-fold margin for NI and

- $\ln(\mu_{20vPnC\ SC})$ is the natural log of the geometric mean IgG concentration in the 20vPnC SC group for that serotype 1 month after Dose 3.
- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), $\ln(\mu_{13vPnC\ SC})$ is the natural log of the geometric mean IgG concentration in the 13vPnC SC group 1 month after Dose 3.
- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\ln(\mu_{13vPnC\ SC})$ is the natural log of the geometric mean IgG concentration for the serotype with the lowest IgG GMC 1 month after Dose 3 among the 13 serotypes from the 13vPnC SC group, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC SC group is from serotype 3, the next lowest GMC in the 13vPnC SC group will be used in the comparison. As stated in Section 5.1.1.1, historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the NI of the 7 additional serotypes.
- The null hypothesis (H_{0B}) will be rejected and NI of the 20vPnC SC group to the 13vPnC SC group for the pneumococcal serotype-specific IgG GMC will be declared for a serotype if the lower bound of the 2-sided 95% CI for the IgG GMR of the 20vPnC SC group to the 13vPnC SC group is greater than 0.5 (2-fold NI margin).

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).[4] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen[3] 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.

5.2.2.1. Geometric Means

For immunogenicity results of serotype-specific IgG concentrations and OPA titers, the geometric means will be computed along with associated 95% CIs. The geometric mean 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 Ratios

Where appropriate, GMRs and their 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale of the assay results based on the t-distribution (allowing for unequal variances), and then exponentiating the results. The difference in means, on the natural log scale, will be the 20vPnC SC group minus the 13vPnC SC group, or the 20vPnC IM group minus the 20vPnC SC group.

5.2.2.3. Geometric Mean Fold Rises

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

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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. A complete missing start date for an AE is not allowed in the data collection.

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 set to 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

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 SC group – 13vPnC SC group, or 20vPnC IM group – 20vPnC SC group) 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. Confirmed e-diary errors will be excluded from the analysis.

- 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 SC group – 13vPnC SC group, or 20vPnC IM group – 20vPnC SC group) in these percentages and their 2-sided 95% CIs will also be provided. The denominator used in the percentage calculation will be the number of participants with any e-diary data reported after the specified vaccination.

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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 SC group – 13vPnC SC group, or 20vPnC IM group – 20vPnC SC group) 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. Confirmed e-diary errors will be excluded from the analysis.

- 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 SC group – 13vPnC SC group, or 20vPnC IM group – 20vPnC SC group) in these percentages and their 2-sided 95% CIs will also be provided. The denominator used in the percentage calculation will be the number of participants with any e-diary data reported after the specified vaccination.

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6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimands:

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

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

- Analysis set: Safety population (Section 4).
- Analysis time points: Dose 1 to 1 month after Dose 3 and Dose 4 to 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 and associated 2-sided 95% CIs (20vPnC SC group – 13vPnC SC group, or 20vPnC IM group – 20vPnC SC group) 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.

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[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 to 1 month after Dose 4 (Section 2.1).
  - The percentage of participants reporting NDCMCs from Dose 1 to 1 month after Dose 4 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 to 1 month after Dose 4.
- 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, each system organ class, and each preferred term within system organ class will be presented by vaccine group. SAEs and NCDMCs will be presented separately.

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6.1.2. Primary Immunogenicity Endpoints

6.1.2.1. Participants With Predefined Pneumococcal Serotype-Specific IgG Concentrations at 1 Month After Dose 3

6.1.2.1.1. Main Analysis

- (For 20vPnC SC) Estimands:
  - For each of the 13 matched serotypes in 20vPnC, the difference in percentages of participants with predefined serotype-specific IgG concentrations between the 20vPnC SC group and the 13vPnC SC group (Section 2.1).

  - For each of the 7 additional serotypes in 20vPnC, the difference in the percentages of participants with predefined serotype-specific IgG concentrations between the 20vPnC SC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC SC group, excluding serotype 3.

- (For 20vPnC IM) Estimand: For each of the 20 serotypes in 20vPnC, the difference in percentages of participants with predefined serotype-specific IgG concentrations between the 20vPnC IM group and the 20vPnC SC group (Section 2.1).

- Analysis set: Dose 3 evaluable immunogenicity population (Section 4).

- Analysis time point: 1 Month after Dose 3.

- Analysis methodology: The between-group difference (20vPnC SC – 13vPnC SC and 20vPnC IM – 20vPnC SC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1) for each serotype. NI of 20vPnC SC relative to 13vPnC SC will be assessed by comparing the lower bound of the 95% CI for the between-group difference (Section 5.1.1.1).

- 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 20 vaccine serotypes, the numerator (n), 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, as well as the percentage difference and the associated 95% CI, will be presented.

Figures:

- A forest plot of between-group differences (20vPnC SC – 13vPnC SC and 20vPnC IM – 20vPnC SC) with 95% CIs for the percentages will be presented.

- Percentages (and corresponding 95% CIs) of participants achieving predefined serotype-specific IgG concentrations 1 month after Dose 3 will be presented in 2 vertical bar charts, 1 for the 13 matched serotypes and 1 for the 7 additional serotypes.

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6.2. Secondary Endpoints

6.2.1. Secondary Immunogenicity Endpoints

6.2.1.1. Pneumococcal Serotype-Specific IgG Concentrations 1 Month After Dose 3

6.2.1.1.1. Main Analysis

- (For 20vPnC SC) Estimands:
    - For each of the 13 matched serotypes in 20vPnC, GMRs of serotype-specific IgG concentrations from the 20vPnC SC group to the 13vPnC SC group 1 month after Dose 3 (Section 2.1).
    - For each of the 7 additional serotypes in 20vPnC, GMRs of serotype-specific IgG concentrations from the 20vPnC SC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC SC group, excluding serotype 3.
- (For 20vPnC IM) Estimand: For each of the 20 serotypes in 20vPnC, GMRs of serotype-specific IgG concentrations from the 20vPnC IM group to the 20vPnC SC group 1 month after Dose 3.
- Analysis set: Dose 3 evaluable immunogenicity population (Section 4).
- Analysis time point: 1 Month after Dose 3.
- Analysis methodology: The serotype-specific IgG GMRs of the 20vPnC SC group to the 13vPnC SC group, as well as the the 20vPnC IM group to the 20vPnC SC group, and their 2-sided 95% CIs will be derived (Section 5.2.2.2) based on the t-distribution. NI of 20vPnC SC relative to 13vPnC SC will be assessed by comparing the lower bound of the 95% CI for the GMR against the NI margin (Section 5.1.1.2).
- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Concentrations below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. Missing data will not be imputed.
- Reporting results: For each of the 20 vaccine serotypes, the GMC and corresponding 2-sided 95% CI from each vaccine group, as well as the GMR of the 20vPnC SC group to the 13vPnC SC group and the GMR of the 20vPnC IM group to the 20vPnC SC group and their 2-sided 95% CIs, will be presented.

Figures:

A forest plot of IgG GMRs (20vPnC SC to 13vPnC SC and 20vPnC IM to 20vPnC SC) with 95% CIs from all 20 serotypes will be presented.

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GMCs and corresponding 95% CIs of serotype-specific IgG concentrations 1 month after Dose 3 will be presented in 2 vertical bar charts, 1 for the 13 matched serotypes and 1 for the 7 additional serotypes.

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6.2.1.2. Pneumococcal Serotype-Specific IgG Concentration 1 Month After Dose 4

- Estimand: For each of the 20 vaccine serotypes, GMCs of serotype-specific IgG concentrations 1 month after Dose 4 (Section 2.1).
- Analysis set: Dose 4 evaluable immunogenicity population (Section 4).
- Analysis time point: 1 Month after Dose 4.
- Analysis methodology: GMCs and the 2-sided 95% CIs for each vaccine group based on Student's t-distribution (Section 5.2.2.1)
- Reporting results: For each of the 20 vaccine serotypes, the GMC and corresponding 2-sided 95% CI for serotype-specific IgG concentrations will be presented for all vaccine groups.

Figures:

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Antibody response curves showing the IgG GMCs, with corresponding 95% CIs, for the 3 blood draw time points will be presented by vaccine group.

GMCs and corresponding 95% CIs of serotype-specific IgG concentrations before and 1 month after Dose 4 will be presented in 2 vertical bar charts, 1 for the 13 matched serotypes and 1 for the 7 additional serotypes.

6.2.1.3. Pneumococcal Serotype-Specific OPA Titers

- Estimand: GMTs of serotype-specific OPA 1 month after Dose 3, before Dose 4, and 1 month after Dose 4 (Section 2.1).

- Analysis sets: Dose 3 evaluable immunogenicity population for 1 month after Dose 3 and before Dose 4, and Dose 4 evaluable immunogenicity population for 1 month after Dose 4 (Section 4), restricted to the subsets of participants who are selected for serotypes-specific OPA titers.

- Analysis time points: 1 Month after Dose 3, before Dose 4, and 1 month after Dose 4.

- Analysis methodology: GMTs and the 2-sided 95% CIs for each vaccine group based on Student's t-distribution (Section 5.2.2.1).

- Reporting results: For each of the 20 vaccine serotypes, the GMTs and 95% CIs for serotype-specific OPA will be presented for all vaccine groups at the specified time points.

Figures:

Antibody response curves showing the OPA GMTs, with corresponding 95% CIs, for the 3 blood draw time points will be presented by vaccine group.

GMTs and corresponding 95% CIs of serotype-specific OPA titers 1 month after Dose 3 will be presented in 2 vertical bar charts, 1 for the 13 matched serotypes and 1 for the 7 additional serotypes. Similarly, GMTs and corresponding 95% CIs of serotype-specific OPA titers before Dose 4 and 1 month after Dose 4 will be presented in 2 vertical bar charts, 1 for the 13 matched serotypes and 1 for the 7 additional serotypes.

6.2.1.4. Participants With Predefined Pneumococcal Serotype-Specific IgG Concentrations at 1 Month After Dose 4

- Estimand: For each of the 20 vaccine serotypes, the percentages of participants with predefined serotype-specific IgG concentrations 1 month after Dose 4 (Section 2.1).

- Analysis set: Dose 4 evaluable immunogenicity population (Section 4).

- Analysis time point: 1 Month after Dose 4.

- Analysis methodology: The percentages of participants with predefined serotype-specific IgG concentrations and the corresponding 2-sided 95% CI will be presented for all vaccine groups.

- Reporting results: For each of the 20 vaccine 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.

Figures:

- Percentages (and corresponding 95% CIs) of participants achieving predefined serotype-specific IgG concentrations 1 month after Dose 4 will be presented in 2 vertical bar charts, 1 for the 13 matched serotypes and 1 for the 7 additional serotypes.

6.2.1.5. Fold Changes in Pneumococcal Serotype-Specific IgG Concentrations

- Estimand: GMFRs of pneumococcal serotype-specific IgG concentrations 1 month after Dose 3 to before Dose 4, from before Dose 4 until 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 (Section 2.1).

- Analysis sets: Dose 3 evaluable immunogenicity population for the geometric mean fold change from 1 month after Dose 3 to before Dose 4, Dose 4 evaluable immunogenicity population for GMFRs from before Dose 4 to 1 month after Dose 4, and participants in both the Dose 3 evaluable and Dose 4 evaluable populations for the GMFRs from 1 month after Dose 3 to 1 month after Dose 4.

- Analysis time points: 1 Month after Dose 3, before Dose 4, and 1 month after Dose 4.

- Analysis methodology: Descriptive statistics (Section 5.2.2.3).

- Reporting results: For each of the 20 vaccine serotypes, the GMCs, the GMFRs, and the corresponding 2-sided 95% CIs for serotype-specific IgG concentrations will be presented for all vaccine groups at the specified time points.

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6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographic Characteristics

Demographic characteristics, including age in months at each dose, sex, race, and ethnicity, will be summarized for the safety population for each vaccine group and overall. Similar summaries will be done for the Dose 3 evaluable population and the Dose 4 evaluable population. CCI [redacted]

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 vaccine group for the safety population.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Participant Disposition

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the numbers and percentages of participants who receive each vaccination (Dose 1, 2, 3, or 4), who complete the follow-up visits (1 month after Dose 3, 1 month after Dose 4), who complete all visits, who withdraw before Dose 1, who withdraw after Dose 1 but before the visit 1 month after Dose 3, who withdraw after the visit 1 month after Dose 3 but prior to Dose 4, and who withdraw after Dose 4 but before 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 or immunogenicity analysis populations will also be summarized separately, along with the reasons for exclusion, by vaccine group.

6.5.2.2. Blood Samples for Assay

The number and percentage of randomized participants providing blood samples within and outside of protocol-prespecified time frames will be tabulated separately for 1 month after Dose 3, before Dose 4, and 1 month after Dose 4.

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6.5.3. Study Vaccination Exposure

6.5.3.1. Vaccination Timing and Administration

For each dose, the number and percentage of participants randomized and receiving each investigational product (20vPnC SC, 13vPnC SC, or 20vPnC IM), as well as the corresponding concomitant vaccines, will be tabulated for each vaccine group and overall for all randomized participants. The denominator for the percentages is the total number of 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 SC, 13vPnC SC, or 20vPnC IM) at each dose will be presented.

6.5.4. 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 the randomized vaccine schedule for all randomized participants. Summarization will be provided for concomitant vaccines received:

- with Dose 1, Dose 2, Dose 3, or Dose 4, separately
- before Dose 1
- between Dose 1 and Dose 2
- between Dose 2 and Dose 3
- between Dose 3 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 until the 1-month-after-Dose 4 visit. The safety population will be used.

6.6. Safety Summaries and Analyses

The summaries and analyses of the safety measures local reactions, systemic events, AEs, SAEs, and NDCMCs are described under the Primary 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 are available.

CCI [redacted]

7.1. Introduction

Not applicable.

7.2. Analysis Timings

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

- Final analysis: complete safety and immunogenicity data through 1 month after Dose 4 from all participants

For the safety data review for the first 45 participants, listings for demographic characteristics, medical history, nonstudy vaccines, and local reactions/systemic events/AEs through 7 days of follow-up after Dose 1 will be generated.

The study team will remain blinded up to the final analysis.

8. REFERENCES

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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
BLQ	below the limit of quantitation
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DTaP	diphtheria, tetanus, and acellular pertussis vaccine
e-diary	electronic diary
CCI [redacted]	[redacted]
FHA	filamentous hemagglutinin
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBV	hepatitis B virus
Hib	*Haemophilus influenzae* type b
ICD	informed consent document
IgG	immunoglobulin G
IM	intramuscular
IPV	inactivated poliovirus vaccine
IRT	interactive response technology
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
OPA	opsonophagocytic activity
CCI [redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
WHO	World Health Organization