Protocol B7471011

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

**Statistical Analysis Plan
(SAP)**

Version: 2

Date: 19 May 2022

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APPENDICES

1. VERSION HISTORY

Table 1.   Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 28 Aug 2020	Amendment 1 23 Apr 2020	N/A	N/A
2 19 May 2022	Amendment 2 01 Apr 2022	Made updates for consistency across the 20vPnC pediatric program, as well as, to increase clarity and correct minor errors in original version.	• CCI ███████████████ • CCI ███████████████ • Section 5 and Section 7.2 – Updated to remove Primary Analysis 1. • CCI ███████████████ • General – Made other minor edits/changes to be consistent with other 20vPnC studies, increased clarity, and fixed minor errors made in the original version of the document.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471011. 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 ████████ objective are described in Table 2. The estimands to evaluate the immunogenicity objectives for NI are based on evaluable populations (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 maximum potential difference between 2 groups (20vPnC and 13vPnC), 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 $0.5 \times$ 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, Endpoints, and Estimands

Primary Safety Objective	Estimands	Primary Safety Endpoints
• To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product with safety follow-up after any vaccination: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after each vaccination in each group • The percentage of participants reporting AEs from Dose 1 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 6 months after Dose 4 in each group • The percentage of participants reporting NDCMCs up to 6 months 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
Primary Pneumococcal Immunogenicity Objectives	**Estimands**	**Primary Pneumococcal Immunogenicity Endpoints**
• To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC group are noninferior to the percentages for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants defined in Section 4) at 1 month after Dose 3: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined serotype-specific IgG concentrations between the 20vPnC group and the 13vPnC group	• Pneumococcal serotype-specific IgG concentration

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

• To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest percentage among the 13 serotypes in the 13vPnC 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 percentages of participants with predefined serotype-specific IgG concentrations, between the 20vPnC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 4	In evaluable participants at 1 month after Dose 4: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC group at 1 month after Dose 4	In evaluable participants at 1 month after Dose 4: • For each of the 7 additional serotypes in 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
Primary Concomitant Immunogenicity Objective	**Estimand**	**Primary Concomitant Immunogenicity Endpoints**
• To demonstrate that percentages of participants with prespecified antibody levels to specific concomitant vaccine antigens when given with 20vPnC are noninferior to the corresponding percentages when the antigens are given with 13vPnC at 1 month after Dose 3	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib between the 20vPnC group and the 13vPnC group at 1 month after Dose 3	• Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) • Antibody levels to HBsAg • Antibody levels to poliovirus strains (types 1, 2, and 3) • Antibody levels to Hib

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

Key Secondary Pneumococcal Immunogenicity Objectives	Estimands	Key Secondary Pneumococcal Immunogenicity Endpoints
• To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC 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 group to the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC 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 group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
Secondary Pneumococcal Immunogenicity Objective	**Estimands**	**Secondary Pneumococcal Immunogenicity Endpoints**
• To further describe the immunogenicity of 20vPnC	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 In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: percentages of participants with the predefined serotype-specific IgG concentration in each group 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 OPA titers • Pneumococcal serotype-specific IgG concentrations

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

Secondary Concomitant Immunogenicity Objectives	Estimands	Secondary Concomitant Immunogenicity Endpoints
• To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with alternative prespecified antibody levels to Hib between the 20vPnC group and the 13vPnC group at 1 month after Dose 3	• Antibody levels to Hib
• To demonstrate that GMCs to specific concomitant vaccine antigens when given with 20vPnC are noninferior to the corresponding GMCs when the antigens given with 13vPnC at 1 month after Dose 4	• GMRs of antibody levels to measles, mumps, rubella, and varicella viruses from the 20vPnC group to the 13vPnC group at 1 month after Dose 4	• Antibody levels to measles, mumps, rubella, and varicella viruses
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Table 2.   **List of Primary, Secondary,** CCI **Objectives, Endpoints, and Estimands**

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2.2. Study Design

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in the United States and Puerto Rico.

Approximately 2000 infants ≥42 to ≤98 days of age at the time of consent, by their parent(s)/legal guardian(s), will be enrolled. Participants will be randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at 2, 4, 6, and 12 to 15 months of age (Doses 1, 2, 3, and 4, respectively) by site-based randomization. Participants will receive the same vaccine (20vPnC or 13vPnC) for all 4 doses. Specific concomitant vaccines containing diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib antigens will also be administered at 2, 4, and 6 months of age and containing measles, mumps, rubella, and varicella antigens at 12 to 15 months of age, respectively.

Blood will be collected 1 month after Dose 3 (7 months of age), immediately prior to Dose 4 (12-15 months of age), and 1 month after Dose 4 (13-16 months of age) to assess immunogenicity. Participants will be observed for 30 minutes after each vaccination and any reactions occurring during that time will be recorded as AEs. Prompted local reactions (redness, swelling, and pain at the 20vPnC or 13vPnC injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and use of antipyretic/pain medications occurring within 7 days after each vaccination will be collected via a provided e-diary (or e-diary application). AEs, including nonserious AEs, will be collected from the signing of informed consent to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4. SAEs and NDCMCs will be collected for the entire duration of the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Safety Endpoints

- Prompted local reactions (redness, swelling, and pain at the injection site) within 7 days after each dose

- Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) within 7 days after each dose

- AEs from Dose 1 to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4

- SAEs during the study (from Dose 1 to 6 months after Dose 4)

- NDCMCs during the study (from Dose 1 to 6 months after Dose 4)

3.1.1.1. Local Reactions

The local reactions assessed and reported in the e-diary are redness, swelling, and pain at the 20vPnC or 13vPnC injection site, from Day 1 through Day 7 after each dose, where Day 1 is the day of each dose. This section describes derivations with details for the assessment of local reactions: severity level, duration, and onset day.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device (caliper) units, 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	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe pain (tenderness) at injection site

Abbreviation: CRF = case report form.
Note: If the size of the redness and/or swelling falls between 2 measuring device units, the higher measuring device unit number will be recorded in the e-diary.

a.   Parents/legal guardians of the participants experiencing local reactions >14 caliper units (>7.0 cm) are to be contacted by the study site. An unscheduled visit may be required.
b.   Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF.

For each local reaction after each dose, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of each dose) as follows:

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

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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. The derivations for systemic events will be handled similarly to the way local reactions are handled for severity level, duration, and onset day (see Section 3.1.1.1). 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.

Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius first for reporting. Fever will be grouped into ranges for the analysis according to Table 5.

Table 5.   Ranges for Fever

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

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

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3.1.1.4. Adverse Events

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

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

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

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

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

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

- Tier 2 events: These are events that are not Tier 1, but are "relatively common." A MedDRA preferred term is defined as a Tier 2 event if there are at least 1% 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 Pneumococcal Immunogenicity Endpoints

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

- Pneumococcal serotype-specific IgG concentration 1 month after Dose 4

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 in all participants at 1 month after Dose 3 and 1 month after Dose 4 using the Luminex assay. Results will be reported as IgG concentrations.

To support the primary pneumococcal immunogenicity estimands, IgG concentrations will be classified based on serotype-specific IgG reference concentrations as 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, 6C, 15C	≥0.35

3.1.3. Primary Concomitant Immunogenicity Endpoints

- Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) 1 month after Dose 3

- Antibody levels to HBsAg 1 month after Dose 3

- Antibody levels to poliovirus strains (types 1, 2, and 3) 1 month after Dose 3

- Antibody levels to Hib 1 month after Dose 3

Antibody concentrations to each concomitant vaccine will be determined on sera collected 1 month after Dose 3 from a randomly selected subset of participants with sufficient sera volumes. Further details of the subsetting will be described in a memo to the unblinded statistician before any testing proceeds.

To support the primary concomitant immunogenicity estimands, antibody concentrations will be classified based on prespecified antibody thresholds for the concomitant vaccine antigens:

Antigen	Prespecified Level
Diphtheria	≥0.1 IU/mL
Tetanus	≥0.1 IU/mL
Acellular pertussis (PT, FHA, PRN)	≥ the observed antipertussis antibody concentration achieved by 95% of 13vPnC recipients
Hepatitis B	≥10 mIU/mL
Poliomyelitis (types 1, 2, and 3)	≥1:8
Hib	≥0.15 µg/mL anti-PRP Alternative: ≥1.0 µg/mL anti-PRP[a]

a. Secondary concomitant immunogenicity endpoint 1 month after Dose 3.

3.2. Secondary Endpoints

3.2.1. Key Secondary Pneumococcal Immunogenicity Endpoints

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

3.2.2. Secondary Pneumococcal Immunogenicity Endpoints

- Pneumococcal serotype-specific OPA titers 1 month after Dose 3, before Dose 4, and 1 month after Dose 4

- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4 and change 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

3.2.2.1. OPA Titers

OPA titers will be determined on serum from randomly selected subsets of participants provided by an unblinded statistician. The random selection will assure 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.

3.2.2.2. 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.

3.2.3. Secondary Concomitant Immunogenicity Endpoints

- Antibody levels to Hib 1 month after Dose 3 (see Section 3.1.3 for alternative prespecified level)

- Antibody levels to measles, mumps, rubella, and varicella viruses at 1 month after Dose 4

Antibody concentrations to each concomitant vaccine antigen (measles, mumps, rubella, and varicella) will be determined on sera collected 1 month after Dose 4 from a randomly selected subset of participants with sufficient sera volumes. Further details of the subsetting will be described in a memo to the unblinded statistician before any testing proceeds.

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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 days), sex (male or female), race (black/African American, American Indian or Alaskan native, Asian, Native Hawaiian or other Pacific Islander, white, multiracial, and not reported), ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, and not reported), and geographic region (United States or Puerto Rico). Age at each dose in days will be derived as (dose date – date of birth + 1). For participants who were randomized but not vaccinated, the randomization date will be used in place of the date of Dose 1 for the Dose 1 age calculation. If the randomization date is also missing, then the informed consent date will be used for Dose 1 age calculation.

In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

Medical history will be categorized according to MedDRA.

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3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

The participant will receive vaccines with diphtheria toxoid, tetanus toxoid, acellular pertussis (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib at 2, 4, and 6 months of age with Doses 1, 2, and 3. Specific concomitant vaccines containing measles, mumps, rubella, and varicella antigens will be administered at 12 to 15 months of age with Dose 4. Other vaccines licensed and recommended 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 (randomized or actual received vaccination), data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database for analysis, and the classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
Dose 3 evaluable immunogenicity	All participants who 1. are eligible and randomized, 2. are 42 to 98 days of age, inclusive, on the day of Dose 1, 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, and 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 pneumococcal immunogenicity results from the blood collected up to before Dose 4. The statistical analysis of concomitant immunogenicity results 1 month after Dose 3 will be primarily based on the Dose 3 evaluable immunogenicity population restricted to those who also receive the appropriate concomitant vaccines with the first 3 doses. Participants will be grouped as randomized in the immunogenicity analysis.
Dose 4 evaluable immunogenicity	All participants who 1. are eligible and randomized, 2. are 42 to 98 days of age, inclusive, on the day of Dose 1, 3. receive all 4 vaccinations as randomized, and are 365 to 455 days of age, inclusive, on the day of Dose 4, 4. have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 4, and 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 after Dose 4. The statistical analysis of concomitant immunogenicity results 1 month after Dose 4 will be primarily based on the Dose 4 evaluable immunogenicity population restricted to those who also receive the appropriate concomitant vaccines at the Dose 4 visit. Participants will be grouped as randomized in the immunogenicity analysis.

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Safety	All participants who receive at least 1 dose of the investigational product with safety follow-up after any dose. Participants will be grouped according to the vaccine as administered in the safety analysis.		
	Safety data after Dose 4 will be summarized 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.		

For the Dose 3 and Dose 4 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 defined in the protocol, for consistency with established rules in the Prevnar 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.

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5. GENERAL METHODOLOGY AND CONVENTIONS

Primary analysis 1, which was specified in the protocol, will not be conducted because of internal business decisions. The first of the planned statistical analyses (see Section 7.2) will be carried out when the safety and immunogenicity data through 1 month after Dose 4 are available and released. For this reason, the study team will be unblinded after the last participant completes Visit 6 (1 month after Dose 4) and the database snapshot has been taken for the planned analysis. The investigator site staff will remain blinded to participant vaccine group until the last participant completes the final visit and the database has been locked for final analysis. Laboratory personnel performing the assays will remain blinded until all assays are completed and assay results finalized.

5.1. Hypotheses and Decision Rules

5.1.1. Pneumococcal Immunogenicity Hypotheses

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

Hypothesis testing will be used to assess the NI of 20vPnC to 13vPnC 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

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

with a 10% margin for NI, where

- π_{20vPnC} is the percentage of participants achieving the IgG concentration of predefined level in the 20vPnC 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, π_{13vPnC} is the percentage of participants achieving the predefined IgG concentration level for the serotype from the 13vPnC group 1 month after Dose 3;

- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, π_{13vPnC} 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 group, provided that the lowest percentage is not from serotype 3. If the lowest percentage in the 13vPnC group is from serotype 3, the next lowest percentage in the 13vPnC 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 20vPnC to 13vPnC for the percentage of participants with predefined IgG concentration level will be declared for a serotype if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages, based on the Miettinen and Nurminen method,[1] is greater than –10% (10% NI margin).

5.1.1.2. Pneumococcal Serotype-Specific IgG GMCs 1 Month After Dose 4 (Primary Pneumococcal Immunogenicity Objectives)

Hypothesis testing will be used to assess NI of 20vPnC to 13vPnC for pneumococcal serotype-specific IgG GMCs 1 month after Dose 4. The null hypothesis (H_{0B}) for a serotype is

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

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

- $\ln(\mu_{20vPnC})$ is the natural log of the geometric mean IgG concentration in the 20vPnC group for that serotype 1 month after Dose 4;

- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration in the 13vPnC group 1 month after Dose 4;

- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration for the serotype with the lowest IgG GMC 1 month after Dose 4 among the 13 serotypes from the 13vPnC group, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC group is from serotype 3, the next lowest GMC in the 13vPnC 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 20vPnC to 13vPnC 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 20vPnC to 13vPnC is greater than 0.5 (2-fold NI margin).

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

Hypothesis testing to assess NI of 20vPnC to 13vPnC for pneumococcal serotype-specific IgG GMCs 1 month after Dose 3 will be performed similarly to that for IgG GMCs 1 month after Dose 4, as described in Section 5.1.1.2, with $\ln(\mu_{20vPnC})$ and $\ln(\mu_{13vPnC})$ being the natural log of the geometric mean IgG concentrations 1 month after Dose 3 from the 20vPnC and 13vPnC groups, respectively. If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\ln(\mu_{13vPnC})$ 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 group, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC group is from serotype 3, the next lowest GMC in the 13vPnC group will be used in the hypothesis testing.

The null hypothesis H_{0B} will be rejected and NI of 20vPnC to 13vPnC 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 20vPnC to 13vPnC for the serotype is greater than 0.5 (2-fold NI margin).

5.1.2. Concomitant Immunogenicity Hypotheses

5.1.2.1. Percentage of Participants With Prespecified Antibody Level to Each Concomitant Vaccine Antigen at 1 Month After Dose 3 (Primary Concomitant Immunogenicity Objectives)

Hypothesis testing to assess NI of the 20vPnC group to the 13vPnC group for percentage of participants with prespecified antibody level to each concomitant vaccine antigen will be performed similarly to that for the percentage of participants with predefined serotype-specific IgG concentrations, as described in Section 5.1.1.1, with π_{20vPnC} and π_{13vPnC} being the percentages of participants with prespecified antibody levels (Section 3.1.3) to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, or Hib at 1 month after Dose 3 from the 20vPnC and 13vPnC groups, respectively.

The null hypothesis will be rejected and NI will be declared for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for the difference (20vPnC - 13vPnC) in percentages is greater than –10% (10% NI margin) for that concomitant vaccine antigen.

5.1.2.2. GMCs of Antibody Levels to Concomitant Vaccine Antigen at 1 Month After Dose 4 (Secondary Concomitant Immunogenicity Objectives)

Hypothesis testing to assess NI of the 20vPnC group to the 13vPnC group for GMCs of antibody levels to each concomitant vaccine antigen 1 month after Dose 4 will be performed similarly to that for the pneumococcal serotype-specific IgG concentration, as described in Section 5.1.1.2, with $\ln(\mu_{20vPnC})$ and $\ln(\mu_{13vPnC})$ being the natural log of the GMCs for antibody levels to measles, mumps, rubella, and varicella viruses at 1 month after Dose 4 from the 20vPnC and 13vPnC groups, respectively.

The null hypothesis will be rejected and NI will be declared for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for GMR of the 20vPnC group to the 13vPnC group is greater than 0.5 (2-fold NI margin) for that concomitant vaccine antigen.

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).[2] The 95% CI for the between-group difference for binary endpoints will be calculated using the Miettinen and Nurminen method.[1]

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.[1] 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, OPA titers and the antibody levels of the concomitant vaccines, the geometric means 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 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 group minus the 13vPnC group.

5.2.2.3. 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 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 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.

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 $0.5 \times$ LLOQ for analysis.

No additional imputation will be applied to other missing data.
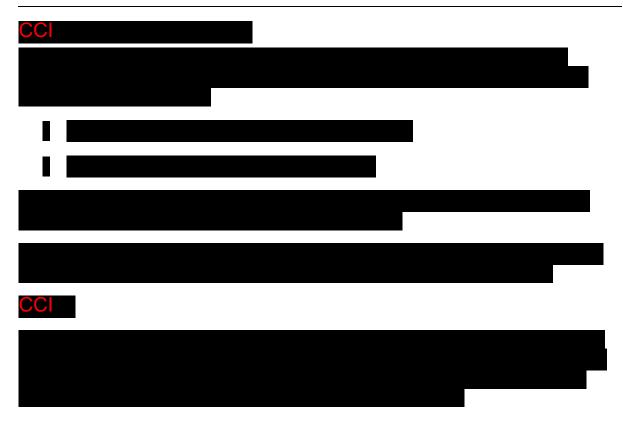
6. ANALYSES AND SUMMARIES

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 – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method[1] (Section 5.2.1) for each reaction.

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

- Reporting results: Count and percentage of participants with the indicated endpoint and the associated 2-sided 95% CI for each and any local reaction after each dose in each vaccine group will be presented by maximum severity across severity levels. Between-group differences (20vPnC – 13vPnC) in these percentages and their 2-sided 95% CIs will also be provided. The denominator used in the percentage calculation will be the number of participants with any e-diary data reported after 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 – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method[1] (Section 5.2.1) for each event.

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

- Reporting results: Count and percentage of participants with the indicated endpoint and the associated 2-sided 95% CI for each and any systemic event after each dose in each vaccine group will be presented by maximum severity across severity levels. Between-group differences (20vPnC – 13vPnC) in these percentages and their 2-sided 95% CIs will also be provided. The denominator used in the percentage calculation will be the number of participants with any e-diary data reported after 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, by each system organ class and each preferred term within system organ class, will be presented by vaccine group.

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

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

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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 6 months after Dose 4 (Section 2.1).

  - The percentage of participants reporting NDCMCs from Dose 1 to 6 months after Dose 4 (Section 2.1).

- Analysis set: Safety population (Section 4).

- Analysis time point: Dose 1 to 6 months 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, by 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 Pneumococcal 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

- Estimands:

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

  o 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 group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC group, excluding serotype 3.

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

- Analysis time point: 1 Month after Dose 3.

- Analysis methodology: The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method[1] (Section 5.2.1) for each serotype. The NI will be assessed by comparing the lower bound of the 95% CI against the NI margin (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) 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, as well as the percentage difference and the associated 95% CI, will be presented.

Figures:

A forest plot of between-group differences (20vPnC – 13vPnC) 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.

6.1.2.1.2. Supplementary Analysis

As a supplemental analysis to the main analysis that assesses NI, for each of the 7 additional serotypes, the percentage difference (and its 2-sided 95% CI) between the 2 groups (20vPnC – 13vPnC), with the comparator being the percentage of participants achieving predefined IgG concentrations for that corresponding serotype from the 13vPnC group, will be provided.

As a supportive analysis to the main analysis, an additional summary may be provided using an alternative reference concentration of 0.15 µg/mL for all serotypes.

6.1.2.2. Pneumococcal Serotype-Specific IgG Concentrations 1 Month After Dose 4

6.1.2.2.1. Main Analysis

- Estimands:

  o For each of the 13 matched serotypes in 20vPnC, GMRs of serotype-specific IgG concentrations from the 20vPnC group to the 13vPnC group 1 month after Dose 4 (Section 2.1).

  o For each of the 7 additional serotypes in 20vPnC, GMRs of serotype-specific IgG concentrations from the 20vPnC group to the lowest IgG GMC among the 13 serotypes from the 13vPnC group, excluding serotype 3.

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

- Analysis time point: 1 Month after Dose 4.

- Analysis methodology: The serotype-specific IgG GMRs of the 20vPnC group to the 13vPnC group and their 2-sided 95% CIs will be derived (Section 5.2.2.2) based on the t-distribution. The lower limit of the CI will be used in the hypothesis test for NI of 20vPnC to 13vPnC (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 group to the 13vPnC group and the 2-sided 95% CI, will be presented.

Figures:

A forest plot of GMRs with 95% CIs from all 20 serotypes will be presented.

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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.

6.1.2.2.2. Supplementary Analysis

As a supplementary analysis to support the interpretation of the main analysis, for each of the 7 additional serotypes, the GMR (and its 2-sided 95% CI) of 20vPnC to 13vPnC at 1 month after Dose 4, with the comparator being the IgG GMC of the corresponding serotype in the 13vPnC group, will be calculated.

6.1.3. Primary Concomitant Immunogenicity Endpoints

6.1.3.1. Participants With Prespecified Antibody Levels to Each Concomitant Vaccine Antigen 1 Month After Dose 3

6.1.3.1.1. Main Analyses

- Estimand: Differences in percentages of participants with prespecified antibody levels (Section 3.1.3) to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains (types 1, 2, and 3), and Hib at 1 month after Dose 3 between the 20vPnC group and the 13vPnC group (Section 2.1).

- Analysis set: Dose 3 evaluable immunogenicity population restricted to those who received the corresponding concomitant vaccine with the specified concomitant vaccine antigen (Section 4).

- Analysis time point: 1 Month after Dose 3.

- Analysis methodology: The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method[1] (Section 5.2.1). The NI will be assessed by comparing the lower bound of the 95% CI against the NI margin (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. 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 concomitant vaccine antigen, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI for participants with prespecified antibody 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 – 13vPnC) with 95% CIs for all concomitant antigens will be presented.

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6.2. Secondary Endpoints

6.2.1. Key Secondary Pneumococcal Immunogenicity Endpoint

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

6.2.1.1.1. Main Analyses

- Estimands:

  o For each of the 13 matched serotypes in 20vPnC, GMRs of serotype-specific IgG concentrations from the 20vPnC group to the 13vPnC group 1 month after Dose 3 (Section 2.1).

  o For each of the 7 additional serotypes in 20vPnC, GMRs of serotype-specific IgG concentrations from the 20vPnC group to the lowest IgG GMC among the 13 serotypes from the 13vPnC group, excluding serotype 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 group to the 13vPnC group and their 2-sided 95% CIs will be derived (Section 5.2.2.2) based on the t-distribution. The lower limit of the CI will be used in the hypothesis test for NI of 20vPnC to 13vPnC (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% CIs from each vaccine group, as well as the GMR of the 20vPnC group to the 13vPnC group and the 2-sided 95% CI, will be presented.

Figures:

A forest plot of IgG GMRs 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.

6.2.1.1.2. Supplementary Analysis

As a supplementary analysis to support the interpretation of the main analysis of NI, for each of the 7 additional serotypes, the GMR (and its 2-sided 95% CI) of 20vPnC to 13vPnC at 1 month after Dose 3, with the comparator being the IgG GMC of the corresponding serotype in the 13vPnC group, will be calculated.

6.2.2. Secondary Pneumococcal Immunogenicity Endpoints

6.2.2.1. 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 set: 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 serotype-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 the 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 both vaccine groups at the specified time points.

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

- Estimands:

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

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

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

- Analysis time point: 1 Month after Dose 4.

- Analysis methodology: The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method[1] (Section 5.2.1) for each serotype.

- 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, as well as the percentage difference and the associated 95% CI, will be presented.

As a supplemental analysis, for each of the 7 additional serotypes, the percentage difference (and its 2-sided 95% CI) between the 2 groups (20vPnC – 13vPnC), with the comparator being the percentage of participants achieving predefined IgG concentrations for that corresponding serotype from the 13vPnC group, will be provided.

6.2.2.3. 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 set: 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 both vaccine groups at the specified time points.

6.2.3. Secondary Concomitant Immunogenicity Endpoints

6.2.3.1. Antibody Levels to Hib 1 Month After Dose 3

- Estimand: Differences in percentages of participants with alternative prespecified antibody levels to Hib (Section 3.1.3) at 1 month after Dose 3 between the 20vPnC and the 13vPnC groups (Section 2.1).

- Analysis set: Dose 3 evaluable immunogenicity population restricted to those who received the corresponding concomitant vaccine with the specified concomitant vaccine antigen (Section 4).

- Analysis time point: 1 Month after Dose 3.

- Analysis methodology: The between-group difference (20vPnC – 13vPnC) and the corresponding 95% CI will be calculated using the Miettinen and Nurminen method[1] (Section 5.2.1).

- Reporting results: For each concomitant vaccine antigen, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided 95% CI for participants with prespecified antibody from each vaccine group, as well as the percentage difference and the associated 95% CI, will be presented.
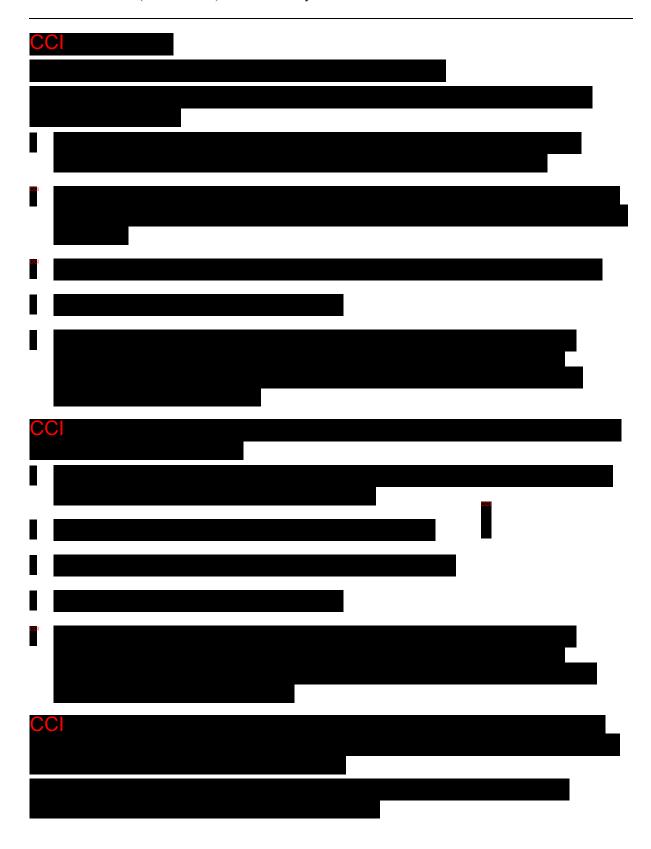
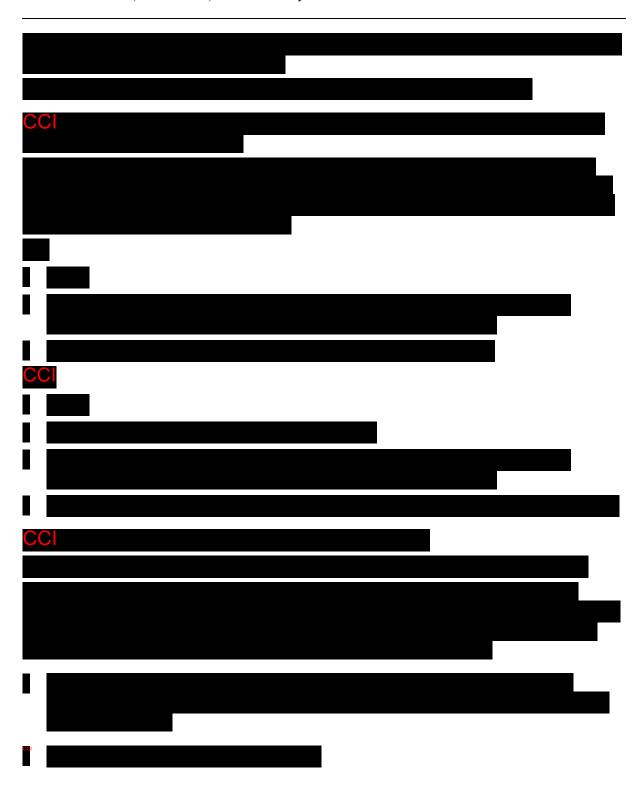### 6.2.3.2. Antibody Levels to Concomitant Vaccine Antigens 1 Month After Dose 4

- Estimand: GMRs of antibody levels to measles, mumps, rubella, and varicella antigens from the 20vPnC group to the 13vPnC group 1 month after Dose 4 (Section 2.1).

- Analysis set: Dose 4 evaluable immunogenicity population restricted to those who received the corresponding concomitant vaccine with the specified concomitant vaccine antigen (Section 4).

- Analysis time point: 1 Month after Dose 4.

- Analysis methodology: The GMRs of the 20vPnC group to the 13vPnC group and their 2-sided 95% CIs will be derived (Section 5.2.2.2). The lower limit of the CI will be used in the hypothesis test for NI of 20vPnC to 13vPnC (Section 5.2.2.2).

- 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 $0.5 \times$ LLOQ for analysis. Missing data will not be imputed.

- Reporting results: For each antibody level to measles, mumps, rubella, and varicella viruses, the GMC and corresponding 2-sided 95% CIs for each vaccine group, as well as the GMR of the 20vPnC group to the 13vPnC group and the 2-sided 95% CI, will be presented.
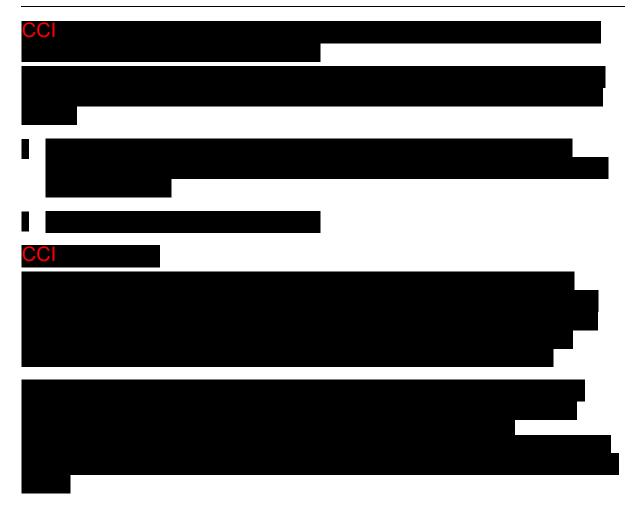
Figures:

A forest plot of GMRs with 95% CIs for measles, mumps, rubella, and varicella will be presented.

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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 at each dose, sex, race, ethnicity, and geographic region (United States or Puerto Rico), 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

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

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

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

6.5.4. Prior/Concomitant Vaccinations 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 randomized vaccine schedule for all randomized participants. Summarization will be done separately 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 6-month follow-up telephone contact. The safety population will be used.

6.6. Safety Summaries and Analyses

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 for the specified analyses are available.

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7.1. Introduction

Not applicable.

7.2. Analysis Timings

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

- Primary analysis: complete safety and immunogenicity data through 1 month after Dose 4;

- Final safety analysis: complete safety data from 1 month after Dose 4 through the visit occurring 6 months after Dose 4.

The study team will remain blinded up to the primary analysis. The investigator site staff will remain blinded to participant vaccine group until the last participant completes the final visit telephone call. Laboratory personnel performing the assays will remain blinded until all assays are completed.

8. REFERENCES

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

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

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 limit of quantitation
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
e-diary	electronic diary
CCI	███████████████████████
FHA	filamentous haemagglutinin
GM	geometric mean
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBsAg	hepatitis B surface antigen
Hib	*Haemophilus influenzae* type b
ICD	informed consent document
IgG	immunoglobulin G
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
PRN	pertactin
PRP	polyribosylribitol phosphate
PT	pertussis toxin
CCI	███████████████████████
SAE	serious adverse event
SAP	statistical analysis plan
WHO	World Health Organization