Protocol B7471012

A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE GIVEN AS A SERIES OF 2 INFANT DOSES AND 1 TODDLER DOSE IN HEALTHY INFANTS

Statistical Analysis Plan (SAP)

Version: 1

Date: 21 Jun 2021

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CCI [redacted]

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 21 Jun 2021	Amendment 2 18 June 2021	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7471012. 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 analysis of safety and immunogenicity results from the primary study population, and the SAP will be amended accordingly to account for these impacts, if needed.

2.1. Study Objectives, Endpoints, and Estimands

The estimands corresponding to each primary, secondary, CCI [redacted] objective are described in Table 2. The objectives, estimands, and endpoints table for the Russian cohort can be found in Appendix 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, denoted as BLQ, will be set to 0.5 × LLOQ in the analysis.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE 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 for Primary Study Population

Primary Safety Objective	Estimands	Primary Safety Endpoints
To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after each dose • The percentage of participants reporting prompted systemic events within 7 days after each dose • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 • The percentage of participants reporting SAEs through 1 month after Dose 3 • The percentage of participants reporting NDCMCs through 1 month after Dose 3	• 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 those of the corresponding serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants defined in Section 4 at 1 month after Dose 2: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the 13vPnC group	• Pneumococcal IgG concentrations
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 among the 13 serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations

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

To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to those for the corresponding serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 13 matched serotypes: GMRs of IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest among the 13 serotypes in the 13vPnC group at 1 month after Dose 2	In evaluable participants at 1 month after Dose 2: • For each of the 7 additional serotypes in 20vPnC: GMRs of IgG concentrations from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to those 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: GMRs of IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal IgG concentrations
To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest 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: GMRs of IgG concentrations from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal IgG concentrations
Primary Concomitant Immunogenicity Objective	**Estimands**	**Primary Concomitant Immunogenicity Endpoints**
To demonstrate that the immune responses induced by concomitant vaccine antigens given with 20vPnC are noninferior to immune responses induced by concomitant vaccine antigens 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 1 month after Dose 3 between the 20vPnC and the 13vPnC groups • GMRs of antibody levels to MMR and varicella antigens from the 20vPnC group to the 13vPnC group 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 • Antibody levels to MMR and varicella viruses

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

Secondary Pneumococcal Immunogenicity Objective	Estimands	Secondary Pneumococcal Immunogenicity Endpoints
To further describe the immune responses induced by 20vPnC	In evaluable participants: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the 13vPnC group at 1 month after Dose 3 • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group at 1 month after Dose 3 • For each of the 20 serotypes in 20vPnC: OPA GMTs 1 month after Dose 2 and 1 month after Dose 3 in each vaccine group • For each of the 20 serotypes in 20vPnC: GMFRs in IgG concentrations from before Dose 3 to 1 month after Dose 3 in each vaccine group	• Pneumococcal IgG concentrations • Pneumococcal OPA titers
Secondary Concomitant Immunogenicity Objective	**Estimand**	**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 appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), poliovirus strains, and Hib 1 month after Dose 2 between the 20vPnC and the 13vPnC groups	• Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) • 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 for Primary Study Population

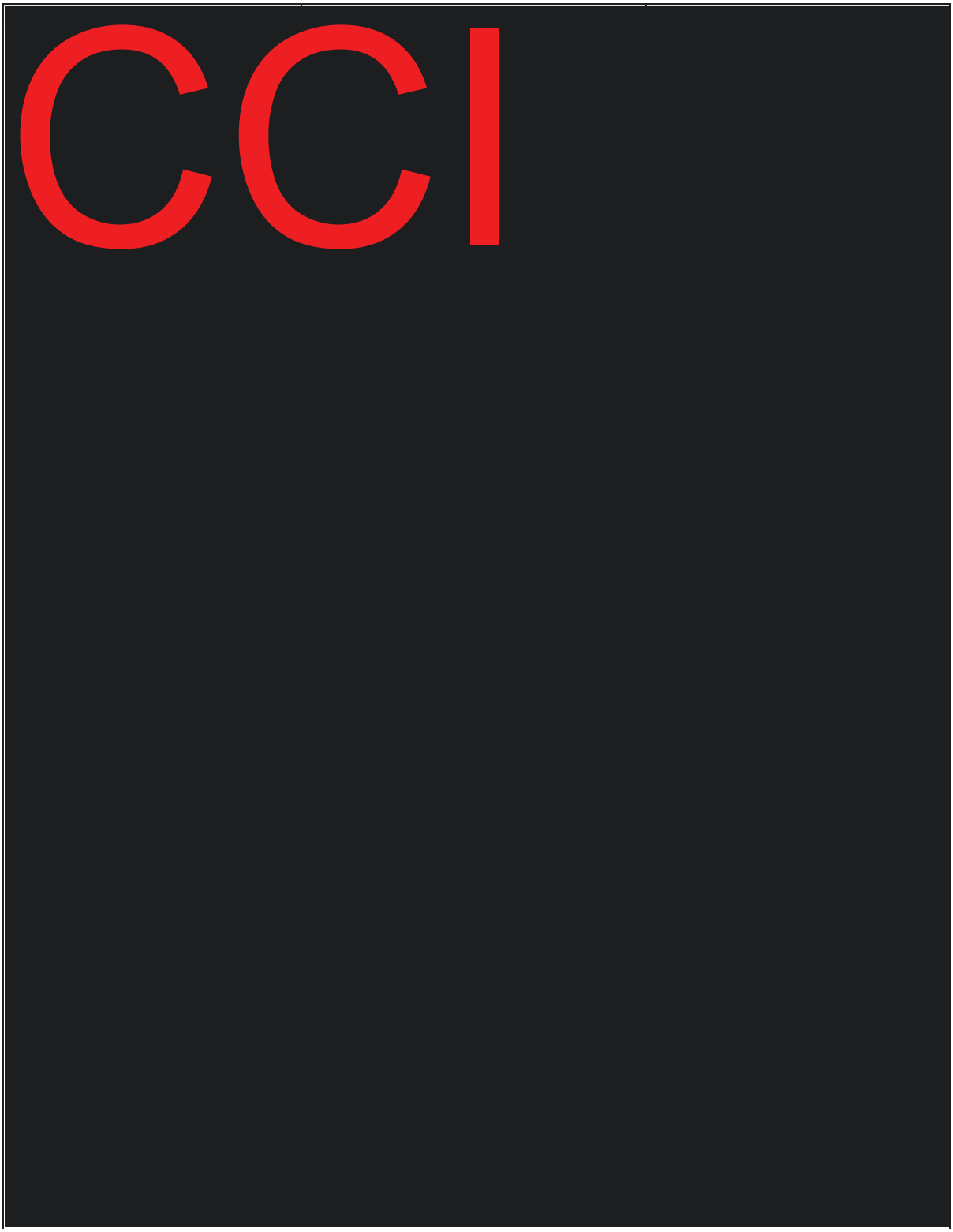

Table 2. List of Primary, Secondary, CCI Objectives, Endpoints, and Estimands for Primary Study Population

2.2. Study Design

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in the European Union and Australia (primary study population), with an additional cohort from Russia (Russian cohort).

The primary study population will consist of 1200 infants >36 weeks of gestation and ≥42 to ≤112 days of age at the time of consent by a parent(s)/legal guardian(s). Participants will be randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) by site-based randomization. Participants will receive the same vaccine (either 20vPnC or 13vPnC) for all 3 doses at roughly 2, 4, and 11 to 12 months of age (Doses 1, 2 , and 3, respectively). A specific vaccine containing DTaP, HBV, IPV, and Hib antigens will be administered concomitantly with all doses of 20vPnC or 13vPnC. Vaccines containing MMR and varicella antigens are also to be administered with Dose 3. These vaccines are intended to be given to all participants. However, in case of circumstances due to local practice/recommendations, some sites may not administer them to their participants at Dose 3, in which case MMR and varicella vaccines will be considered nonstudy vaccines.

Blood will be drawn from all participants for immunogenicity assessments 1 month after Dose 2, immediately prior to receipt of Dose 3, and 1 month after Dose 3. A subset of participants, based on consent to additional optional blood draws offered at certain sites, will have blood collected for immunogenicity assessments prior to Dose 1 and prior to Dose 2. 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) and 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 2 and from Dose 3 to 1 month after Dose 3. SAEs and NDCMCs will be collected for the entire duration of the study.

Approximately 60 additional participants will be enrolled in the Russian cohort. Due to timing of the submission of the clinical trial application, the Russian cohort will begin enrollment after the completion of enrollment of the primary study population. The schedule of visits for Russian participants will have a narrower window for age at enrollment and follow a somewhat modified visit window, in line with the Russian NIP (these are described in Section 10.10.4 of the protocol appendix). Russian participants will not receive MMR and varicella vaccinations as part of the study. They will receive MMR and varicella as per local requirements/NIP. Russian participants will not be requested to take part in the blood draws prior to Dose 1 and prior to Dose 2 but will participate in the required blood draws 1 month after Dose 2, before Dose 3, and 1 month after Dose 3.

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 2 and from Dose 3 to 1 month after Dose 3
- SAEs during the study (from Dose 1 to 1 month after Dose 3)
- NDCMCs during the study (from Dose 1 to 1 month after Dose 3)

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: presence, severity level, duration, and onset day.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device (caliper) units (range: 1 to 14 and >14) 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; e-diary = electronic diary.
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. The parent(s)/legal guardian(s) of the participants experiencing local reactions >14 caliper units (>7.0 cm) are to be contacted by the study site. An unscheduled visit may be required.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected 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 in a way similar to the way local reactions are handled for presence of event, 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 the participant's parent(s)/legal guardian(s) 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 Event Symptoms

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

Abbreviation: CRF = case report form; e-diary = electronic diary.

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 a 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 2 and from Dose 3 through 1 month after Dose 3.

AEs will be summarized by SOC 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. Standard algorithms for handling missing AE dates will be applied as described in the Pfizer Vaccines data standards 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 2 and, separately, from Dose 3 through 1 month after Dose 3. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.1.1.3.1).

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

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

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

3.1.1.5. Serious Adverse Events and Newly Diagnosed Chronic Medical Conditions

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

The safety endpoint "SAEs and NDCMCs from Dose 1 to the end of study" will be summarized by SOC and preferred term on participant level.

3.1.2. Primary Pneumococcal Immunogenicity Endpoints

- Pneumococcal IgG concentrations 1 month after Dose 2 and classification of IgG concentrations 1 month after Dose 2 using the reference concentrations

- Pneumococcal IgG concentrations 1 month after Dose 3

Concentrations of anticapsular IgG for the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) in 13vPnC and 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC will be determined in all participants using the Luminex assay. Results will be reported as IgG concentrations.

To support the primary pneumococcal immunogenicity endpoints, IgG concentrations will be classified based on serotype-specific IgG reference concentrations as defined below (Table 6).

Table 6. Serotype-Specific IgG Reference Concentrations

Serotypes	Reference Concentration (µg/mL)
1, 3, 4, 6A, 7F, 9V, 14, 18C, 19F, 23F	≥0.35
5	≥0.23
6B	≥0.10
19A	≥0.12
8, 10A, 11A, 12F, 15B, 22F, 33F	≥0.35
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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 levels to MMR and varicella virus 1 month after Dose 3

Antibody concentrations to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) will be determined on sera collected 1 month after Dose 3 for all randomized participants. Antibody concentrations to HBsAg, poliovirus strains (types 1, 2, and 3), Hib, and MMR and varicella will be determined on sera collected 1 month after Dose 3 from randomly selected subsets of participants with sufficient sera volumes. The subsets will be selected by a designated unblinded statistician to assure each subset has equal representation of both vaccine groups. Further details on subset selection will be described in a memo to the unblinded statistician before any testing is done.

To support the primary concomitant immunogenicity estimands, the antibody concentrations will be classified based on prespecified antibody thresholds for the concomitant vaccine antigens (Table 7).

Table 7. Prespecified Antibody Thresholds for the Concomitant Vaccine Antigens

Antigen	Prespecified Level
Diphtheria toxoid	≥0.1 IU/mL
Tetanus toxoid	≥0.1 IU/mL
Pertussis antigens (PT, FHA, PRN)	≥ The observed antipertussis antibody concentration achieved by 95% of 13vPnC recipients
HBsAg	≥10 mIU/mL
Poliovirus strains (types 1, 2, and 3)	≥1:8
Hib	≥0.15 µg/mL anti-PRP Alternative: ≥1.0 µg/mL anti-PRP[a]

Abbreviations: 13vPnC = 13-valent pneumococcal conjugate vaccine; anti-PRP = anti–polyribosylribitol phosphate; FHA = filamentous hemagglutinin; HBsAg = hepatitis B surface antigen; Hib = *Haemophilus influenzae* type b; PRN = pertactin; PT = pertussis toxin.

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

3.2. Secondary Endpoints

3.2.1. Secondary Pneumococcal Immunogenicity Endpoints

- Classification of IgG concentrations 1 month after Dose 3 using the same reference concentrations defined in Table 6
- Fold rise of pneumococcal IgG concentrations from before Dose 3 to 1 month after Dose 3
- Pneumococcal OPA titers 1 month after Dose 2
- Pneumococcal OPA titers 1 month after Dose 3

3.2.1.1. OPA Titers

OPA titers will be determined on serum from randomly selected subsets of participants provided by the designated unblinded statistician to assure each subset has equal representation of both vaccine groups. Further details on subset selection for OPA titers will be included in the memo to the unblinded statistician on the subset selection for the concomitant vaccine response testing (Section 3.1.3).

3.2.1.2. IgG Concentrations

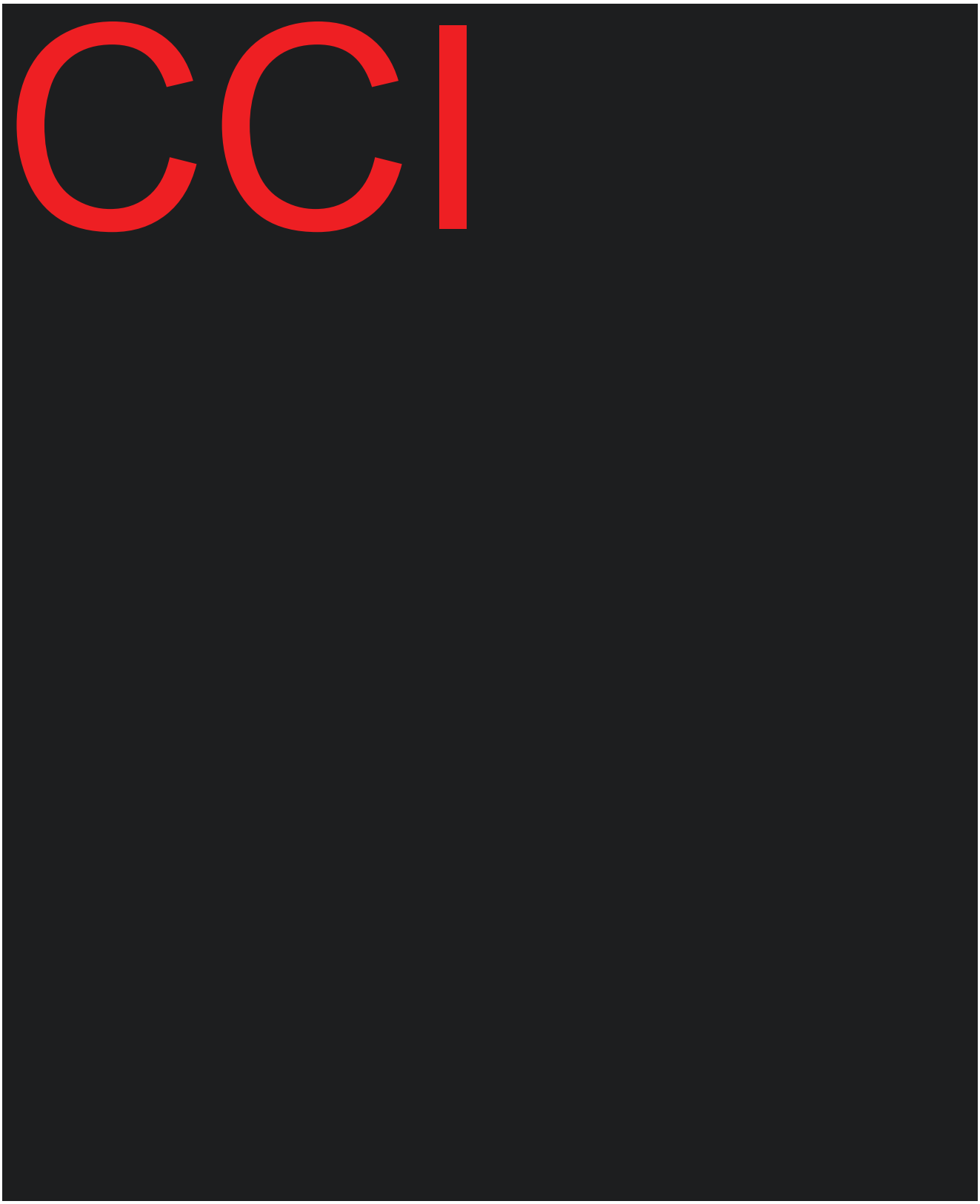
IgG concentrations at 1 month after Dose 3 will be classified using the same reference concentrations as described in Table 6. Fold changes will be calculated for each participant by taking the ratio of IgG concentrations from before Dose 3 to 1 month after Dose 3.

3.2.2. Secondary Concomitant Immunogenicity Endpoints

- Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) 1 month after Dose 2
- Antibody levels to poliovirus strains (types 1, 2, and 3) 1 month after Dose 2
- Antibody levels to Hib 1 month after Dose 2

Antibody concentrations to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) will be determined on sera collected 1 month after Dose 2 from a randomly selected subset of participants with sufficient sera volumes. Antibody concentrations to poliovirus strains and Hib will be determined on sera collected 1 month after Dose 2 from the same subset of participants selected for 1 month after Dose 3 concomitant vaccine assessment. Further details on subset selection will be described in the same memo described in Section 3.1.3 to the unblinded statistician before any testing proceeds.

Antibody concentrations at 1 month after Dose 2 will be classified using the same prespecified antibody thresholds defined in Table 7 (Section 3.1.3).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3.4. Baseline and Other Variables

3.4.1. Demographics and Medical History

The demographic variables are age at each dose (in days), sex (male or female), country/geographic region, race (black/African American, American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, white, selection of racial designations, multiracial, and not reported), and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino, not reported). 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 vaccination at Dose 1 for the Dose 1 age calculation. If the randomization date is also missing, then the informed consent date will be used for age calculation.

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

Medical history will be categorized according to MedDRA.

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3.4.3. Prior/Concomitant Vaccines and Concomitant Medications

The participants will receive a combination vaccine (Infanrix Hexa) with diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib with Doses 1, 2, and 3. For the primary study population, specific vaccines containing MMR and varicella antigens will also be administered concomitantly with Dose 3, although not in all participants, as in the case of circumstances due to local practice/recommendations in which some sites may not administer MMR and varicella to their participants at Dose 3. In such cases, MMR and varicella vaccines will be considered nonstudy vaccines; this is the case for all the Russian sites as well. 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 the specified 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 2 evaluable immunogenicity	Any participants who 1. Are eligible and randomized, 2. Are within the protocol-defined age window (ie, 42-112 days of age, inclusive) on the day of Dose 1, 3. Receive the first 2 vaccinations to which they are randomized, 4. Have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 2, and 5. Have no other major protocol deviations as determined by the clinician.

Population	Description
	The Dose 2 evaluable immunogenicity population will be the primary analysis population for the pneumococcal immunogenicity results from the blood collected before Dose 3. The statistical analysis of concomitant immunogenicity results 1 month after Dose 2 will be primarily based on the Dose 2 evaluable immunogenicity population restricted to those who also receive the appropriate concomitant vaccines with the first 2 doses. Participants will be grouped as randomized in the immunogenicity analysis.
Dose 3 evaluable immunogenicity	Any participants who 1. Are eligible and randomized, 2. Are within the protocol-defined age window (ie, 42-112 days of age, inclusive) on the day of Dose 1, 3. Receive all 3 vaccinations as randomized, with Dose 3 received within the protocol-defined window (ie, 335-386 days of age, inclusive), 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 pneumococcal immunogenicity results after Dose 3. The statistical analysis of concomitant immunogenicity results 1 month after Dose 3 will be primarily based on the Dose 3 evaluable immunogenicity populations restricted to those who also receive the appropriate concomitant vaccines at the Dose 3 visit. Participants will be grouped according to their randomized vaccine in the immunogenicity analysis.
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Population	Description
Safety	All participants who receive at least 1 dose of the investigational product and have safety data assessed after any dose. Participants will be grouped according to the vaccine as administered in the safety analysis. Safety data after Dose 3 will be summarized for participants in the safety population who receive Dose 3 with safety follow-up after Dose 3.

For the Dose 2 and Dose 3 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 13vPnC development program. The major protocol deviations will be determined by clinical review or medical monitor. 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 a 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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Local reactions and systemic events based on the e-diary will be summarized from participants with any e-diary data reported in the safety population.

5. GENERAL METHODOLOGY AND CONVENTIONS

Statistical analyses will be carried out when the safety and immunogenicity data through 1 month after Dose 3 for the primary study population are available and released. Additional analysis will be conducted on the Russian cohort when the data are available and released from those participants.

Sponsor personnel and investigators involved in evaluating participant data in the primary study population will be blinded to vaccine assignment until the analysis at the completion of the primary study population. The study team and investigators involved in evaluating the Russian cohort will remain blinded to the vaccine assignments of the Russian cohort until that cohort has completed the study. Laboratory personnel performing the assays will remain blinded until all assays are completed and assay results finalized.

5.1. Hypotheses and Decision Rules

All hypothesis testing will be performed on the data from the primary study population.

5.1.1. Pneumococcal Immunogenicity Hypotheses

5.1.1.1. Percentage of Participants With Prespecified Pneumococcal IgG Concentrations at 1 Month After Dose 2 (Primary Pneumococcal Immunogenicity Objectives)

Hypothesis testing will be used to assess the NI of 20vPnC to 13vPnC for the percentage of participants with predefined pneumococcal IgG concentrations 1 month after Dose 2 (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 predefined IgG antibody concentration for the serotype from the 20vPnC group 1 month after Dose 2;
- 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 for the serotype from the 13vPnC group 1 month after Dose 2;
- 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 the predefined IgG concentration for the serotype with the lowest percentage among the 13 matched serotypes from the 13vPnC group 1 month after Dose 2, 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 a predefined IgG concentration for a serotype will be declared if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages, computed using the Miettinen and Nurminen[1] method, is greater than –10% (10% NI margin).

5.1.1.2. Pneumococcal IgG GMCs 1 Month After Dose 2 (Primary Pneumococcal Immunogenicity Objectives)

Hypothesis testing will be used to assess the NI of 20vPnC to 13vPnC for pneumococcal IgG GMCs 1 month after Dose 2. 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 2;
- 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 2;
- 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 among the 13 serotypes from the 13vPnC group 1 month after Dose 2, 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 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 group to the 13vPnC group is greater than 0.5 (2-fold NI margin).

5.1.1.3. Pneumococcal IgG GMCs 1 Month After Dose 3 (Primary 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 2, 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, except for the 7 additional serotypes in 20vPnC, where $\ln(\mu_{13vPnC})$ is the natural log of the geometric mean IgG concentration for the serotype with the lowest IgG GMC 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_{0C}: $\ln(\mu_{20vPnC}) - \ln(\mu_{13vPnC}) \leq \ln(0.5)$) 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 the 20vPnC group to the 13vPnC group 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 Levels to Each Concomitant Vaccine Antigen at 1 Month After Dose 3 (Primary Concomitant Immunogenicity Objectives)

Hypothesis testing will be used to assess the NI of the 20vPnC group to the 13vPnC group for the percentage of participants with the prespecified antibody level to each concomitant vaccine antigen at 1 month after Dose 3. For each of the applicable concomitant vaccine antigens (diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib) at 1 month after Dose 3, the null hypothesis is:

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

where

- 10% is the margin for NI.
- π_{20vPnC} is the percentage of participants with a prespecified antibody level to the specific concomitant vaccine antigen at 1 month after Dose 3 in the 20vPnC group.
- π_{13vPnC} is the percentage of participants with a prespecified antibody level to the specific concomitant vaccine antigen at 1 month after Dose 3 in the 13vPnC group.

The prespecified antibody thresholds for the concomitant vaccine antigens are listed in Section 3.1.3. The null hypothesis (H_{0C}) testing for NI will be rejected for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for the difference (20vPnC – 13vPnC) in percentages, computed using the Miettinen and Nurminen method, is greater than –10% (10% NI margin) for that concomitant vaccine antigen.

5.1.2.2. GMCs of Antibody Levels to Concomitant Vaccine Antigens 1 Month After Dose 3 (Primary Concomitant Immunogenicity Objectives)

Hypothesis testing will be used to assess the NI of the 20vPnC group to the 13vPnC group for GMCs of antibody levels to each concomitant vaccine antigen 1 month after Dose 3. For each of the applicable concomitant vaccine antigens (MMR and varicella) at 1 month after Dose 3, the null hypothesis is:

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

where

- ln(0.5) corresponds to a 2-fold margin for NI.
- $\ln(\mu_{20vPnC})$ is the natural log of the GMCs for antibody levels to the specific concomitant vaccine at 1 month after Dose 3 in the 20vPnC group.
- $\ln(\mu_{13vPnC})$ is the natural log of the GMCs for antibody levels to the specific concomitant vaccine at 1 month after Dose 3 in the 13vPnC group.

The null hypothesis (H_{0D}) testing for NI will be rejected for a concomitant vaccine antigen if the lower bound of the 2-sided 95% CI for the concomitant antibody GMR (20vPnC over 13vPnC) 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% CIs 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.

The 3-tier approach (Section 3.1.1.4) 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, the descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Means

For immunogenicity results of IgG concentrations, OPA titers, and the antibody levels of the concomitant vaccines, GMs will be computed along with associated 95% CIs. The GMs and the 95% CIs will be calculated as the means and the CIs of the assay results on the natural

log scale and then exponentiating the results. Two-sided 95% CIs will be calculated based on the t-distribution.

5.2.2.2. Geometric Mean Ratios

Where appropriate, GMRs and their 2-sided 95% CIs will be derived by calculating differences in means (20vPnC – 13vPnC) and CIs on the natural log scale of the concentrations/titers and then exponentiating the results. Two-sided 95% CIs will be calculated based on the t-distribution (allowing for unequal variances).

5.2.2.3. Geometric Mean Fold Rises

GMFRs will be calculated as the mean of the difference of antibody levels (later result minus earlier result) on the natural log scale and exponentiating the results. The associated 2-sided 95% CIs are computed by exponentiating the CIs 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 dates. 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 × LLOQ for analysis.

No additional imputation will be applied to other missing data.

6. ANALYSES AND SUMMARIES

Unless otherwise specified, the analyses and summaries are based on the primary study population. The analyses and summaries on the Russian cohort will be described separately in Section 9, Appendix 2.

6.1. Primary Endpoints

6.1.1. Primary Safety Endpoints

6.1.1.1. Local Reactions

Results from local reactions after each dose (Doses 1, 2, and 3) 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: For percentages of each vaccine group, the 2-sided Clopper-Pearson CIs will be calculated. The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1).
- Intercurrent events and missing data: Missing values will not be imputed. CCI 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.

6.1.1.2. Systemic Events

Results from systemic events after each dose (Doses 1, 2, and 3) 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: For percentages, the 2-sided Clopper-Pearson CIs will be calculated for each vaccine group. The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1).

- Intercurrent events and missing data: Missing values will not be imputed.
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- Reporting result: Counts and percentages of participants with the indicated endpoint and the associated 2-sided 95% CIs for 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.

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6.1.1.3. Adverse Events

6.1.1.3.1. Main Analysis

- Estimands:
  - The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 (Section 2.1).
  - The percentage of participants reporting AEs from Dose 3 to 1 month after Dose 3 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time points: Dose 1 to 1 month after Dose 2 and Dose 3 to 1 month after Dose 3.
- 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 result: For all 3 tiers, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided Clopper-Pearson 95% CI for participants reporting any AE, each SOC, and each preferred term within SOCs will be presented by vaccine group.

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

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 based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed 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 1 month after Dose 3 (Section 2.1).
  - The percentage of participants reporting NDCMCs from Dose 1 to 1 month after Dose 3 (Section 2.1).
- Analysis set: Safety population (Section 4).
- Analysis time point: Dose 1 to 1 month after Dose 3.
- Analysis methodology: For percentages, the 2-sided Clopper-Pearson CIs will be calculated for each vaccine group (Section 5.2.1).
- Intercurrent events and missing data: No missing values will be imputed except for partial SAE/NDCMC start dates (Section 5.3).
- Reporting results: The numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 2-sided Clopper-Pearson 95% CI for participants reporting any SAEs/NDCMCs, by each SOC, and each preferred term within SOCs will be presented by vaccine group. SAEs and NDCMCs will be presented separately.

6.1.2. Primary Pneumococcal Immunogenicity Endpoints

6.1.2.1. Participants With Predefined Pneumococcal IgG Concentrations 1 Month After Dose 2

6.1.2.1.1. Main Analyses

- Estimands:
    - For each of the 13 matched serotypes, the difference in the percentages of participants with predefined IgG concentrations between the 20vPnC and the 13vPnC groups (Section 2.1).
    - For each of the 7 additional serotypes in 20vPnC, the difference in the percentages of participants with predefined IgG concentrations between the 20vPnC group and the lowest percentage of participants with predefined IgG concentrations among the 13 serotypes from the 13vPnC group, excluding serotype 3 (Section 2.1).
- Analysis set: Dose 2 evaluable immunogenicity population (Section 4).
- Analysis time point: 1 Month after Dose 2.
- Analysis methodology: The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1) for each 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 for all 20 serotypes 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 IgG Concentrations 1 Month After Dose 2

6.1.2.2.1. Main Analyses

- Estimands:
    - For each of the 13 matched serotypes in 20vPnC, the GMR of IgG concentrations from the 20vPnC group to the 13vPnC group (Section 2.1).
    - For each of the 7 additional serotypes in 20vPnC, the ratio of IgG GMC from the 20vPnC group to the lowest IgG GMC among the 13 serotypes from the 13vPnC group, excluding serotype 3 (Section 2.1).
- Analysis set: Dose 2 evaluable immunogenicity population (Section 4).
- Analysis time point: 1 Month after Dose 2.
- Analysis methodology: The 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, 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 GMCs and the corresponding 2-sided 95% CIs from each vaccine group, as well as the GMRs of the 20vPnC group to the 13vPnC group and the 2-sided 95% CIs, will presented.

Figures:

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

Antibody response line plots showing the IgG GMCs, with the corresponding 95% CIs, for the 5 blood draw time points (before Dose 1, before Dose 2, 1 month after Dose 2, before Dose 3, and 1 month after Dose 3) will be presented by vaccine group.

The GMCs, and the corresponding 95% CIs, of serotype-specific IgG concentrations 1 month after Dose 2, before Dose 3, and 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.

6.1.2.2.2. Supplementary Analysis

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

6.1.2.3. Pneumococcal IgG Concentrations 1 Month After Dose 3

This endpoint will be analyzed the same way as for pneumococcal IgG concentrations 1 month after Dose 2 (Section 6.1.2.2) except that the analysis time point is 1 month after Dose 3.

6.1.3. Primary Concomitant Immunogenicity Endpoints

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

6.1.3.1.1. Main Analyses

- Estimand: Differences in percentages of participants with prespecified antibody levels 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: For percentages, the 2-sided Clopper-Pearson CIs will be calculated for each vaccine group. The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1). The NI will be assessed by comparing the lower bound of the 95% CI against the NI margin (Section 5.1.2.1).

- 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 applicable 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 levels from each vaccine group, as well as the percentage difference (20vPnC – 13vPnC) and the associated 95% CI, will be presented.

Figures:

A forest plot of between-group differences (20vPnC – 13vPnC) with 95% CIs for all concomitant vaccine antigens will be presented.

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6.1.3.2. Antibody Levels to Concomitant Vaccine Antigens 1 Month After Dose 3

6.1.3.2.1. Main Analyses

- Estimand: The GMRs of antibody levels to MMR and varicella antigens from the 20vPnC group to the 13vPnC group 1 month after Dose 3 (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 GMR 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 5.1.2.2).

- Intercurrent events and missing data: Serology data deemed unevaluable because of noncompliance with the key protocol criteria will be excluded. Concentrations below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for analysis. Missing data will not be imputed.

- Reporting results: For each applicable vaccine antigen (MMR and varicella), 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 GMRs with 95% CIs for each antigen will be presented.

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6.2. Secondary Endpoints

6.2.1. Secondary Pneumococcal Immunogenicity Endpoints

6.2.1.1. Participants With Predefined Pneumococcal IgG Concentrations 1 Month After Dose 3

This endpoint will be analyzed the same way as the endpoint described in Section 6.1.2.1 on Dose 3 evaluable immunogenicity population, except that the analysis time point is 1 month after Dose 3 and no hypothesis test will be performed.

6.2.1.2. OPA Titers 1 Month After Dose 2 and 1 Month After Dose 3

- Estimand: The GMTs of OPA 1 month after Dose 2 and 1 month after Dose 3 (Section 2.1).
- Analysis sets: Dose 2 evaluable immunogenicity population for 1 month after Dose 2 and Dose 3 evaluable immunogenicity population for 1 month after Dose 3 (Section 4).
- Analysis time points: 1 Month after Dose 2 and 1 month after Dose 3.
- Analysis methodology: The GMTs and the 2-sided 95% CIs from each vaccine group will be derived based on the t-distribution (Section 5.2.2.1).
- Reporting results: For each of the 20 vaccine serotypes, the GMTs and the 95% CIs for OPA will be presented for both vaccine groups.

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6.2.1.3. Fold Change of IgG Concentrations From Before Dose 3 to 1 Month After Dose 3

- Estimand: The GMFRs of pneumococcal IgG concentrations from before Dose 3 to 1 month after Dose 3 in each vaccine group (Section 2.1).
- Analysis set: Dose 3 evaluable immunogenicity population (Section 4).
- Analysis time points: Before Dose 3 and 1 month after Dose 3.
- Analysis methodology: The GMFRs and the 2-sided 95% CIs from each vaccine group will be based on the t-distribution (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 IgG concentrations will be presented for both vaccine groups at the specified time points.

6.2.2. Secondary Concomitant Immunogenicity Endpoints

6.2.2.1. Participants With Prespecified Antibody Levels to Each Concomitant Vaccine Antigen at 1 Month After Dose 2

- Estimand: Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), poliovirus strains (types 1, 2, and 3), and Hib at 1 month after Dose 2 in each vaccine groups (Section 2.1).
- Analysis set: Dose 2 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 2.
- Analysis methodology: Percentages and the 2-sided Clopper-Pearson CIs will be calculated for each vaccine group. The between-group difference (20vPnC – 13vPnC) and the corresponding 2-sided 95% CI will be calculated using the Miettinen and Nurminen method (Section 5.2.1).
- Reporting results: For each concomitant vaccine antigen, the numerator (n) and the denominator (N) used in the percentage calculation, the percentage (%), and the corresponding 95% CI for participants with prespecified antibody levels from each vaccine group, as well as the percentage difference (20vPnC – 13vPnC) and the associated 95% CI, 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 (in days), sex, race, ethnicity, and country, will be summarized for the safety population for each vaccine group and overall. Similar summaries will be done for the Dose 2 evaluable immunogenicity population and the Dose 3 evaluable immunogenicity population. CCI

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6.5.1.2. Medical History

Each reported medical history term will be mapped to a SOC 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 SOC and preferred term level, will be summarized by vaccine group and overall by cohort for the overall 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 number and percentage of participants who received vaccinations (Dose 1, 2, or 3), who completed the follow-up visits (1 month after Dose 2, 1 month after Dose 3), who completed all visits, who withdrew before the visit 1 month after Dose 2, who withdrew after the visit 1 month after Dose 2 but prior to Dose 3, who withdrew after Dose 3 but before the visit 1 month after Dose 3 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 each analysis population 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 the optional blood draws before Dose 1 and before Dose 2 and for the protocol-specific blood draws 1 month after Dose 2, before Dose 3, and 1 month after Dose 3.

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 and 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 vaccine to which they were randomized 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 vaccines 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 assigned vaccine schedule. Summarization will be done separately for the following schedules:

- with Dose 1, Dose 2, or Dose 3, by dose
- between Dose 1 and 1 month after Dose 2
- between 1 month after Dose 2 and Dose 3
- between Dose 3 and 1 month after Dose 3

A listing of concomitant medications used to treat SAEs and NDCMCs from Dose 1 to 1 month after Dose 3 will be provided for the safety population.

6.6. Safety Summaries and Analyses

Safety summaries and analyses of the local reactions, systemic events, AEs, SAEs, and NDCMCs are described under the primary safety endpoints section (see Section 6.1.1).

7. INTERIM ANALYSES

No interim analysis is planned for this study. Statistical analyses will be carried out after the completion of study visits by the primary study population, and the analysis for the Russian cohort will be conducted when those participants have completed their study visits.

7.1. Introduction

Not applicable.

7.2. Analysis Timings

The safety and immunogenicity results in this study will be analyzed and reported when the safety and immunogenicity data 1 month after Dose 3 are available from all participants in the primary study population.

The safety and pneumococcal immunogenicity results of the Russian cohort will be analyzed and reported when safety and pneumococcal immunogenicity data are available from all participants in the Russian cohort.

Sponsor personnel involved in evaluating participant data in the primary study population will be blinded to vaccine assignment in that population until the analysis at the completion of the primary study population. The study team will remain blinded to the vaccine assignments of the Russian cohort until that cohort has completed the study. Laboratory personnel performing the assays will remain blinded until all assays are completed and assay results of each population/cohort are finalized.

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

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 (classification system)
BLQ	below 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
FHA	filamentous hemagglutinin
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
HBV	hepatitis B virus
Hib	*Haemophilus influenzae* type b
ICD	informed consent document
IgG	immunoglobulin G
IPV	inactivated poliovirus vaccine
IRT	interactive response technology
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, and rubella vaccine
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
NIP	National Immunization Program
OPA	opsonophagocytic activity
PRN	pertactin
PRP	polyribosylribitol phosphate
PT	pertussis toxin
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
WHO	World Health Organization

Appendix 2. Analysis for the Russian Cohort

Objectives, Estimands, and Endpoint for the Russian Cohort

Safety Objective	**Estimands**	**Safety Endpoints**
To describe the safety profile of 20vPnC in the Russian cohort	In Russian participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination • The percentage of participants reporting prompted systemic events within 7 days after each vaccination • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 • The percentage of participants reporting SAEs through 1 month after Dose 3 • The percentage of participants reporting NDCMCs through 1 month after Dose 3	• 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 describe the IgG responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC for each vaccine group: • Percentages of participants with predefined IgG concentrations at 1 month after Dose 2 • IgG GMCs at 1 month after Dose 2 • IgG GMCs at 1 month after Dose 3	• Pneumococcal IgG concentrations
Secondary Pneumococcal Immunogenicity Objectives	**Estimands**	**Secondary Pneumococcal Immunogenicity Endpoints**
To further describe immune responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC for each vaccine group: • Percentages of participants with predefined IgG concentration at 1 month after Dose 3 • OPA GMTs at 1 month after Dose 2 • OPA GMTs at 1 month after Dose 3	• Pneumococcal IgG concentrations • Pneumococcal OPA titers

After the final data from the Russian participants become available, a separate analysis based on the Russian cohort will be conducted. The analysis methods will be similar to the analysis conducted for the primary study population, except that:

- Only descriptive statistics will be displayed.
- The evaluable immunogenicity population definitions for the Russian cohort are similar to that for the primary study population (Section 4), with the exception that the protocol defined age window for Dose 1 is 42 to 70 days, inclusive, and for Dose 3 is 335 to 455 days, inclusive.