Protocol B1851178

A PHASE 3 OPEN-LABEL TRIAL TO ASSESS THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN INFANTS AND YOUNG CHILDREN IN CHINA WHO ARE NAIVE TO PNEUMOCOCCAL VACCINATION

Statistical Analysis Plan
(SAP)

Version: 3

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B1851178 is based on protocol amendment 1 dated 19JAN2018. The study protocol was amended on 19 February 2019. The main purpose of this SAP amendment is to ensure the consistency between protocol amendment 2 and the SAP.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	Add GMFR analyses compare between Cohorts of children 7 months to < 6 years of age (Cohort 2, 3,4) and Cohort of infants 6 weeks to 2 months of age (Cohort 1), and analyses to address Center for Drug Evaluation (CDE) requests	Protocol Amendment 2
3	Section 2. Add statement to include the additional 280 subjects into analyses	Request by regulatory authorities

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B1851178. 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. An additional 280 subjects stated in protocol amendment 2 will be analyzed similarly to that of the original 280 subjects enrolled from town level immunization clinics which were under the Huaiyin county Center for Disease Control (CDC). Analyses for primary study report will include data collected from originally enrolled subjects including 280 subjects from town level immunization clinics, this may be repeated with study data from originally enrolled subjects from town level CDC replaced with these additional subjects.

In response to the request that was provided to Study B1851178 team by Center for Drug Evaluation (CDE) of China National Medical Products Administration (NMPA) on 22 November 2021 about age expansion NDA, the study team was requested to include the 280 additional subjects stated in protocol amendment 2 into the analyses outlined in this SAP.

Among the 280 additional subjects, a total of 177 subjects were enrolled into Cohort 2, 73 subjects were enrolled into Cohort 3 and 30 subjects were enrolled into Cohort 4. All study endpoints, analysis sets, statistical analyses and summaries defined in this SAP had been performed for the primary study report and these will be repeated again by including the additional 280 subjects in to Cohorts 2-4 as a supplemental study report.

2.1. Study Objectives

2.1.1. Primary Immunogenicity Objective

- To assess the immune responses to the 13 pneumococcal serotypes induced by 13-valent pneumococcal conjugate vaccine (13vPnC) in infants and children 7 months to <6 years of age (Cohorts 2, 3, and 4) compared to immune responses in infants 6 weeks to 2 months of age (Cohort 1).

2.1.2. Primary Safety Objective

- To evaluate the safety profile of 13vPnC in infants and children 7 months to <6 years of age (Cohorts 2, 3, and 4) as measured by the incidence rates of local reactions, systemic events (including the use of antipyretic medication), and adverse events (AEs).

2.1.3. Secondary Immunogenicity Objectives

- To describe the functional antibody responses as measured by opsonophagocytic activity (OPA) to the 13 pneumococcal serotypes induced by 13vPnC in infants and children 7 months to <6 years of age (Cohorts 2, 3, and 4) compared to responses in infants 6 weeks to 2 months of age (Cohort 1).

- To describe the immune responses to 13vPnC compared to *Haemophilus influenzae* type b (Hib)-vaccinated controls in Cohorts 2, 3, and 4.

- To describe the circulating antibody levels to the 13 pneumococcal serotypes from before vaccination through 5 years of age (4 years after the last study vaccination) in Cohort 1.

2.1.4. Secondary Safety Objective

- To evaluate the safety profile of 13vPnC as measured by the incidence rates of AEs in Cohort 1.

2.2. Study Design

- This is a phase 3 randomized, open-label study to evaluate the safety, tolerability, and immunogenicity of 13vPnC in infants and young children who are naïve to pneumococcal vaccination.

- Subjects will be stratified into 4 cohorts defined by their age pleat consent:

  - Cohort 1: Subjects 6 weeks (42 days) to 2 months (56 days) of age;

  - Cohort 2: Subjects 7 months (210 days) to <12 months (<365 days) of age;

  - Cohort 3: Subjects ≥1 year to <2 years of age;

  - Cohort 4: Subjects ≥2 years to <6 years of age.

- Subjects in Cohort 1 will all receive 13vPnC at 2, 4, 6 and 12 to 15 months of age. See Table 2 below.

- Subjects in Cohorts 2, 3, and 4 will be randomized into 2 groups in a 2:1 ratio to receive 13vPnC or comparator (Hib vaccine) according to age-appropriate schedules. See Table 2 below.

Table 2. Age at Vaccination

		Age at first vaccination	Age at second vaccination	Age at third vaccination	Age at fourth vaccination
Cohort 1	13vPnC	42 to 56 Days of Age	42 to 70 Days After Visit 1	42 to 70 Days After Visit 2	365 to 455 Days of Age
Cohort 2	13vPnC or Hib	7 to <12 Months of Age	At Least 28 Days After Visit 1	365 Days to <450 Days of Age and at Least 56 Days After Visit 2[a]	
Cohort 3	13vPnC or Hib	≥1 to <2 Years of Age	At Least 56 Days After Visit 1[b]		
Cohort 4	13vPnC or Hib	≥2 to <6 Years of Age			

a. Subjects in Cohort 2 randomized to Hib vaccine will not receive a vaccination at Visit 3. These subjects may receive a third dose of Hib vaccine according to local practice or national recommendations, at the discretion of the investigator.
b. Subjects in Cohort 3 randomized to Hib vaccine will not receive a vaccination at Visit 2.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary Immunogenicity Endpoint

- The serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) for each of the pneumococcal serotypes measured 1 month after the last dose of 13vPnC in Cohort 2, 3, 4 compared to IgG GMCs measured 1 month after the infant series in Cohort 1.

3.1.2. Primary Safety Endpoints

- The incidence of local reactions and systemic events (including the use of antipyretic medication) in the 7 days after each vaccination (13vPnC or Hib) in Cohorts 2, 3 and 4.

- The incidence of AEs from the signing of the informed consent document (ICD) to 1 month after the last vaccination (13vPnC or Hib) in Cohort 2, 3 and 4.

- The incidence of newly diagnosed chronic medical conditions from 1 month after the last study vaccination (13vPnC or Hib) to 6 months after the last study vaccination in Cohort 2, 3 and 4.

- The incidence of serious adverse events (SAEs) from the signing of the ICD to 6 months after the last study vaccination (13vPnC or Hib) in Cohort 2, 3 and 4.

3.2. Secondary Endpoint(s)

For OPA-related immunogenicity endpoints below, a random subset of approximately 50 subjects randomized to receive 13vPnC for each cohort (Cohort 1, 2, 3, 4) will be selected for OPA testing, and a random subset of approximately 25 subjects randomized to receive Hib vaccine for each cohort (Cohort 2, Cohort 3, Cohort 4) will be selected for OPA testing. Those random subsets will be performed by randomly ordering all subjects with adequate serum volume and selecting enough subjects (probably more than 50) assigned to receive 13vPnC in each cohort and enough subjects (probably more than 25) assigned to receive Hib vaccine in Cohort 2, 3, 4 to provide around 50 results for each serotype in 13vPnC at each planned blood draw visit for each cohort, and around 25 results for each serotype in Hib vaccine at each planned blood draw visit for each Cohort 2, 3 and 4.

3.2.1. Secondary Immunogenicity Endpoints

- The serotype-specific OPA geometric mean titers (GMTs) for each of the pneumococcal serotypes measured in a subset of approximately 50 subjects per cohort measured 1 month after the last dose of 13vPnC in Cohort 2, 3, 4 compared to OPA GMTs measured 1 month after the infant series in Cohort 1.

- Serotype-specific IgG GMCs in all subjects and OPA GMTs in approximately 50 subjects per cohort vaccinated with 13vPnC (Cohort 2 ,3, 4) and approximately 25 subjects per cohort vaccinated with Hib (Cohort 2, 3, 4) using blood drawn at the following visits:

    - Cohort 2: Visit 1, Visit 4
    - Cohort 3: Visit 1, Visit 3
    - Cohort 4: Visit 1, Visit 2

- Serotype-specific IgG GMCs in all subjects and OPA GMTs in approximately 50 subjects at all times points in Cohort 1.

- Proportion of subjects achieving a serotype-specific IgG concentration ≥0.35 μg/mL for each of the pneumococcal serotypes measured 1 month after the last dose in all subjects per cohort vaccinated with 13vPnC (Cohort 2 ,3, 4) and all subjects per cohort vaccinated with Hib (Cohort 2, 3, 4), and 1 month after the infant series in all subjects vaccinated with 13vPnC in Cohort 1.

- Proportion of subjects achieving a serotype-specific OPA titer ≥ the lower limit of quantitation (LLOQ) for each of the pneumococcal serotypes measured 1 month after the last dose in approximately 50 subjects per cohort vaccinated with 13vPnC (Cohort 2, 3, 4) and approximately 25 subjects per cohort vaccinated with Hib (Cohort 2, 3, 4) and

1 month after the infant series in approximately 50 subjects vaccinated with 13vPnC in Cohort 1.

3.2.2. Secondary Safety Endpoints

- The incidence of AEs from the signing of the ICD to 1 month after vaccination 3 in Cohort 1.
- The incidence of newly diagnosed chronic medical conditions from 1 month after vaccination 3 to vaccination 4 in Cohort 1.
- The incidence of AEs from vaccination 4 to 1 month after vaccination 4 in Cohort 1.
- The incidence of newly diagnosed chronic medical conditions from 1 month after vaccination 4 to 6 months after vaccination 4 in Cohort 1.
- The incidence of SAEs from the signing of the ICD to 6 months after vaccination 4 in Cohort 1.

3.3. Other Endpoints

Not applicable.

3.4. Safety Endpoints

3.4.1. Adverse Events

CCI [redacted]

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

Tier-2 events: These are events that are not tier-1 but are "common". A Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is defined as a tier-2 event if there are at least 5% in any vaccine group.

CCI [redacted]

3.4.2. Reactogenicity Endpoints

Reactogenicity data captured in the electronic diary (e-diary) for Cohorts 2, 3, and 4 after each investigational product (13vPnC or Hib vaccine) vaccination consist of local reactions (redness, swelling, and tenderness), systemic events (fever, decreased appetite, drowsiness, irritability, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and use of antipyretic medication to prevent or treat symptoms.

3.4.2.1. Local Reactions

Local reactions for Cohorts 2, 3, and 4 reported in the e-diary are redness, swelling, and tenderness.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 14) for 7 days following vaccination (Day 1 to 7), and then categorized using the scale shown in Table 3 below. The measurements will then be recorded in the e-diary.

A measuring device will be given to the caregiver(s) with instructions for measuring any redness or swelling at the injection site. Each unit is equivalent to 0.5 cm. The caregiver(s) will be asked to measure and to report the largest diameters of a local reaction. In case a measurement is between 2 values, the higher value should be reported. At the time of entry into the e-diary, the caregiver(s) should record the maximum severity of the reaction since the previous entry into the e-diary.

Table 3. Redness and Swelling

Absent	No redness or swelling present (0 units)
Mild	0.5 to 2.0 cm (1 to 4 units)
Moderate	2.5 to 7.0 cm (5 to 14 units)
Severe	>7.0 cm (>14 units)

The caregiver will be asked to assess whether tenderness is present at the investigational product (13vPnC or Hib vaccine) injection site and grade it according to the scale shown in Table 4. The caregiver will then record the assessment in the e-diary. For events that were ongoing on the last day that the e-diary was completed, the end date will be collected in the case report form (CRF).

Table 4. Tenderness

Absent	No discernible tenderness
Present	Tenderness present
Significant	Tenderness interfering with limb movement

Although the e-diary was designed in such a way that the parent could not skip a question without answering it, the possibility of conflicting responses still exists. For redness and swelling, device units could be recorded with no or missing answer to the root question; or, redness/swelling could be recorded as yes with a measuring device unit of zero (if defaulted by database). The combination of no with a device unit recorded will result in the answer to the root question being considered yes. The combination of yes with a device equal to 0 will result in the measuring device unit being considered as ">0". A missing value for the root question with a positive value for measuring device units will result in the answer to the root question being considered yes. These rules are summarized in Table 5 below.

Table 5. Data Conventions for Redness and Swelling in the Presence of Inconsistent or Missing Responses

Reported Response		Recoded Response	
Present	**Measuring Device Units**	**Present**	**Measuring Device Units**
Missing	Missing	Missing	Missing
Missing	0	Missing	Missing
Missing	1-14	Yes	1-14
Missing	14+	Yes	14+
Yes	Missing	Yes	Missing
Yes	0	Yes	>0
Yes	1-14	Yes	1-14
Yes	14+	Yes	14+
No	Missing	No	Missing
No	0	No	Missing
No	1-14	Yes	1-14
No	14+	Yes	14+

Redness and swelling will be further categorized according to the following scale based on the recoded responses:

= •, if both variables (presence/absence and device units) are missing or otherwise unavailable, or if present and device units is missing;

= 0 (absent) if not present and device unit is missing;

= 1 (mild), if present and area is 0.5 to 2.0 cm (1 to 4 device units), or if present and measuring device units are ">0";

= 2 (moderate), if present and area is >2.0 to 7.0 cm (5 to 14 device units);

= 3 (severe), if present and area is >7.0 cm (>14 device units).

In addition, the maximum diameter of the affected area for redness and swelling will be determined. The maximum diameter will be derived as follows:

= xx (maximum actual value), if present on at least 1 day in the required interval and measuring device units >0;

= •, if values are a mixture of absent and missing for required days in the interval;

= 0, if all values are absent for all required days in the interval.

[redacted]

[redacted]

For the purpose of creating an indicator variable for tenderness on each day, the following algorithm will be used:

= •, if tenderness is missing;

= 0 (absent), if tenderness is recorded as none discernible;

= 1 (present), if tenderness is recorded as present;

= 2 (significant), if tenderness is recorded as interferes with limb movement.

For the local reactions, 3 more derivations are required: whether or not a specific reaction occurred on "any day", whether or not the subject experienced "any local reaction" on a given day, and whether or not the subject experienced "any local reaction" on "any day".

For the occurrence of a specific reaction on "any day", the following algorithm is used and is summarized in Table 6:

= 1 (yes), if the subject reports the specified reaction as yes (or present) on any day in the required interval;

= 0 (no), if the subject reports the specified reaction as no (or absent) for all days in the required interval;

= •, if the subject reports the specified reaction as a combination of no and missing for all days in the required interval.

Table 6. Derivation of "Each Day" and "Any Day" for Local Reactions in the Presence of Missing Values

Subject	Day	Response	Each Day	Any Day
1	1	missing	missing	
	2	no	No	
	3	yes	Yes	
	4	no	No	yes
2	1	no	No	
	2	yes	Yes	
	3	missing	missing	
	4	no	No	yes
3	1	no	No	
	2	missing	missing	
	3	no	No	
	4	no	No	missing
4	1	no	No	
	2	no	No	
	3	no	No	
	4	no	No	no

For "any local reaction" on a given day, a similar rule applies:

= 1 (yes), if the subject reports any reaction as yes (or present) on the given day in the required interval;

= 0 (no), if the subject reports all reactions as no (or absent) on the given day in the required interval;

= •, if the subject reports all reactions as a combination of no and missing on the given day in the required interval.

For "any local reaction on any day", a similar rule applies:

= 1 (yes), if the subject reports any reaction as yes (or present) on any day in the required interval;

= 0 (no), if the subject reports all reactions as no (or absent) for all days in the required interval;

= •, if the subject reports all reactions as a combination of no and missing.

In summarizing local reactions (over all expected days), the derivation of "any reaction" in the presence of missing values is depicted in Table 7.

Table 7. Derivation of Any Reaction for Local Reactions in the Presence of Missing Values

Number of Reactions Reported	Number of Missing Values	Summary Value
One or more	None	Reaction
One or more	One or more	Reaction
None	None	No Reaction
None	One or more	Missing

The duration of each reaction will be calculated in days from start of first reported reaction to resolution of last reported reaction, inclusive. Resolution information is the last day on which the report was recorded in the e-diary, or, the date the reaction ended if it continued beyond day 7 (or the last record in the e-diary if before day 7). If there is no known date the reaction ended, then duration will be missing. Subjects with no reported reaction have no duration because it is not applicable.

3.4.2.2. Systemic Events

The systemic events reported in the e-diary after each vaccination are decreased appetite, drowsiness, and irritability (for Cohorts 2 and 3) and fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain (for Cohort 4). These will be recorded as present or absent. Fever and use of antipyretic medication will also be included as systemic events.

3.4.2.2.1. Fever: Cohorts 2, 3 and 4

The subject's axillary temperature will be recorded in the e-diary for 7 days (Day 1 to Day 7) after each vaccination. If more than 1 temperature was taken for a subject on the same day, the highest temperature was to be recorded in the e-diary.

The protocol defines fever as a temperature ≥38.0°C (or ≥100.4°F). In the event of a fever, temperature will be taken daily until fever has resolved (1 day of temperature less than 38.0°C [100.4°F]). An end date will be captured in the CRF for any fever persisting on the last day that the e-diary was completed.

Fever will be classified as following for a given day based on the following scale:

= •, if temperature is missing, or otherwise unavailable;

= 0 (absent), if temperature is not missing and <38.0°C (100.4°F);

= 1 (mild), if temperature is ≥38.0°C (100.4°F) but ≤39.0°C (102.2°F);

= 2 (moderate), if temperature is >39.0°C (102.2°F) but ≤40°C (104.0°F);

= 3 (severe), if temperature is >40.0°C (104.0°F).

In addition, following the guidelines published by China State Food and Drug Administration (SFDA), fever will be also classified for a given day defined by China SFDA based on the following scale:

= •, if temperature is missing, <35.0°C (95.0°F), >42.0°C (107.6°F), or otherwise unavailable;

= 0 (absent), if temperature is not missing and <37.1°C (98.8°F);

= 1 (mild), if temperature is ≥37.1°C (98.8°F) but <37.6°C (99.7°F);

= 2 (moderate), if temperature is ≥37.6°C (99.7°F) but ≤39.0°C (102.2°F);

= 3 (severe), if temperature is >39.0°C (102.2°F).

Similar to the derivations specified for local reactions, any day, any fever, any fever on any day, and duration of fever will be derived. Duration will be calculated for any fever (temperature ≥38.0°C [≥100.4°F]) and for any fever (temperature ≥37.1°C [≥98.8°F]). Each category of fever will be included as a separate event in summaries of systemic events.

3.4.2.2.2. Other Systemic Events: Cohorts 2, 3, and 4

The presence of systemic events will be recorded in the e-diary daily for 7 days (Day 1 to Day 7) after each vaccination, using the grading scales in Table 8 and Table 9.

Table 8. Other Systemic Events for Infants Aged 7 Months to <2 Years (Cohort 2 and 3)

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 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 or severe 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

a. Grade 4 assessment should be made by an investigator; Grade 4 will not be collected in the e-diary but as an adverse event on the case report form.

Table 9. Other Systemic Events for Children Aged ≥ 2 to <6 Years (Cohort 4)

Systemic Event	GRADE 1 mild	GRADE 2 moderate	GRADE 3 severe	GRADE 4[a]
Fatigue (= tiredness in e-diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for severe vomiting
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea

Table 9. Other Systemic Events for Children Aged ≥ 2 to <6 Years (Cohort 4)

Systemic Event	GRADE 1 mild	GRADE 2 moderate	GRADE 3 severe	GRADE 4[a]
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

a. Grade 4 assessment should be made by an investigator; Grade 4 will not be collected in the e-diary but as an adverse event on the case report form.

For decreased appetite or loss of appetite on each day, an indicator variable will be created for decreased appetite on each day, using the following algorithm:

= •, if decreased appetite is missing;

= 0 (none), if no loss of appetite;

= 1 (mild), if decreased interest in eating;

= 2 (moderate), if decreased oral intake;

= 3 (severe), if refusal to feed.

For drowsiness (synonym with increased sleep) on each day, an indicator variable will be created for drowsiness on each day, using the following algorithm:

= •, if increased sleep is missing;

= 0 (none), if no synonym with increased sleep;

= 1 (mild), if increased or prolonged sleeping bouts;

= 2 (moderate), if slightly subdued; interfering with daily activity;

= 3 (severe), if disabling; not interested in usual daily activity.

For irritability (fussiness, synonym with restless sleep; decreased sleep) on each day, an indicator variable will be created for irritability on each day, using the following algorithm:

= •, if irritability is missing;

= 0 (none), if no fussiness;

= 1 (mild), if easily consolable;

= 2 (moderate), if requiring increased attention;

= 3 (severe), if inconsolable; crying that cannot be comforted.

For fatigue (synonym with tiredness in e-diaries), headache, muscle pain, and joint pain on each day, an indicator variable will be created for them on each day separately, using the following algorithm:

= •, if fatigue, headache, muscle pain, or joint pain is missing;

= 0 (none), if no fatigue, headache, muscle pain, or joint pain;

= 1 (mild), if does not interfere with activity;

= 2 (moderate), if some interference with activity;

= 3 (severe), if prevents daily routine activity.

For vomiting on each day, an indicator variable will be created on each day using the following algorithm:

= •, if vomiting is missing;

= 0 (none), if no vomiting;

= 1 (mild), if 1 to 2 times in 24 hours;

= 2 (moderate), if > 2 times in 24 hours;

= 3 (severe), if requires intravenous hydration.

For diarrhea on each day, an indicator variable will be created on each day using the following algorithm:

= •, if diarrhea is missing;

= 0 (none), if no diarrhea;

= 1 (mild), if 2 to 3 loose stools in 24 hours;

= 2 (moderate), if 4 to 5 loose stools in 24 hours;

= 3 (severe), if 6 or more loose stools in 24 hours.

For the systemic events, 3 more derivations are required: whether or not a specific reaction occurs on any day, whether or not the subject experiences any other systemic event on a given day, and whether or not the subject experiences any other systemic events on any day; similar algorithms described in Section 3.4.2.1 will be used.

3.4.2.2.3. Use of Antipyretic Medication

The caregiver will be instructed to record the use of antipyretic medications for prevention or treatment of symptoms daily during the active safety observation periods (Day 1 to Day 7) after each vaccination and record the information in the e-diary.

An end date will be collected in the CRF for any antipyretic medication use persisting on the last day that the e-diary was completed. Data on the use of other concomitant medication will not be collected.

Similar to the derivation specified for local reactions, "any day" (for data from Day 1 to Day 7), "any medication" (for data from Day 1 to Day 7), "any medication on any day" (for data from Day 1 to Day 7) and duration will be derived for use of antipyretic medications. The same algorithms as specified in Section 3.4.2.1 will be used.

3.4.3. Hospitalization

Hospitalization information will be captured in the SAE form, including dates of admission, discharge, and whether continuing.

3.4.4. Death

Date and cause of death will be captured in the CRF. Subjects narratives will be produced for subjects with SAEs leading to outcome of death.

3.5. Study Conduct

3.5.1. E-Diary Completion

An e-diary will be considered transmitted if any data for the local reactions and the systemic events are present on any day. If all data are missing for all items on the e-diary for all 7 days following vaccination, then the e-diary will be considered not transmitted.

For transmitted e-diaries, the following variables will be defined: "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," "Day 7," "Day 1 – Day 7".

An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing) and data are valid. Otherwise, the e-diary will be considered incomplete.

For any given day, an e-diary will be considered complete if all expected data are available.

For completed e-diaries, the following variables will be defined: "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," "Day 7," "Day 1 – Day 7".

For e-diaries that are incomplete, an indicator variable for the percentage of days without data will be derived as follows:

= 1, if data have been transmitted, and are complete for 7 days (100%);

= 2, if data have been transmitted, and are complete for 6 days (≥75% to <100%);

= 3, if data have been transmitted, and are complete for 4 or 5 days (≥50% to <75%);

= 4, if data have been transmitted, and are complete for 2 or 3 days (≥25% to <50%);

= 5, if data have been transmitted, and are complete for 0 or 1 day (<25%).

3.5.2. Demographic, Medical History, and Baseline Characteristics Variables

The demographic variables are age at randomization/first vaccination visit (in month) at Visit 1, sex, race, and ethnicity. Age will be calculated as 12 × (randomization/first vaccination date – date of birth + 1)/365.25 and rounded to 1 decimal place.

Medical history will be categorized according to MedDRA.

Clinically significant findings for physical examination will be recorded as yes or no in the CRF.

3.5.3. Nonstudy Vaccines and Medications

Nonstudy vaccines and concomitant medications will be categorized according to the World Health Organization (WHO) Drug Dictionary (WHODD).

3.5.3.1. Prior Treatment

Details of any medication or vaccines received prior to enrollment into the study will not be collected in the CRF.

3.5.3.2. Concomitant Vaccines and Medication(s)

The name and date of administration of any nonstudy vaccines given from the time of signing the ICD until 6 months after the last vaccination visit will be recorded in the CRF. Other medications (except for antipyretic medication use) will not be recorded in the CRF. Antipyretic medication taken will be reported in the subject's e-diary and stop date recorded in the e-diary/CRF (as part of the symptoms resolved dates CRF).

3.5.3.3. Permitted Vaccines

Vaccinations, including Hib vaccination, may be given ≥4 days before or ≥7 days after study vaccination, except for bacille Calmette-Guérin (BCG) vaccine and oral vaccines, which are allowed at any time, according to local practice or national recommendations, at the discretion of the investigator.

3.5.3.4. Permitted Treatments

- A local anesthetic may be used at the site of the blood draw.
- Topical and inhaled corticosteroids may be used.
- Antipyretic medication may be used; however, prophylactic use should be discouraged.

***Haemophilus influenzae* Type b Vaccine:**

- 13vPnC recipients in Cohort 1, 2, 3 or 4 will be offered Hib vaccinations according to local practice or national recommendations, at the discretion of the investigator. Refer to Section 3.5.3.3 for further details of when Hib vaccine may be given. Investigational sites will be reimbursed for any Hib vaccinations given. Hib vaccinations will be given outside of the study.

- Hib recipients in Cohort 2 will all be offered additional Hib vaccination(s) according to local practice or national recommendations, at the discretion of the investigator. Refer to Section 3.5.3.3 for further details of when Hib vaccine may be given. Investigational sites will be reimbursed for any Hib vaccinations given. Hib vaccinations will be given outside of the study.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

4.1. Evaluable Analysis Set

One evaluable analysis set will be defined for Cohort 1 infant series and Cohort 2, 3, 4; it will include all subjects who:

1. Are eligible for the study at randomization.

2. Have received all study vaccinations to which they are randomized for Cohort 2, 3 and 4; received all 3 infant series doses to which they are assigned for cohort 1.

3. Have blood drawn for assay testing within the required time frame (27 to 56 days after third vaccination for Cohort 1, 27 to 56 days after visit 3 for Cohort 2, 27 to 56 days after visit 2 for Cohort 3, 27 to 56 days after visit 1 for Cohort 4) and the sample from this blood draw provides at least 1 valid and determinate assay result.

4. Receive no prohibited vaccines.

5. Have no major protocol violations as determined by the study clinician.

The evaluable immunogenicity population defined for Cohort 1 post-toddler dose will include all subjects who:

1. Are eligible for the study.

2. Have received all 4 study vaccinations to which they were assigned (3 infant doses and 1 toddler dose).

3. Have blood drawn for assay testing within the required time frame (27 to 56 Days after vaccination 4 [Visit 5]) and the sample from this blood draw provides at least 1 valid and determinate assay result.

4. Receive no prohibited vaccines before blood draw after the toddler dose.

5. Have no major protocol violations as determined by the study clinician.

The evaluable immunogenicity population will be the primary analysis population for all immunogenicity endpoints. The immunogenicity results will be summarized according to the vaccine group as randomly assigned for Cohort 2, 3 and 4.

Subjects vaccinated but not randomized in Cohort 2, 3, 4 and subjects randomized but who receive the wrong vaccine in Cohort 2, 3, 4 will be excluded from the evaluable immunogenicity population.

4.2. All-available Immunogenicity Analysis Set

Separate all-available immunogenicity analysis set will be defined for Cohort 1 infant series, Cohort 2, 3, 4; and also be defined for Cohort 1 toddler dose.

All-available immunogenicity analysis set will include all subjects who have at least 1 valid and determinate assay result for the proposed analysis. This analysis set is for the purpose of immunogenicity analysis, for which it will be secondary analysis population.

Subjects randomized but not vaccinated in Cohort 2, 3, and 4 will be included in the all-available immunogenicity analysis set if any valid and determinate assay results are available.

Subjects vaccinated but not randomized in Cohort 2, 3 and 4 will be excluded from the all-available immunogenicity analysis set.

4.3. Full Analysis Set

Not applicable.

4.4. Per Protocol Analysis Set

Not applicable.

4.5. Safety Analysis Set

The safety population will include all subjects who receive at least 1 dose of the investigational product. Separate safety populations will be defined for subjects in Cohort 1 with infant dose series and subjects in Cohort 2, 3, 4, and also be defined for subjects in Cohort 1 with toddler dose.

Subjects vaccinated but not randomized in Cohort 2, 3, 4 will be included in the safety population for safety analysis, and results from these subjects will be reported under the group corresponding to the vaccine they actually received.

Subjects who were randomized but received the wrong vaccine in Cohort 2, 3 and 4 will be included in the safety population for safety analysis, and results from these subjects will be reported under the group corresponding to the vaccine they actually received.

4.6. Other Analysis Sets

Not applicable.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal statistical hypothesis test will be performed as this is a descriptive study and no formal hypotheses were predetermined. There are also no formal statistical decision rules for this study and a descriptive estimation approach will be used to assess all study objectives regarding safety and immunogenicity in the study.

Point estimates and nominal 95% confidence intervals (CIs) will be provided for all safety and immunogenicity endpoints at each planned analysis.

No formal multiplicity adjustments will be applied due to multiple endpoints or multiple looks of the same endpoint.

5.2. General Methods

Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the percentage (%) and the numerator (n) and the denominator (N) used in the percentage calculation.

5.2.1. Analyses for Binary Data

For immunogenicity results, the exact 2-sided 95% CIs (Clopper-Pearson CIs) will be provided for the proportions of subjects achieving an IgG concentration ≥ 0.35 μg/mL, and the proportion of subjects with pneumococcal OPA titer ≥ LLOQ for each vaccine group at defined sampling time point in each cohort, as defined in Section 3.2.1.

The exact CIs (Clopper-Pearson) for the various proportions of individual groups will be computed using the F distribution. If r is the number of responses and n is the number of subjects, then it follows that p=r/n is the estimate of the proportion of responses. An exact 95% CI can be computed by solving the following 2 equations. For the lower limit P_L,

$$p_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$

and for the upper limit P_U,

$$p_U = \frac{(r+1)F_U}{(n-r) + (r+1)F_U}$$

where F_L is the quantile from the F distribution for α=0.025, with numerator degrees of freedom equal to 2r and denominator degrees of freedom equal to 2(n–r+1). F_U is the quantile from the F distribution for α=0.975, with numerator degrees of freedom equal to 2(r+1) and denominator degrees of freedom equal to 2(n–r). When r equals 0, F_L should be set equal to 1.0 so P_L equals 0. When r equals n, F_U should be set equal to 1.0 so P_U equals 1.0.

The CI using the F distribution is described in Collett (1991) and implemented in SAS PROC FREQ.

The proportion differences for each serotype in 13vPnC between 1 month after the last vaccination of each cohort (Cohort 2, Cohort 3, Cohort 4) and 1 month after last vaccination of infant series of Cohort 1; and proportion differences between 13vPnC and Hib vaccine in Cohort 2, Cohort 3, Cohort 4 will be provided along with associated exact 2-sided 95% CIs by Chan and Zhang's method (1999).

Similarly, for the safety results in infants and children 7 months to <6 years of age (Cohorts 2, 3, and 4), the exact 2-sided 95% CIs will be provided by vaccine group in each Cohort for all primary safety endpoints, proportions of subjects reporting local reactions, systemic events, and AEs (including AEs occurring within the first 30 minutes after each vaccination).

For tier 1 AEs, an unconditional exact method for deriving the 95% CI for the risk difference and p-value proposed by Chan and Zhang (1999) will be used to compare 13vPnC with Hib vaccine.

For tier 2 AEs, the Miettinen and Nurminen method will be used to derive the 95% CI for the risk difference between 13vPnC and Hib vaccine.

5.2.2. Analyses for Continuous Data

For each of the 13 serotypes contained in 13vPnC, GMCs will be calculated at 1 month after the last vaccination for Cohort 2, Cohort 3, Cohort 4, and 1 month after infant series for Cohort 1, along with 2-sided 95% CIs on the GMCs, which will be constructed by back transformation of the CIs for the mean of the logarithmically transformed IgG computed using Student's t distribution. In addition, the 2-sided 95% CI on the geometric mean ratios (GMRs) (the GMC of 13vPnC at 1 month after the last vaccination of Cohort 2, Cohort 3, Cohort 4 to the GMC of 13vPnC at 1 month after the last vaccination of infant series of Cohort 1, and the GMT of 13vPnC at 1 month after the last vaccination of Cohort 2, Cohort 3, Cohort 4 to the GMT of 13vPnC at 1 month after the last vaccination of infant series of Cohort 1) for all 13 serotypes will be also provided and those 95% CIs will be calculated using Student's t distribution for the mean difference of the measures on the natural log (ln) scale. GMRs with IgG and OPA assessments from blood samples taken before vaccination between Cohort 2, 3, or 4 and Cohort 1 will also be provided with associated 2-sided 95% CIs.

Within each cohort in the age of 7 months to < 6 years (Cohort 2, Cohort 3, Cohort 4), the GMRs (IgG GMC of 13vPnC/GMC of Hib vaccine and OPA GMT of 13vPnC/GMT of Hib vaccine) and associated 2-sided 95% CIs on GMRs produced by a similar approach as described above will be provided.

The GMCs and GMTs at each blood draw time point in each cohort will be provided by vaccine group. The geometric mean fold rises (GMFRs) in IgG and OPA from before vaccination to after vaccination at all postbaseline blood sampling time points thought 1 month after infant series for Cohort 1, and all postbaseline blood sampling time points for Cohort 2, 3 and 4, will be summarized with 2-sided 95% CIs, also computed using the logarithmically transformed assay results. In addition, the GMFRs in IgG and OPA from before toddler dose to after toddler dose at all post–toddler dose blood sampling time points for Cohort 1 will be summarized with corresponding 2-sided 95% CIs. The ratios of GMFRs in IgG and OPA (the GMFR of 13vPnC at 1 month after the last vaccination of Cohort 2, Cohort 3, Cohort 4 to the GMFR of 13vPnC at 1 month after the last vaccination of infant series of Cohort 1) and corresponding 2-sided, 95% CIs will be calculated. The CIs will be computed by back transformation of the CIs using the Student t distribution for the mean difference of the measures on the logarithmic scale (IgG/OPA difference between 1 month after the last vaccination of Cohort 2, 3, or 4 and their prevaccination relative to IgG/OPA difference between 1 month after Cohort 1 infant series and its prevaccination).

GMRs between GMCs/GMTs of Cohort 1 persistency blood samples and GMCs/GMTs of Cohort 2, 3, 4 prevaccination blood samples and associated 2-sided 95% CIs will also be provided.

Reverse cumulative distribution curves (RCDCs) will be presented graphically by vaccine group separately for each serotype-specific pneumococcal IgG concentration and OPA titer at each blood draw time point in each cohort.

The persistence of antibody response for cohort 1 (post–toddler dose) will be displayed graphically for both IgG concentrations and OPA titers.

5.3. Methods to Manage Missing Data

In general, nonmissing values will not be excluded from the analysis. However, certain statistical procedures that compare 2 or more variables, or values at more than 1 time point, for the same subject require all values to be available. In such cases, nonmissing values will be dropped to the extent necessary to perform the procedure.

5.3.1. Immunogenicity Data

Immunogenicity data collected for this study are the results of immunologic assays performed by the National Institutes for Food and Drug Control (NIFDC) on the blood samples collected.

The LLOQ in micrograms per mL (μg/mL) for each serotype is shown in Table 10.

Table 10. The LLOQ in Micrograms per mL from NIFDC

Serotype	LLOQ
1	0.02
3	0.03
4	0.02
5	0.03
6A	0.03
6B	0.03
7F	0.04
9V	0.02
14	0.04
18C	0.02
19A	0.02
19F	0.03
23F	0.03

Antibody concentrations above LLOQ are considered accurate and their quantitated values will be reported. The Limit of detection (LOD) was established as 50% of the LLOQ. Values below the LLOQ or denoted Below Limit of Quantification (BLQ) will be set to **0.5 × LOD** for analysis.

The NIFDC's OPA LLOQ in titers for all serotypes was set as 8. For the results of antibody titers that are below the LLOQ, or denoted as BLQ, **0.5 × LLOQ** will be assigned for analysis.

No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

For each serotype's antibody concentrations or antibody titers, the number of subjects with missing values at each blood sampling point will be provided.

5.3.2. Safety Data

Handling of missing information related to safety data, such as missing or partially missing date, will be in accordance with Pfizer reporting standards.

For derived variables in reactogenicity data, if any day of the 7-day e-diary is available, the "Day 1 – Day 7" data will be considered as nonmissing for analyses after each dose of Cohorts 2, 3 and 4. The proportion of subjects with missing reactogenicity data will also be summarized by each dose in Cohort 2, 3, and 4 for each vaccine group. The denominator will be the number of subjects who receive the scheduled vaccination.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Immunogenicity Endpoints

6.1.1.1. Primary Analysis

Endpoints: Primary immunogenicity endpoints in Section 3.1

- Analysis time points:

  Cohort 1: 1 month after the infant series.

  Cohort 2, 3, 4: 1 month after the last dose of 13vPnC.

- Analysis population: Evaluable immunogenicity and all-available immunogenicity populations.

- Analysis methodology: See Section 5.2.2.

- Supporting objective: Primary Objective.

Reporting Results:

The number, GMC, and associated 95% CI at the above analysis time points will be presented for 13vPnC group in each Cohort; and GMR (compared with GMC of 13vPnC in Cohort 1), and associated 95% CI at the above analysis time points will be presented for Cohort 2, 3, 4.

Figures:

RCDCs will be presented graphically for each serotype-specific pneumococcal IgG antibody concentration of 13vPnC at the time point described as above in each Cohort. The RCDCs will plot all Cohorts on the same graph, distinguishable by symbol and/or line style choice.

6.1.2. Primary Safety Endpoints

6.1.2.1. Primary Analysis

Endpoints: Safety endpoints in Section 3.1.

- Analysis time points:

  Endpoints for Local reactions and systemic events: 7 days after each vaccination in Cohort 2, 3 and 4.

  Endpoints for AEs and SAEs: from the signing of the ICD to 1 month after the last vaccination (13vPnC or Hib vaccine) in Cohort 2, 3 and 4.

  Endpoints for SAEs: from the signing of the ICD to 6 month after the last vaccination (13vPnC or Hib vaccine) in Cohort 2, 3 and 4.

  Endpoint for newly diagnosed chronic medical conditions: from 1 month after the last vaccination (13vPnC or Hib vaccine) in Cohort 2, 3, and 4 to 6 months after the last study vaccination in Cohort 2, 3, and 4.

- Analysis population: Safety population.

- Analysis methodology: Descriptive.

- Supporting objective: Primary Objective.

Reporting Results:

The number, proportion, and the corresponding 95% CI will be presented for each vaccine group in Cohort 2, 3 and 4.

6.2. Secondary Endpoint(s)

6.2.1. Immunogenicity Endpoints in Section 3.2

Endpoint: The Serotype-specific OPA geometric mean titers (GMTs) for each of the pneumococcal serotypes measured in a subset of approximately 50 subjects per cohort.

- Analysis time points:

  Cohort 1: 1 month after the infant series.

  Cohort 2, 3, 4: 1 month after the last dose of 13vPnC.

- Analysis population**:** evaluable immunogenicity population and all-available immunogenicity population.

- Analysis methodology: See Section 5.2.

- Supporting objective: Secondary Objectives.

Reporting Results:

The number, GMT, and associated 95% CI at the above analysis time points will be presented for 13vPnC in each Cohort; and GMR (compared with GMT of 13vPnC in Cohort 1), and associated 95% CI at the above analysis time points will be presented for Cohort 2, 3, 4.

The numerator and denominator used for percentage , the percentage, and associated 95% CI will be presented for each vaccine group for infant series and toddler dose, and their percentage difference and corresponding CI will also be presented.

Figures:

RCDCs will be presented graphically for each serotype-specific pneumococcal OPA at 1 month after the last dose of 13vPnC in Cohort 2, 3, 4 and 1 month after the infant series in Cohort 1, and those RCDCs will be plotted on the same graph, distinguishable by symbol and/or line style choice.

Endpoint: Serotype-specific IgG GMCs in all subjects and OPA GMTs in approximately 50 subjects per cohort vaccinated with 13vPnC (Cohort 2, 3, 4) and approximately 25 subjects per cohort vaccinated with Hib (Cohort 2, 3, 4).

- Analysis time points:

  Cohort 2: Visit 1, Visit 4.

  Cohort 3: Visit 1, Visit 3.

  Cohort 4: Visit 1, Visit 2.
- Analysis population: evaluable immunogenicity population and all-available immunogenicity population.
- Analysis methodology: See Section 5.2.2.
- Supporting objective: Secondary Objectives.

Reporting Results:

The number, GMCs, and associated 95% CI at the above analysis time points will be presented for each vaccination for Cohort 2, 3, 4; and GMR (GMC comparison between 13vPnC and Hib vaccine) with associated 95% CI at the above analysis time points will be presented for Cohort 2, 3, 4.

The number, GMTs, and associated 95% CI at the above analysis time points will be presented for each vaccination for Cohort 2, 3, 4; and GMR (GMT comparison between 13vPnC and Hib vaccine) with associated 95% CI at the above analysis time points will be presented for Cohort 2, 3, 4.

The number, GMCs, and associated 95% CI at the above analysis time points will be presented for each vaccination in all Cohorts; and GMFR from Baseline (visit 1) with associated 95% CI will be presented for each vaccination in Cohort 2, 3, 4.

The number, GMTs, and associated 95% CI at the above analysis time points will be presented for each vaccination in all Cohorts; and GMFR from Baseline (visit 1) with associated 95% CI will be presented for each vaccination in Cohort 2, 3, 4.

The number, GMC, and associated 95% CI at visit 1 will be presented for 13vPnC group in each Cohort 2, 3, 4; and GMR at visit 1 (compared with GMC of 13vPnC in Cohort 1), and associated 95% CI will be presented for Cohort 2, 3, 4.

The number, GMT, and associated 95% CI at visit 1 will be presented for 13vPnC group in each Cohort 2, 3, 4; and GMR at visit 1 (compared with GMT of 13vPnC in Cohort 1), and associated 95% CI will be presented for Cohort 2, 3, 4.

The number, GMFRs, and associated 95% CI at post 13vPnC vaccination visit (4, 3, or 2) and the ratio of GMFRs(GMCs at post 13vPnC vaccination of Cohort 2, 3, 4 compared with GMCs at post infant series of Cohort 1) along with associated 95% CI will be presented.

The number, GMFRs, and associated 95% CI at post 13vPnC vaccination visit (4, 3, or 2) and the ratio of GMFRs(GMTs at post 13vPnC vaccination of Cohort 2, 3, 4 compared with GMTs at post infant series of Cohort 1) along with associated 95% CI will be presented.

Figures:

RCDCs will also be presented graphically for each serotype-specific pneumococcal IgG antibody concentration and OPA titer separately in each Cohort. The RCDCs will be plotted by vaccine group on the same graph for each Cohort, distinguishable by symbol and/or line style choice.

Endpoint: Serotype-specific IgG GMCs in all subjects and OPA GMTs in approximately 50 subjects in Cohort 1.

- Analysis time points:

  Cohort 1: all time points in Cohort 1.

[redacted]

[redacted]

- Analysis population: evaluable immunogenicity population and all-available immunogenicity population.
- Analysis methodology: See Section 5.2.2.
- Supporting objective: Secondary Objectives.

Reporting Results:

The number, GMCs, and associated 95% CI at the above analysis time points; and GMFR from Baseline (visit 1) with associated 95% CI, will be presented in Cohort 1.

The number, GMTs, and associated 95% CI at the above analysis time points; and GMFR from Baseline (visit 1) with associated 95% CI, will be presented in Cohort 1.

Figures:

The antibody-response line plot of each serotype-specific GMCs and the associated 95% CI at time points after infant series of Cohort 1 will be presented.

The antibody-response line plot of each serotype-specific GMCs and the associated 95% CI at time points after infant series of Cohort 1 will be presented.

Endpoint: Proportion of subjects achieving a serotype-specific IgG concentration ≥0.35 μg/mL for each of the pneumococcal serotypes measured 1 month after the last dose in all subjects per cohort vaccinated with 13vPnC (Cohort 2, 3, 4) and all subjects per cohort vaccinated with Hib (Cohort 2, 3, 4) and 1 month after the infant series in all subjects vaccinated with 13vPnC in Cohort 1

- Analysis time points:

  Cohort 1: 1 month after the infant series.

  Cohort 2, 3, 4: 1 month after the last dose.
- Analysis population**:** evaluable immunogenicity population and all-available immunogenicity population.
- Analysis methodology**:** See Section 5.2.1.
- Supporting objective: Secondary Objectives.

Reporting Results:

The number, proportion, and the corresponding 95% CI will be presented for 13vPnC group in Cohort 1, 2, 3 and 4; and proportion difference with Cohort 1 along with associated 95% CI will be presented for Cohort 2, 3, 4.

[redacted]

[redacted]

The number, proportion, and the corresponding 95% CI will be presented for each group in Cohort 2, 3 and 4; and proportion difference between 13vPnC and Hib vaccine, along with associated 95% CI will be presented for Cohort 2, 3, 4.

Endpoint: Proportion of subjects achieving a serotype-specific OPA titer ≥ LLOQ for each of the pneumococcal serotypes measured 1 month after the last dose in approximately 50 subjects per cohort vaccinated with 13vPnC (Cohort 2, 3, 4) and approximately 25 subjects per cohort vaccinated with Hib (Cohort 2, 3, 4) and 1 month after the infant series in approximately 50 subjects in Cohort 1.

- Analysis time points:

  Cohort 1: 1 month after the infant series.

  Cohort 2, 3, 4: 1 month after the last dose.

- Analysis population: evaluable immunogenicity population and all-available immunogenicity population.

- Analysis methodology: See Section 5.2.1.

- Supporting objective: Secondary Objectives.

Reporting Results:

The number, proportion, and the corresponding 95% CI will be presented for 13vPnC group in Cohort 1, 2, 3 and 4; and proportion difference with Cohort 1 along with associated 95% CI will be presented for Cohort 2, 3, 4.

The number, proportion, and the corresponding 95% CI will be presented for each group in Cohort 2, 3 and 4; and proportion difference between 13vPnC and Hib vaccine, along with associated 95% CI will be presented for Cohort 2, 3, 4.

6.2.2. Safety Endpoints in Section 3.2.2

Endpoints: Safety endpoints in Section 3.2.2.

- Analysis time points:

  Endpoint for the incidence of AEs from the signing of the ICD to 1 month after vaccination 3 in Cohort 1: from the signing of the ICD to 1 month after vaccination 3.

  Endpoint for the incidence of newly diagnosed chronic medical conditions from 1 month after vaccination 3 to vaccination 4 in Cohort 1: from 1 month after vaccination 3 to vaccination 4.

Endpoint for the incidence of AEs from vaccination 4 to 1 month after vaccination 4 in Cohort 1: from vaccination 4 to 1 month after vaccination 4.

Endpoint for the incidence of newly diagnosed chronic medical conditions from 1 month after vaccination 4 to 6 months after vaccination 4 in Cohort 1: from 1 month after vaccination 4 to 6 months after vaccination 4.

Endpoint for incidence of SAEs from the signing of the ICD to 6 months after vaccination 4 in Cohort 1: from the signing of the ICD to 6 months after vaccination 4.

- Analysis population**:** Safety population.
- Analysis methodology: Descriptive.
- Supporting objective: Secondary Safety Objective.

Reporting Results:

The number, proportion, and the corresponding 95% CI will be presented.

6.3. Baseline and Other Summaries and Analyses

6.3.1. Study Conduct

6.3.1.1. Subject Disposition, Vaccination Administration, Blood Samples, and Screen Failures

The number and percentage of subjects who are randomized will be included in the subject disposition summary: subjects who withdraw during the vaccination phase, complete the vaccination phase, complete the study, and withdraw after the vaccination phase will be summarized. The reasons for withdrawal will also be tabulated. The reasons for withdrawal will be those specified in the database; no rewording/recoding will be done.

Subjects excluded from the evaluable immunogenicity population will also be summarized with reasons for exclusion.

The number and percentage of subjects randomized, vaccinated, and providing blood samples within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and total sample in each cohort.

A listing of noncompliant vaccine administration will be provided. The protocol deviations will also be listed. Subjects who do not receive the vaccine as randomized will be listed as well. A listing of subjects who withdrew because of AEs will be provided.

All assigned or randomized subjects will be used to generate these tables. All of the summary tables will be presented for each vaccine group and for the total in each cohort.

Subjects who sign the ICD but are screen failures will be also summarized separately for each vaccine group for each cohort.

6.3.1.2. Demographic, Medical History, and Baseline Characteristics

Descriptive summary reports for demographic characteristics will be provided for each vaccine group, separately for each cohort for the evaluable immunogenicity, all-available immunogenicity, and safety analysis populations.

If the evaluable and all-available immunogenicity populations differ by a small amount (eg, <5%), then demographics table will be produced for the evaluable immunogenicity population only.

Descriptive summary reports for medical history will be provided for each vaccine group for the safety population only.

6.3.1.3. E-Diary Completion

Variables defined in Section 3.5.1 will be summarized with descriptive statistics for each vaccine group and for the total after each dose for Cohort 2, 3 and 4. The safety population will be used to generate this table.

6.3.1.4. Analyses of Below LLOQ

A table summarizing the number of subjects with assay data below the LLOQ will be produced for each vaccine group separately for infant series and toddler dose. If the evaluable and all-available immunogenicity populations differ by a small amount (<5%), this table will be generated for the evaluable immunogenicity population only.

6.4. Safety Summaries and Analyses

All safety analyses will be summarized based on the safety population in accordance with Pfizer reporting standards. All safety summaries will be provided by vaccine group separately for each dose in infant series and toddler dose.

6.4.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. CCI [redacted]

[redacted]

[redacted]

For tier 1 and tier 2 events, the proportion of AEs observed in each vaccine group will be presented along with the point estimates and associated 95% CIs of the risk difference (the difference of incidence rates) between 13vPnC and Hib vaccine in Cohort 2, 3, 4.

For tier 1 events, 95% CIs will be calculated using the exact methods proposed by Chan and Zhang described in Section 5.2.1.

For tier 2 events, 95% CIs will be calculated using the Miettinen and Nurminen method described in Section 5.2.1.

For tier 1 events, p-values from Chan and Zhang's method will be calculated and included in the presentations. AEs will be arranged in the output sorted in descending order of point estimates of the risk difference (the difference of incidence rates) within system organ class.

6.4.2. Reactogenicity Data

The derived endpoints (Section 3.4.2) for each local reaction, systemic event, and use of antipyretic/pain medication to prevent or treat symptoms will be summarized.

The presence and maximum severity of the local reaction and systemic event at "any day (Day 1 – Day 7)" for each vaccination (13vPnC or Hib) following each dose in Cohort 2, 3, 4 will be summarized by proportions of subjects with the associated 95% Clopper-Pearson CIs.

The presence of each local reaction and systemic event on any day (Day 1- 7), any local reaction on any day (Day 1-7), maximum severity of each local reaction and systemic event on any day (Day 1-7) following any vaccination in Cohort 2, 3, 4 will also be summarized by proportions of subjects with associated Clopper-Pearson CIs. For local reactions, systemic events, and use of antipyretic/pain medication to prevent or treat symptoms, descriptive summary statistics of the maximum duration of the event will be provided.

For the onset of local reactions, systemic events, and use of antipyretic/pain medication to prevent or treat symptoms, descriptive summary statistics of the onset day will be provided.

6.4.3. Unscheduled Visits (Unplanned Visits) for Severe Reactions

A listing will be generated for all of the subjects with unscheduled/unplanned visits because of severe (Grade 3) and Grade 4 reactions.

6.4.4. Immediate AEs

Descriptive summaries and listing of subjects reporting AEs during the protocol-specified first 30-minute observation period will be summarized by vaccine group after each dose for each cohort. Also, Clopper-Pearson 95% CIs will be included with the percentages.

6.4.5. Newly Diagnosed Chronic Medical Conditions

Descriptive summary tables and listings will be provided for subjects reporting newly diagnosed chronic medical conditions that occur from 1 month to 6 months after vaccination 4 in Cohort 1.

6.4.6. Physical Examinations, Including Vital Signs

Descriptive summary tables will be provided in accordance with Pfizer reporting standards.

6.4.7. Nonstudy Vaccination and Nonstudy Medication

Nonstudy vaccination and nonstudy medication summaries will be provided with descriptive summaries. Each vaccine will be summarized according to the Anatomic Therapeutic Chemical (ATC) 4 classification system. The number and percentage of subjects receiving each vaccine will be tabulated for each vaccine group and total sample for each cohort. The denominator for the percentages is the number of subjects in the vaccine group or total sample in each cohort.

6.4.8. Hospitalization

Hospitalization during the study will be listed for each vaccine group separately for each cohort.

6.4.9. Death

Deaths during the study will be listed for each vaccine group separately for each cohort.

7. INTERIM ANALYSES

7.1. Introduction

This is a Phase 3, randomized, open-label study. In addition to the planned analyses described in Section 7.2, some analyses may be performed to support regulatory interactions.

7.2. Interim Analyses and Summaries

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment or to support clinical development. This includes compilation of results of the infant series before completion of the toddler dose.

The primary analysis will be performed when the following data are available:

- IgG immunogenicity data 1 month after the infant series in Cohort 1;
- IgG immunogenicity data 1 month after the last dose of 13vPnC in Cohorts 2, 3, 4;
- Safety data up to 6 months after the last study vaccination for Cohorts 2, 3 and 4.

[redacted]

[redacted]

The above data will be summarized in the primary study report and will be submitted to regulatory authorities to support licensure of 13vPnC in infants and children 15 months to 5 years of age. Type I error of the study will all be spent for this primary analysis. In addition, supplemental summaries of immunogenicity and safety data may be generated to support renewal of the 13vPnC license.

Additionally, other data from the study that were not included in the primary report for 13vPnC licensure for infants and children 15 months to 5 years and summary reports for the 13vPnC renewal package will be analyzed and reported separately once all subjects have completed the study and all data are available. No changes to the study design or conduct of the study are intended to be made based on these results. The study will continue for the remaining subjects regardless of the results submitted to the regulatory authorities.

All analyses included in the final study report will be purely descriptive; therefore, no type I error adjustment is needed.

A list of protocol deviations will be compiled prior to the primary analysis, and will be updated prior to the final analysis. Subjects who do not meet the eligibility criteria and subjects who have major protocol violations will be excluded from the evaluable immunogenicity population. A major protocol violation is a protocol violation that, in the opinion of the clinicians, would materially affect assessment of immunogenicity, eg, subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. Clinicians will identify those subjects with protocol violations before the primary analyses and the final analysis of immunogenicity results.

8. REFERENCES

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2. Chan ISF, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55:1201-9.

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