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

Investigational Product Number:	PF-05208760
Investigational Product Name:	13-valent Pneumococcal Conjugate Vaccine
United States (US) Investigational New Drug (IND) Number:	Not applicable (N/A)
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	B1851178
Phase:	Phase 3

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	13 September 2017	Not applicable (N/A)
Amendment 1	19 January 2018	- Protocol Summary – Study Design (Table: Age at Vaccination); Study Schedule of Activities Table 2; Section 3.1 Table 5; Section 6.2.3: Changed the age at 3rd vaccination for Cohort 2 from "365 Days to <450 Days of Age and at Least 28 Days After Visit 2" to "365 days to <450 Days of Age and at Least 56 Days After Visit 2". *Rationale*: Changed to be consistent with the core data sheet (CDS). - Table of Contents: Updated to reflect changes. Section 7.3.2 – - Table 10: Changed the table name from "Other Systemic Events for Infants Aged 7 months to ≤2 Years (Cohort 2 and 3)" to "Other Systemic Events for Infants Aged 7 months to <2 Years (Cohort 2 and 3)". Changed the Grade 4 for drowsiness from "Emergency room visit or hospitalization or severe increased sleep" to "Emergency room visit or hospitalization for severe increased sleep". *Rationale*: Corrected the typo error. - Section 7.3.2 – Table 11: Changed the table name from "Other Systemic Events for Children Aged >2 to <5 Years (Cohort 4)" to "Other Systemic Events for Children Aged ≥2 to <6 Years (Cohort 4)". *Rationale*: Corrected the typo error. - Section 7.4: Further clarified the sample management. The newly added text is *italicized* and underlined, the deleted text

Document	Version Date	Summary of Changes and Rationale
		is highlighted with strikethrough: Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. ~~Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the informed consent, stored samples may be used for additional testing to better understand the immune responses to the vaccines under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the subject's genetic material will be performed.~~ *All serologic testing will be conducted by the National Institutes for Food and Drug Control (NIFDC). After completion of the study, all remaining serum samples will be under the custody of NIFDC.* The subject's parent/legal guardian may request that his or her child's samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. ~~The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the subject's genetic material is performed.~~ *Rationale*: Added specificity and clarity. - Section 7.5: Added the information regarding NIFDC. *Rationale*: Added specificity and clarity.

Document	Version Date	Summary of Changes and Rationale
		- Section 9.2.2: The newly added text is *italicized* and underlined, the deleted text is highlighted with strikethrough: The proportion of subjects achieving an ~~antibody~~ *IgG* concentration ≥ 0.35 µg/mL, *as well as* the proportion of subjects with pneumococcal OPA titer ~~≥ 1:8~~ *above a defined level* will be computed for each *tested* blood sample obtained from subjects in all cohorts *Rationale*: Added specificity and clarity. - Appendix 1: Added NIFDC in the abbreviation table.
Amendment 2	07 February 2019	- Protocol Summary, Section 1.2, Section 3.4, Section 7.5.1, Section 7.5.2, Section 9.4: Added the enrollment of additional 280 subjects from county CDCs. *Rationale:* To provide additional data in the event that only subjects recruited at municipal and county level CDCs should be included in vaccine clinical studies. - Section 3.4: Change "Randomized subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal" to "Randomized subjects who withdraw from the study may be replaced to maintain adequate numbers to achieve study objectives". Rationale: May need to recruit additional subjects due to higher than expected subject withdrawal in order to achieve study objective. - Section 7.5.2: Delete "13vPnC" from "the blood samples taken before vaccination and 1 month after the last 13vPnC vaccination in each of the 3 cohorts" in Cohorts 2, 3, 4. Rationale: Added

Document	Version Date	Summary of Changes and Rationale
		specificity and clarity. - Section 6.1.1, Section 6.2.1, Section 6.3.1, and Section 6.4.1: Change "including date of birth, sex and race" into "including full date of birth, sex and race. The date of birth will be collected to critically evaluate the immune response and safety profile by age". Rationale: Added specificity and clarity. - References: Updated to reflect changes. - Appendix 1: Added CDC in the abbreviation table.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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APPENDICES

PROTOCOL SUMMARY

This study is designed to support licensure of 13-valent Pneumococcal Conjugate Vaccine (13vPnC) through 5 years of age.

This study includes 4 separate cohorts broken down by age. Cohort 1 will include infants 6 weeks to 2 months of age that will be vaccinated with 13vPnC according to the currently licensed infant schedule (2, 4, 6 and 12 to 15 months). Cohorts 2, 3 and 4 range in age from 7 months to 5 years of age (Cohort 2 - 7 months to <12 months of age; Cohort 3 - ≥1 year to <2 years; Cohort 4 - ≥2 years to <6 years of age). These three cohorts are of primary interest in obtaining licensure in the 15 month to 5 year age range and addressing the Center for Drug Evaluation (CDE) request to obtain data in this age group. Immune responses before and after the last vaccination in each of these age groups will be measured and used as a surrogate of efficacy. Post vaccination serotype specific serum anticapsular immunoglobulin G (IgG) responses in Cohorts 2, 3, and 4 will be compared to the post infant series responses in Cohort 1 as a bridge to efficacy. Cohorts 2, 3, and 4 will also include a control group vaccinated with *Haemophilus influenzae* type b (Hib) vaccine. The Hib vaccinated infants and children will serve as controls for assessment of the safety and immunogenicity of Cohorts 2, 3, and 4. In addition to serving as a bridge to efficacy for Cohorts 2, 3, and 4, Cohort 1 will provide the antibody persistence data at 12, 24, 36 and 48 months after the last vaccination required by the CDE.

An additional 280 subjects will be recruited because during the conduct of the study, 280 subjects were enrolled from town level immunization clinics which were under the Huaiyin county Center for Disease Control (CDC). Based on the China Vaccine Good Clinical Practice (GCP) guidelines it is unclear if town level immunization clinics are allowed to be included as clinical trial sites under the China regulations. In the review of procedures and data from subjects in the study there were no issues identified with regards to subject safety, data quality, or integrity.

Primary Objective (Immunogenicity):	**Primary Endpoints (Immunogenicity):**
• To assess the immune responses 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 immune responses in infants 6 weeks to 2 months of age (Cohort 1).	• The serotype-specific 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.

Primary Objective (Safety):	Primary Endpoints (Safety):
• 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).	• 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 informed consent document (ICD) to 6 months after the last study vaccination (13vPnC or Hib) in Cohort 2, 3 and 4.

STUDY DESIGN

Description

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

- This study is open-label and subjects will receive the investigational products, 13vPnC or Hib vaccine (comparator).

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.

STATISTICAL ANALYSIS

All of the analyses will be summarized for each cohort separately.

Immunogenicity Analysis Populations

An evaluable immunogenicity population and an all-available immunogenicity population will be defined for the immunogenicity analyses separately. The evaluable immunogenicity population will be the primary population for the immunogenicity analyses.

Safety Analysis

The safety population will be defined for safety analysis. The safety population will include all subjects who receive at least 1 dose of an investigational product.

Analysis Timing:

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.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Study Flowchart for Cohort 1 (2 Months [42 to 56 Days of Age at Consent])

Visit Number	1	2	3	4	5	6	7	8 to 11
Visit Description	**Vaccination 1**	**Vaccination 2**	**Vaccination 3**	**Post-Infant Dose Visit**	**Vaccination 4**	**Post–Toddler Dose Visit**	**6-Month Follow-up Telephone Contact**	**Persistence Blood Draws[a]**
Visit Window	**42 to 56 Days of Age**	**42 to 70 Days After Visit 1**	**42 to 70 Days After Visit 2**	**28 to 42 Days after Visit 3**	**365 to 455 Days of Age**	**28 to 42 Days After Visit 5**	**168 to 196 Days After Last Study Vaccination**	**Annually After Visit 5**
Informed consent	X							
Review inclusion/exclusion criteria	X							
Demography, medical history, and physical examination	X							
Record nonstudy vaccines	X	X	X	X	X	X	X	
Axillary temperature	X	X	X		X			
Assign subject number in the interactive response technology (IRT) or equivalent system	X							
Obtain blood sample	X			X	X	X		X
Vaccination and 30-minute observation	13vPnC	13vPnC	13vPnC		13vPnC			
Confirm continued eligibility		X	X	X	X	X	X	X
Adverse event collection as appropriate for visit	X	X	X	X	X	X	X	X

a. Persistence blood draw visits will take place when the subject is 2 years, 3 years, 4 years and 5 years of age. The permitted visit windows are Visit 8: 2 Years of age to 2 years and 28 days of age; Visit 9: 3 years of age to 3 years and 28 days of age; Visit 10: 4 years of age to 4 years and 28 days of age; Visit 11: 5 years of age to 5 years and 28 days of age.

Table 2. Study Flowchart for Cohort 2 (7 Months [210 Days] to <12 Months of Age at Consent)

Visit Number	**1**	**2**	**3**	**4**	**5**
Visit Description	**Vaccination 1**	**Vaccination 2**	**Vaccination 3**	**Post–Toddler Dose Visit**	**6-Month Follow-up Telephone Contact**
Visit Window	**210 to <365 Days 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]**	**28 to 42 Days After Visit 3**	**168 to 196 Days After Last Study Vaccination**
Informed consent	X				
Review inclusion/exclusion criteria	X				
Demography, medical history, and physical examination	X				
Record nonstudy vaccines	X	X	X	X	X
Axillary temperature	X	X	X[b]		
Randomization in the interactive response technology (IRT) or equivalent system	X				
Obtain blood sample	X			X	
Vaccination and 30-minute observation; investigational product as randomized[c]	13vPnC or Hib vaccine	13vPnC or Hib vaccine	13vPnC[d]		
Confirm continued eligibility		X	X	X	
Provide parent with diary, thermometer, and measuring device, if necessary	X	X	X[b]		
Assess reactogenicity and the use of antipyretic medication	Days 1 to 7	Days 1 to 7	Days 1 to 7[b]		
Review diary data	----------X----------				
Collect the diary			X[e]	X[b]	
Adverse event collection as appropriate for visit	X	X	X	X	X

a. The third dose must be given at age 12 months to less than 15 months of age and at least 56 days after the second vaccination.
b. 13vPnC recipients only.
c. Subjects will receive 13vPnC or active comparator (*Haemophilus influenzae* type b vaccine [Hib vaccine]) according to age-appropriate schedules.
d. Subjects randomized to Hib vaccine will not receive a vaccination at Visit 3. Subjects randomized to Hib may receive a third dose of Hib vaccine according to local practice or national recommendations, at the discretion of the investigator.
e. Hib vaccine recipients only.

Table 3. Study Flowchart for Cohort 3 (≥1 Year to <2 Years of Age at Consent)

Visit Number	1	2	3	4
Visit Description	**Vaccination 1**	**Vaccination 2**	**1 Month After Visit 2**	**6-Month Follow-up Telephone Contact**
Visit Window	**≥1 to <2 Years of Age**	**At Least 56 Days After Visit 1**	**28 to 42 Days After Visit 2**	**168 to 196 Days After Last Study Vaccination**
Informed consent	X			
Review inclusion/exclusion criteria	X			
Demography, medical history, and physical examination	X			
Record nonstudy vaccines	X	X	X	X
Axillary temperature	X	X[a]		
Randomization in the interactive response technology (IRT) or equivalent system	X			
Obtain blood sample	X		X	
Vaccination and 30-minute observation; investigational product as randomized[b]	13vPnC or Hib vaccine	13vPnC[c]		
Confirm continued eligibility		X	X	
Provide parent with diary, thermometer, and measuring device, if necessary	X	X[a]		
Assess reactogenicity and the use of antipyretic medication	Days 1 to 7	Days 1 to 7[a]		
Review diary data	----------X----------			
Collect the diary		X[d]	X[a]	
Adverse event collection as appropriate for visit	X	X	X	X

a. 13vPnC recipients only.
b. Subjects will receive 13vPnC or active comparator (*Haemophilus influenzae* type b vaccine [Hib vaccine]) according to age-appropriate schedules.
c. Subjects randomized to Hib vaccine will not receive a vaccination at Visit 2.
d. Hib vaccine recipients only.

Table 4. Study Flowchart for Cohort 4 (≥2 Years to <6 Years of Age At Consent)

Visit Number	**1**	**2**	**3**
Visit Description	**Vaccination 1**	**1 Month After Vaccination 1**	**6-Month Follow-up Telephone Contact**
Visit Window	**≥2 to <6 Years of Age**	**28 to 42 Days After Visit 1**	**168 to 196 Days After Visit 1**
Informed consent	X		
Review inclusion/exclusion criteria	X		
Demography, medical history, and physical examination	X		
Record nonstudy vaccines	X	X	X
Axillary temperature	X		
Randomization in the interactive response technology (IRT) or equivalent system	X		
Obtain blood sample	X	X	
Vaccination and 30-minute observation; investigational product as randomized[a]	13vPnC or Hib vaccine		
Confirm continued eligibility		X	
Provide parent with diary, thermometer, and measuring device, if necessary	X		
Assess reactogenicity and the use of antipyretic medication	Days 1 to 7		
Review diary data	----------X----------		
Collect the diary		X	
Adverse event collection as appropriate for visit	X	X	X

a. Subjects will receive 13vPnC or active comparator (*Haemophilus influenzae* type b vaccine [Hib vaccine]) according to age-appropriate schedules.

1. INTRODUCTION

1.1. Indication

Prevenar 13® is licensed in China for active immunization for the prevention of invasive pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (including bacteremic pneumonia, meningitis, septicemia, and bacteremia) in infants and children from 6 weeks to 15 months of age. *S pneumoniae* is the most common cause of invasive disease as well as pneumonia and upper respiratory tract infections.

This study is to seek an additional indication for licensure for active immunization for the prevention of invasive pneumococcal disease caused by *S pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (including sepsis, meningitis, bacteremia) in children from 15 months to 5 years of age.

1.2. Background and Rationale

S pneumoniae causes invasive pneumococcal disease (IPD), including bacteremia, sepsis, and meningitis) in infants and young children throughout the world. Noninvasive pneumococcal diseases, including otitis media, sinusitis, and bronchitis, are less severe but much more common than invasive disease, so also pose a significant disease burden. *S pneumoniae* also causes bacteremic and nonbacteremic pneumonia.

According to the World Health Organization (WHO), there is a high burden of pneumococcal disease and it is estimated that 1.6 million people die each year from the disease, 0.7 to 1 million of whom are children aged less than 5 years.[1] Pneumonia was the leading cause of death from 1996 to 2000 in children under 5 years of age[2] and data reported by WHO/United Nations Children's Fund (UNICEF) indicate that 72,000 children less than 5 years of age died of all-cause pneumonia in China in 2004.[3] Pneumococcal meningitis is a severe disease with high mortality and high incidence of neurological sequelae.

In an epidemiological study conducted in 18 provinces and cities in China from 1982 to 1985, 482 out of 10,446 cases of bacterial pneumonia, meningitis, and otitis media were caused by culture-confirmed *S pneumoniae*.[4] The percentages of bacterial pneumonia, meningitis, and otitis media caused by *S pneumoniae* were 1.4%, 7.9%, and 6.8%, respectively. Between 40% and 73% of the infections caused by *S pneumoniae* were in infants and children less than 3 years old. The overall mortality of pneumonia and meningitis caused by culture-confirmed *S pneumoniae* was 16% for both conditions, but in infants less than 1 year old it was as high as 29% and 17%, respectively. Major pathogens causing lower respiratory tract infections in young children are *S pneumoniae* and *H influenzae* and the proportion of lower respiratory tract infections caused by *S pneumoniae* is 13% to 53% depending on the age group.[5,6,7] In a systematic review of *S pneumoniae* cases in reported studies from 1980 to 2010; 48% of bacteremic pneumonia was caused by *S pneumoniae* and the average percentages of cases of meningitis due to *S pneumoniae* were 5% (95% confidence interval [CI]: 2-12%) among 0 – 4 years old and 28% (95% CI: 17-45%) in older children and adults.[8]

A 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been available for many years, but as with other polysaccharide (PS) vaccines, it is not effective in infants.

According to published reports, very high prevalence rates of beta-lactam and macrolide resistance in *S pneumoniae* have been found in Asian countries. Particularly erythromycin, where >70% of clinical isolates were fully resistant. Prevalence rate of penicillin resistance was 57.5% for meningeal isolates. Fully penicillin resistant isolates were 2.2% and erythromycin resistant isolates were 96.4%.[9] In a study in China involving 11 sites looking at IPD isolates among children <14 years old revealed the most common serotypes isolated were 19F, 14, 19A, 6B and 23F. These serotypes accounted for 73.1% of all isolates.[10] Due to the high level of antibiotic resistance and high incidence of IPD, vaccines are important in the attempt to control pneumococcal disease.[11]

In 2005, clinical trials with Prevenar were conducted in China. In the phase 3 study involving Chinese infants, Prevenar was shown to be immunogenic, well-tolerated and safe when given either separately or concomitantly with a diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at 3, 4, and 5 months of age. In a subset of these infants completing a 3-dose primary vaccination series with Prevenar, more than 92% of subjects achieved antibody concentrations ≥0.35 μg/mL for each of the vaccine serotypes, except for serotype 6B, which was 83%.[12]

13vPnC is licensed in the European Union and other European countries, the United States, and other countries globally, now including China, as Prevenar 13/Prevnar 13®. It contains polysaccharides from the 7 serotypes included in 7-valent pneumococcal conjugate vaccine (7vPnC) and an additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A), all conjugated to cross-reactive material 197 (CRM_{197}). It has been shown that the 6 additional serotypes in 13vPnC increase coverage for IPD prevention in children <5 years of age to 74% to 88% globally.[13] Importantly, the additional serotypes in 13vPnC are associated with a high percentage of pneumococcal disease in the developing world.[14,15] Local serotype coverage in China of 13vPnC can range from 80.5% to as high as 87.2%. There is also some regional difference where Northern China appears to have serotype coverage of 75% as compared to Southern China that has serotype coverage of 92%.[16,17,18,19,20]

Prevenar 13, the 13-valent pneumococcal conjugate vaccine (13vPnC) was approved in China in October 2016 for the prevention of invasive pneumococcal disease in infants 6 weeks to 15 months of age. The approved regimen only allows vaccination with Prevenar 13 at 2, 4, 6 months for the primary series and the toddler or booster dose at 12 to 15 months of age. Prevenar, the 7-valent vaccine that was used as a comparator in the Phase 3 study in China had been approved through 5 years of age (up to the 6th birthday). The safety and immunogenicity of 7vPnC in children 7 months up to 5 years of age had been assessed in a post-licensure study (Study number B1841008).

The Center for Drug Evaluation (CDE) requested that safety and immunogenicity of Prevenar 13 be assessed in children 7 months to 5 years of age (before the 6th birthday). CDE also requested that Pfizer provide antibody persistence data through 5 years of age in children vaccinated as infants. This study is designed to support licensure of 13vPnC from

7 months through 5 years of age and to address both of these post licensure commitments from the CDE.

This study includes 4 separate cohorts broken down by age. Cohorts 2, 3 and 4 range in age from 7 months to 5 years of age (Cohort 2 - 7 months to <12 months of age; Cohort 3 - ≥1 year to <2 years; Cohort 4 - ≥2 years to <6 years of age). These three cohorts are of primary interest in obtaining licensure in the 7 months to 5 year age range and addressing the CDE request to obtain safety and immunogenicity data in this age group. Immune responses before and after the last vaccination in each of these age groups will be measured and used as a surrogate of efficacy. Cohort 1 will include infants 6 weeks to 2 months of age that will be vaccinated with 13vPnC according to the currently licensed infant schedule (2, 4, 6 and 12 to 15 months). Post vaccination serotype specific serum anticapsular IgG responses in Cohorts 2, 3, and 4 will be compared to the post infant series responses in Cohort 1 as a bridge to efficacy. Cohorts 2, 3, and 4 will also include a control group vaccinated with *Haemophilus influenzae* type b (Hib) vaccine. The Hib vaccinated infants and children will serve as controls for assessment of the safety and immunogenicity of Cohorts 2, 3, and 4.

In addition to serving as a bridge to efficacy for Cohorts 2, 3, and 4, Cohort 1 will provide the antibody persistence data at 12, 24, 36 and 48 months after the last vaccination required by the CDE.

During the conduct of the study at the Huaiyin county CDC, 280 subjects were enrolled from town level immunization clinics which were under the Huaiyin county CDC. According to the China Vaccine GCP guidelines[21] it is unclear if town level immunization clinics are allowed under the China regulations to be included as clinical trial sites. In reviewing the procedures and data from subjects in the study there were no issues identified with regards to subject safety, data quality, or integrity. An additional 280 subjects will be recruited. The purpose of enrolling these additional 280 subjects is to mitigate the possible risk that the previous 280 enrolled subjects from the town level immunization clinics will not be able to support approval/licensure of 13vPnC for infants and children 7 months through 5 years of age. All additional subjects (total 280) will follow the same study procedures and analyses.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator Brochure. The SRSD for the Hib vaccine is the local package insert.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective (Immunogenicity):	Primary Endpoints (Immunogenicity):
• To assess the immune responses 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 immune responses in infants 6 weeks to 2 months of age (Cohort 1).	• The serotype-specific 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.

Primary Objective (Safety):	**Primary Endpoints (Safety):**
• 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).	• 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 informed consent document (ICD) to 6 months after the last study vaccination (13vPnC or Hib) in Cohort 2, 3 and 4.
Secondary Objectives (Immunogenicity):	**Secondary Endpoints (Immunogenicity):**
• 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).	• 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.
• To describe the immune responses to 13vPnC compared to Hib vaccinated controls in Cohorts 2, 3, and 4.	• Serotype specific IgG GMC in all subjects and OPA GMTs in approximately 50 subjects per cohort vaccinated with 13vPnC (Cohorts 1,2 ,3 4) and approximately 25 subjects per cohorts vaccinated with Hib (Cohort 2, 3, 4) using blood drawn at the following visits: o Cohort 2: Visit 1, Visit 4 o Cohort 3: Visit 1, Visit 3 o Cohort 4: Visit 1, Visit 2
• 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.	• Serotype specific IgG GMC in all subjects and OPA GMTs in approximately 50 subjects at all times points in Cohort 1.

Secondary Objective (Safety):	Secondary Endpoints (Safety):
• To evaluate the safety profile of 13vPnC as measured by the incidence rates of adverse events (AEs) in Cohort 1.	• The incidence of AEs from the signing of the informed consent document (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 serious adverse events (SAEs) from the signing of the informed consent document (ICD) to 6 months after vaccination 4 in Cohort 1.

3. STUDY DESIGN

3.1. Description

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

- Subjects will be stratified into 4 cohorts defined by their age at 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 5 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 5 below.

Table 5. 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.

3.2. Approximate Duration of Subject Participation

Subjects in Cohort 1 are expected to participate from the first vaccination to the final visit which will include an antibody persistence blood draw 4 years after the last 13vPnC vaccination.

Subjects in Cohorts 2, 3 and 4 are expected to participate from the first vaccination to the final phone call, which will be the 6 months after the last vaccination.

The total duration of subject participation is up to approximately:

- Subjects in Cohort 1 will participate for up to approximately 5 years
- Subjects in Cohort 2 will participate for up to approximately 14 months
- Subjects in Cohort 3 will participate for approximately 8 months
- Subjects in Cohort 4 will participate for approximately 6 months

3.3. Approximate Duration of the Study

This study is anticipated to last approximately 66 months, assuming a 6-month recruitment period. The total duration may differ depending on the actual enrollment rate. Enrollment into the 4 cohorts will take place simultaneously. The end of the study is the last visit of the last subject in Cohort 1, which is scheduled approximately 48 months after the last vaccination.

3.4. Approximate Number of Subjects

Approximately 656 Chinese subjects will be randomized in four different age cohorts (Cohorts 1, 2, 3, and 4 with N=125, 177, 177, and 177 respectively).

An additional 280 subjects (177 subjects of Cohort 2, 73 subjects of Cohort 3, and 30 subjects of Cohort 4) will be enrolled from county CDCs.

There will be at least 1 coordinating center which may coordinate the study activities of multiple enrolling sites. Randomized subjects who withdraw from the study may be replaced to maintain adequate numbers to achieve study objectives.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated ICD indicating that the parent(s)/legal guardian has been informed of all pertinent aspects of the study.

2. Subject whose caregiver is willing and able to comply with scheduled visits, treatment plan, and other study procedures. The subject's caregiver must be able to be reached by telephone for the duration of the study.

3. Aged 6 weeks (42 days) to <6 years at the time of consent.

    - Cohort 1: Subjects 6 weeks to 2 months (42 to 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.

4. Healthy infants and children as determined by medical history, physical examination, and judgment of the investigator.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Infant or child who is a family member of:
    - Investigator site staff members directly involved in the conduct of the study;
    - Site staff members otherwise supervised by the investigator;
    - Pfizer employees directly involved in the conduct of the study.
2. Participation in other studies involving investigational drug(s)/vaccine(s) since birth (Cohort 1 only) or in the 6 months prior to study entry (Cohorts 2, 3, and 4) and/or during study participation.
3. Other acute or chronic medical or psychiatric condition, including recent laboratory abnormality, that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
4. Previous vaccination with licensed or investigational pneumococcal vaccine.
5. Previous vaccination with licensed or investigational Hib vaccine.
6. A previous anaphylactic reaction to any vaccine or vaccine-related component.
7. Contraindication to vaccination with pneumococcal or Hib vaccines (refer to local package insert).
8. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection.
9. Known or suspected immune deficiency or suppression.
10. History of culture-proven invasive disease caused by S pneumoniae.
11. Major known congenital malformation or serious chronic disorder.
12. Significant neurological disorder or history of seizure, including febrile seizure, or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Does not include resolving syndromes due to birth trauma such as Erb palsy.
13. Receipt of blood products or gamma globulin. Hepatitis B immunoglobulin may be given.

4.3. Criteria for Temporarily Delaying Vaccine Administration

The following conditions are temporary or self-limiting and a subject may be randomized and/or vaccinated once the condition(s) has resolved:

1. Current febrile illness (axillary temperature greater than or equal to 37.1°C [98.8°F]) or other acute illness within 48 hours before investigational product administration. Investigational product administration need not be delayed in the event of an afebrile illness if, according to local vaccination practice and the investigator's judgment, the subject should be vaccinated.

2. Subject has received any vaccine within the previous 4 days, except for bacille Calmette Guérin (BCG) vaccine and oral vaccines, which are allowed at any time.

3. Subject has received systemic antibiotic therapy within the last 5 days.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. INVESTIGATIONAL PRODUCTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

This study is open-label and subjects will receive the investigational products, 13vPnC or Hib vaccine (comparator).

For this study, the investigational product(s) are 13vPnC and Hib vaccine.

5.1. Allocation to Treatment

Subjects in cohort 1 will receive 13vPnC.

Subjects in Cohort 2, 3 or 4 will be randomized in a 2:1 ratio to receive one of the following investigational products:

- 13vPnC
- Hib vaccine (comparator)

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) system or equivalent system.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system or equivalent system.

5.2. Subject Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

5.3. Investigational Product Supplies

5.3.1. Formulation and Packaging

13vPnC and Hib vaccine will be commercially available vaccines packed and labeled in accordance with applicable legal and regulatory requirements. 13vPnC and Hib vaccine will be sourced locally by the site according to local regulations.

This is an open-label study, as the investigational products have different appearances.

5.3.1.1. 13-valent Pneumococcal Conjugate Vaccine

Commercially available 13vPnC will be provided in accordance with local regulations.

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to cross-reactive material 197 (CRM_{197}). The vaccine is formulated to contain 2.2 μg of each saccharide, except for 4.4 μg of 6B, per 0.5-mL dose. The final formulation contains 5 mM succinate buffer, with 0.125 mg of aluminum as aluminum phosphate per 0.5-mL dose. Polysorbate 80 at 0.02% is added as an excipient.

The SRSD for 13vPnC is the Investigator Brochure.

5.3.1.2. *Haemophilus influenzae* Type b Vaccine

A commercially available Hib vaccine will be provided for vaccination of subjects in Cohorts 2, 3 or 4 randomized to the Hib group. The Hib vaccine will be sourced by the sites in accordance with local regulations.

The SRSD for Hib vaccine is the local package insert.

5.3.2. Preparation and Dispensing

See the Investigational Product Manual (IP manual), package insert, or equivalent for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.3. Administration

Investigational product administration will be documented in the case report form (CRF).

13vPnC or Hib vaccine should be administered intramuscularly into a left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert at the vaccination visits, see Table 5.

Any concomitant vaccines required by local recommendations and permitted by the protocol may be administered concomitantly, but must be given in a different limb.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of investigational products should be performed by an appropriately qualified, Good Clinical Practice (GCP)-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Investigational product administration details will be recorded on the CRF.

5.4. Investigational Product Storage

Upon receipt at the study site, 13vPnC and the Hib vaccine should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage. 13vPnC and the Hib vaccine must be stored in accordance with the product label. The vaccines must not be frozen.

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, 13vPnC and Hib vaccine, are stored in a secured area with

controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.5. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.5.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.6. Concomitant Treatment(s)

The name and date of administration of any nonstudy vaccines given from the time of signing the consent form 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).

5.6.1. Prior Treatment

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

5.6.2. Permitted Vaccines

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

5.6.3. 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 5.6.2 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 5.6.2 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.

5.6.4. Mandatory Concomitant Vaccines

None

5.6.5. Prohibited Vaccines and Medications

No pneumococcal vaccines (licensed or investigational) other than those described in this study may be given prior to or during the study.

Local anesthetic cream should not be used at the site of investigational product administration.

Prophylactic use of antipyretic and other pain medications to prevent symptoms that might occur as a result of investigational product administration should be discouraged; however, it is recognized that use of antipyretic medication is a matter of parental choice and local clinical practice.

6. STUDY PROCEDURES

Before enrollment and before any study-related procedures are performed, voluntary written study-specific informed consent must be obtained from the parent/legal guardian of the subject. Each signature on the informed consent document (ICD) must be personally dated by the signatory. A copy of the signed and dated ICD must be given to the parent/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

Procedures considered to be part of standard routine care (eg, physical examination) may be performed before the ICD is signed but, for the purposes of the study, must be done on the day of first vaccination.

6.1. Cohort 1

6.1.1. Cohort 1: Visit 1, Vaccination 1 (42 to 56 Days of Age)

- Obtained informed consent from the subject's parent(s)/legal guardian(s) prior to performing any protocol-required procedures.

- Assign a subject number using the IRT or equivalent system.

- Obtain and record the subject demography (including full date of birth, sex and race. The date of birth will be collected to critically evaluate the immune response and safety profile by age).

- Obtain and record the subject's medical history.

- Record any nonstudy vaccinations. Note: vaccinations may be given ≥4 days before or ≥ 7 days after study vaccination, except for BCG vaccine and oral vaccines, which are allowed at any time, according to local practice or national recommendations, at the discretion of the investigator.

- Perform a physical examination evaluating any clinically significant abnormalities in the following: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, back/spine, neurological status, and lymph nodes including worsening of medical history conditions. Results must be recorded on source documents and the Medical History or AE page of the CRF as appropriate.

- Measure and record the subject's axillary temperature.

- Ensure that all inclusion criteria and none of the exclusion or temporary delay criteria are met.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Administer a single 0.5-mL intramuscular injection of 13vPnC into the subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.

- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period.

- Schedule an appointment with the caregiver for the next study visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.1.2. Cohort 1: Visit 2, Vaccination 2 (42 to 70 Days After Visit 1)

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.

- Record any nonstudy vaccinations.

- On the day of vaccination, measure and record the subject's axillary temperature.

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Ensure the subject does not meet any of the temporary delay criteria.

- Administer a single 0.5-mL intramuscular injection of 13vPnC into the subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.

- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period.
- Schedule an appointment with the caregiver for the next study visit.
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.1.3. Cohort 1: Visit 3, Vaccination 3 (42 to 70 Days After Visit 2)

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.
- Record any nonstudy vaccinations.
- On the day of vaccination, measure and record the subject's axillary temperature.
- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.
- Ensure the subject does not meet any of the temporary delay criteria.
- Administer a single 0.5-mL intramuscular injection of 13vPnC into the subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.
- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.
- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period.
- Schedule an appointment with the caregiver for the next study visit.
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.1.4. Cohort 1: Visit 4, Post-Infant Dose Follow-up (28 to 42 Days After Visit 3)

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.
- Record any nonstudy vaccinations.
- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Schedule an appointment with the caregiver for the next study visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.1.5. Cohort 1: Visit 5, Vaccination 4 (365 to 455 Days of Age)

- Based on clinical evaluation, determine whether any SAEs and newly diagnosed chronic medical conditions have occurred since the last study visit and record them on the CRF.

- Record any nonstudy vaccinations.

- On the day of vaccination, measure and record the subject's axillary temperature.

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Ensure the subject does not meet any of the temporary delay criteria.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Administer a single 0.5-mL intramuscular injection of 13vPnC into the subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.

- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period.

- Schedule an appointment with the caregiver for the next study visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.1.6. Cohort 1: Visit 6, Post-Toddler Dose Follow-up (28 to 42 Days After Visit 5)

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.
- Record any nonstudy vaccinations.
- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.
- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.
- Schedule an appointment with the caregiver for the 6-month follow-up telephone contact.
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.1.7. Cohort 1: Visit 7, 6-Month Follow-up (168 to 196 Days After the Last Study Vaccination)

- Contact the subject's caregiver by telephone to inquire about SAEs or newly diagnosed chronic medical conditions. This may be a clinic visit if preferred by the caregiver.
- Record any nonstudy vaccinations.
- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.
- The investigator or an authorized designee completes the CRF.

6.1.8. Cohort 1: Visit 8, Persistence Blood Draw Visit (2 Years of Age to 2 Years and 28 Days of Age)

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.
- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.
- Any AEs that occur within 48 hours after the blood draw should be recorded in the source documents and in the AE section of the CRF.
- Schedule an appointment with the caregiver for the next visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- Ask the caregiver to contact the investigator or other site staff if the subject reports any AEs that occur within 48 hours after the blood draw.

6.1.9. Cohort 1: Visit 9, Persistence Blood Draw Visit (3 Years of Age to 3 Years and 28 Days of Age)

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Any AEs that occur within 48 hours after the blood draw should be recorded in the source documents and in the AE section of the CRF

- Schedule an appointment with the caregiver for the next visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- Ask the caregiver to contact the investigator or other site staff if the subject reports any AEs that occur within 48 hours after the blood draw.

6.1.10. Cohort 1: Visit 10, Persistence Blood Draw Visit (4 Years of Age to 4 Years and 28 Days of Age)

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Any AEs that occur within 48 hours after the blood draw should be recorded in the source documents and in the AE section of the CRF.

- Schedule an appointment with the caregiver for the next visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- Ask the caregiver to contact the investigator or other site staff if the subject reports any AEs that occur within 48 hours after the blood draw.

6.1.11. Cohort 1: Visit 11, Persistence Blood Draw Visit (5 Years of Age to 5 Years and 28 Days of Age)

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Any AEs that occur within 48 hours after the blood draw should be recorded in the source documents and in the AE section of the CRF.

- Schedule an appointment with the caregiver for the next visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- Ask the caregiver to contact the investigator or other site staff if the subject reports any AEs that occur within 48 hours after the blood draw.

6.2. Cohort 2

6.2.1. Cohort 2: Visit 1, Vaccination 1 (7 Months [210 Days] to <12 Months [<365 Days] of Age)

- Obtained informed consent from the subject's parent(s)/legal guardian(s) prior to performing any protocol-required procedures.

- Obtain and record the subject demography (including full date of birth, sex and race. The date of birth will be collected to critically evaluate the immune response and safety profile by age).

- Obtain and record the subject's medical history.

- Record any nonstudy vaccinations. Note: vaccinations may be given ≥4 days before or ≥ 7 days after study vaccination, except for BCG vaccine and oral vaccines, which are allowed at any time, according to local practice or national recommendations, at the discretion of the investigator.

- Perform a physical examination evaluating any clinically significant abnormalities in the following: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, back/spine, neurological status, and lymph nodes including worsening of

medical history conditions. Results must be recorded on source documents and the Medical History or AE page of the CRF as appropriate.

- Based on clinical evaluation, determine whether any AEs (including serious adverse events [SAEs]) have occurred since the parent/legal guardian provided informed consent and record them on the CRF.

- Measure and record the subject's axillary temperature.

- Ensure that all inclusion criteria and none of the exclusion or temporary delay criteria are met.

- After all entry criteria are confirmed, the subject is randomized using the IRT or equivalent system.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Administer a single intramuscular dose of investigational product (13vPnC or Hib) into the subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.

- Issue a measuring device and a digital thermometer to the caregiver and provide instructions on their use.

- Issue a subject e-diary to the caregiver and provide instruction on its completion.

- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period, or if the subject reports redness or swelling at the investigational product injection site measuring >14 units on the measuring device.

- Remind the caregiver to bring the e-diary to the next study visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- The e-diary data should be viewed online via the vendor portal at frequent intervals from Day 1 to Day 7 after vaccination to evaluate e-diary completion and compliance and as part of the ongoing safety review.

6.2.2. Cohort 2: Visit 2, Vaccination 2 (At Least 28 Days After Visit 1)

- Review the subject's e-diary data since the previous visit.
- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.
- Record any nonstudy vaccinations.
- On the day of vaccination, measure and record the subject's axillary temperature.
- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.
- Ensure the subject does not meet any of the temporary delay criteria.
- Administer a single intramuscular dose of investigational product (13vPnC or Hib) into the subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.
- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.
- Issue a measuring device and a digital thermometer (if necessary) to the caregiver and provide instructions on their use.
- Issue a subject e-diary (if necessary) to the caregiver and provide instruction on its completion.
- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period, or if the subject reports redness or swelling at the investigational product injection site measuring >14 units on the measuring device.
- Remind the caregiver to bring the e-diary to the next study visit.
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.
- The e-diary data should be viewed online via the vendor portal at frequent intervals from Day 1 to Day 7 after vaccination to evaluate e-diary completion and compliance and as part of the ongoing safety review.

6.2.3. Cohort 2: Visit 3, (365 Days to <450 Days of Age and at Least 56 Days After Visit 2)

- Review the subject's e-diary data since the previous visit.

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.
- Record any nonstudy vaccinations.
- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.
- Collect the e-diary (Hib recipients only).
- Subjects randomized to Hib vaccine will not receive a vaccination at Visit 3. Subjects randomized to Hib may receive a third dose of Hib vaccine according to local practice or national recommendations, at the discretion of the investigator. Investigational sites will be reimbursed for any Hib vaccinations given. Hib vaccinations will be given outside of the study.

13vPnC recipients only:

  - On the day of vaccination, measure and record the subject's axillary temperature.
  - Ensure the subject does not meet any of the temporary delay criteria.
  - Administer a single 0.5-mL intramuscular injection of 13vPnC into subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.
  - Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.
  - Issue a measuring device and a digital thermometer (if necessary) to the caregiver and provide instructions on their use.
  - Issue a subject e-diary (if necessary) to the caregiver and provide instruction on its completion.
  - Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period, or if the subject reports redness or swelling at the investigational product injection site measuring >14 units on the measuring device.
  - Remind the caregiver to bring the e-diary to the next study visit.

- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period.
- Schedule an appointment with the caregiver for the next study visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- The e-diary data should be viewed online via the vendor portal at frequent intervals from Day 1 to Day 7 after vaccination to evaluate e-diary completion and compliance and as part of the ongoing safety review.

6.2.4. Cohort 2: Visit 4, Post-Toddler Dose Follow-up (28 to 42 Days After Visit 3)

- Collect the e-diary (13vPnC recipients only).

- Review the subject's e-diary data since the previous visit (13vPnC recipients only).

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.

- Record any nonstudy vaccinations.

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Schedule an appointment with the caregiver for the 6-month follow-up telephone contact.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.2.5. Cohort 2: Visit 5, 6-Month Follow-up (168 to 196 Days After the Last Study Vaccination)

- Contact the subject's caregiver by telephone to inquire about SAEs or newly diagnosed chronic medical conditions. This may be a clinic visit if preferred by the caregiver.

- Record any nonstudy vaccinations.

- The investigator or an authorized designee completes the CRF.

6.3. Cohort 3

6.3.1. Cohort 3: Visit 1, Vaccination 1 (≥1 Year to <2 Years of Age)

- Obtained informed consent from the subject's parent(s)/legal guardian(s) prior to performing any protocol-required procedures.

- Obtain and record the subject demography (including full date of birth, sex and race. The date of birth will be collected to critically evaluate the immune response and safety profile by age).

- Obtain and record the subject's medical history.

- Record any nonstudy vaccinations. Note: vaccinations may be given ≥4 days before or ≥ 7 days after study vaccination, except for BCG vaccine and oral vaccines, which are allowed at any time, according to local practice or national recommendations, at the discretion of the investigator.

- Perform a physical examination evaluating any clinically significant abnormalities in the following: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, back/spine, neurological status, and lymph nodes including worsening of medical history conditions. Results must be recorded on source documents and the Medical History or AE page of the CRF as appropriate.

- Based on clinical evaluation, determine whether any AEs (including serious adverse events [SAEs]) have occurred since the parent/legal guardian provided informed consent and record them on the CRF.

- Measure and record the subject's axillary temperature.

- Ensure that all inclusion criteria and none of the exclusion or temporary delay criteria are met.

- After all entry criteria are confirmed, the subject is randomized using the IRT or equivalent system.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Administer a single intramuscular dose of investigational product (13vPnC or Hib) into the subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.

- Issue a measuring device and a digital thermometer to the caregiver and provide instructions on their use.

- Issue a subject e-diary to the caregiver and provide instruction on its completion.

- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period, or if the subject experiences redness or swelling at the investigational product injection site measuring >14 units on the measuring device.

- Remind the caregiver to bring the e-diary to the next study visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- The e-diary data should be viewed online via the vendor portal at frequent intervals from Day 1 to Day 7 after vaccination to evaluate e-diary completion and compliance and as part of the ongoing safety review.

6.3.2. Cohort 3: Visit 2, (At Least 56 days After Visit 1)

- Collect the diary (Hib recipients only).

- Review the subject's e-diary data since the previous visit.

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.

- Record any nonstudy vaccinations.

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Subjects randomized to Hib vaccine will not receive a vaccination at Visit 2.

13vPnC recipients only:

- On the day of vaccination, measure and record the subject's axillary temperature.

- Ensure the subject does not meet any of the temporary delay criteria.

- Administer a single 0.5-mL intramuscular injection of 13vPnC into subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.

- Issue a measuring device and a digital thermometer (if necessary) to the caregiver and provide instructions on their use.

  - Issue a subject e-diary (if necessary) to the caregiver and provide instruction on its completion.

  - Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period, or if the subject reports redness or swelling at the investigational product injection site measuring >14 units on the measuring device.

  - Remind the caregiver to bring the e-diary to the next study visit.

- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period.

- Schedule an appointment with the caregiver for the next study visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- The e-diary data should be viewed online via the vendor portal at frequent intervals from Day 1 to Day 7 after vaccination to evaluate e-diary completion and compliance and as part of the ongoing safety review

6.3.3. Cohort 3: Visit 3, 1 Month Follow-up (28 to 42 Days After Visit 2)

- Collect the diary (13vPnC recipients only).

- Review the subject's e-diary data since the previous visit (13vPnC recipients only).

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.

- Record any nonstudy vaccinations.

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Schedule an appointment with the caregiver for the 6-month follow-up telephone contact.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.3.4. Cohort 3: Visit 4, 6-Month Follow-up (168 to 196 Days After the Last Study Vaccination)

- Contact the subject's caregiver by telephone to inquire about SAEs or newly diagnosed chronic medical conditions. This may be a clinic visit if preferred by the caregiver.
- Record any nonstudy vaccinations.
- The investigator or an authorized designee completes the CRF.

6.4. Cohort 4

6.4.1. Cohort 4: Visit 1, Vaccination 1 (≥2 Years to < 6 Years of Age)

- Obtained informed consent from the subject's parent(s)/legal guardian(s) prior to performing any protocol-required procedures.
- Obtain and record the subject demography (including full date of birth, sex and race. The date of birth will be collected to critically evaluate the immune response and safety profile by age).
- Obtain and record the subject's medical history.
- Record any nonstudy vaccinations. Note: vaccinations may be given ≥4 days before or ≥ 7 days after study vaccination, except for BCG vaccine and oral vaccines, which are allowed at any time, according to local practice or national recommendations, at the discretion of the investigator.
- Perform a physical examination evaluating any clinically significant abnormalities in the following: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities, back/spine, neurological status, and lymph nodes including worsening of medical history conditions. Results must be recorded on source documents and the Medical History or AE page of the CRF as appropriate.
- Based on clinical evaluation, determine whether any AEs (including serious adverse events [SAEs]) have occurred since the parent/legal guardian provided informed consent and record them on the CRF.
- Measure and record the subject's axillary temperature.
- Ensure that all inclusion criteria and none of the exclusion or temporary delay criteria are met.
- After all entry criteria are confirmed, the subject is randomized using the IRT or equivalent system.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Administer a single intramuscular dose of investigational product (13vPnC or Hib) into the subject's left limb (left anterolateral thigh muscle or deltoid of the left arm) in accordance with the local package insert.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded in the source documents and in the AE section of the CRF.

- Issue a measuring device and a digital thermometer to the caregiver and provide instructions on their use.

- Issue a subject e-diary to the caregiver and provide instruction on its completion.

- Ask the caregiver to contact the investigator or other site staff immediately if any significant illness or hospitalization occurs during the study period, or if the subject reports redness or swelling at the investigational product injection site measuring >14 units on the measuring device.

- Remind the caregiver to bring the e-diary to the next study visit.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

- The e-diary data should be viewed online via the vendor portal at frequent intervals from Day 1 to Day 7 after vaccination to evaluate e-diary completion and compliance and as part of the ongoing safety review.

6.4.2. Cohort 4: Visit 2, 1 Month Follow-up (28 to 42 Days After Visit 1)

- Collect the diary.

- Review the subject's e-diary data since the previous visit.

- Based on clinical evaluation, determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF.

- Record any nonstudy vaccinations.

- Ensure that the subject continues to be eligible for the study; refer to Subject Withdrawal section of the protocol.

- Collect a blood sample (approximately 5 mL). Blood must be drawn from peripheral veins (eg, arm, foot, or scalp veins). Drawing blood from central veins (eg, jugular or femoral veins), which may increase the risk associated with study participation, is not permitted.

- Schedule an appointment with the caregiver for the 6-month follow-up telephone contact.

- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

6.4.3. Cohort 4: Visit 3, 6-Month Follow-up (168 to 196 Days After the Last Study Vaccination)

- Contact the subject's caregiver by telephone to inquire about SAEs or newly diagnosed chronic medical conditions. This may be a clinic visit if preferred by the caregiver.

- Record any nonstudy vaccinations.

- The investigator or an authorized designee completes the CRF.

6.5. Unscheduled Visits – Cohorts 2, 3 and 4

If a local reaction (redness or swelling) at the 13vPnC or Hib injection site is greater than 14 measuring device units (7.0 cm), a visit will be required to assess the extent of the reaction. The subject's caregiver should contact the study personnel to arrange for an additional visit to the study site or a visit at the subject's home for assessment by the investigator or a medically qualified member of the investigator's staff who will do the following:

- Measure the subject's axillary temperature.

- Measure the minimum and maximum diameters of the redness or swelling in centimeters.

- Assess tenderness in accordance with the criteria provided in the Tenderness section.

- Complete the CRF.

The end date of any ongoing local reaction will be captured following the visit.

If the caregiver is contacted by the site to schedule this visit and the local reaction is no longer present or the caregiver is unable to schedule the visit, this information will be recorded in the CRF.

For the purpose of assessments performed during unscheduled visits, a medically qualified member of the study staff is a study physician or a study nurse, as applicable to the investigator's local practice.

6.6. Subject Withdrawal

Subjects may withdraw from the study at any time at the request of their parent(s)/legal guardian, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject's caregiver. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and their parent(s)/legal guardian also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

The decision to withdraw a subject from the study should be discussed with the sponsor's medical monitor.

When a decision has been made to discontinue further vaccination with the investigational product, the subject should, if possible, be followed for 6 months after the subject's final study vaccination before being permanently withdrawn from the study. In this period, every effort should be made to collect safety data and all data specified by the protocol including post-vaccination blood collection.

Eligibility criteria should be taken into consideration when determining if a subject should be withdrawn.

The following is a list of some examples, but not all, of the AEs that may warrant the withdrawal of a subject from the study unless there was an obvious alternative cause:

- Persistent, inconsolable screaming or crying for 3 or more hours within 48 hours after vaccination.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours after vaccination.
- Temperature greater than or equal to 40.0°C (104.0°F) unexplained by another cause, within 48 hours after vaccination.
- Anaphylactic/anaphylactoid reaction, including shock.
- Encephalopathy.

- A seizure, with or without fever, within 3 days after vaccination.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

A complete medical history and physical examination will be performed on all subjects before randomization. The CRFs will capture the medical history and physical examination done at visit 1 to establish a baseline.

Safety parameters will be assessed as described in the Schedule of Activities Procedures section, Adverse Events section. In addition use of antipyretic medication, local reaction and systemic event data will be collected in an electronic diary for 7 days after each dose of investigational product in Cohorts 2, 3 and 4.

7.1. Electronic Diary – Cohorts 2, 3, and 4

The caregiver will be issued an e-diary, and will be asked to monitor and record the subject's local reactions and systemic events (including the use of antipyretic medication), for 7 days after each investigational product (13vPnC or Hib vaccine) vaccination. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Use of antipyretic medication, local reactions and systemic events reported on the e-diary will be transferred electronically to the e-diary vendor (a trusted third party), where they will be available for review by investigators at all times via an Internet-based portal. At intervals agreed upon between the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator on the CRF.

Investigators will be required to review the e-diary data online at frequent intervals to evaluate the subject's caregiver e-diary completion compliance and as part of the ongoing safety review.

7.2. Local Reactions

Cohorts 2, 3 and 4: Local reactions (redness, swelling, and tenderness) at the site of the investigational product (13vPnC or Hib vaccine) injection will be monitored daily for 7 days (day 1 to day 7) after each vaccination. An end date will be captured for all reactions either via the e-diary or CRF as applicable.

7.2.1. Redness and Swelling

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 14), and then categorized as absent, mild, moderate, or severe based on the scale given below. Each unit represents 0.5 centimeters. A measuring device will be given to the caregiver with instructions for measuring any redness or swelling at the injection site. The caregiver will be asked to measure and to report the largest diameter of a local reaction. In case a measurement is between 2 values, the higher value should be reported. The caregiver will then record the measurements in the e-diary.

Table 6. 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)

If a reaction is greater than 14 units (7.0 cm), an additional visit to the study site will be required for an assessment by the investigator or other medically qualified study staff (refer to Unscheduled Visits – Cohorts 2, 3 and 4). If the caregiver is contacted by the site to schedule this visit and the local reaction is no longer present or the caregiver is unable to schedule the visit, this information will be recorded in the CRF.

7.2.2. Tenderness

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 following scale. The caregiver will then record the assessment in the e-diary. For events that were ongoing on the last day that they diary was completed, the end date will be collected in the CRF.

Table 7. Tenderness

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

7.3. Systemic Events

7.3.1. Temperature: Cohorts 2, 3 and 4

A digital thermometer will be given to the caregiver with instructions on how to measure the subject's axillary temperature at home. Temperature will be collected at bedtime daily for 7 days (day 1 to day 7) and at any time during the 7 days that fever is suspected. The highest temperature for each day will be recorded in the e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized according to the following scale:

Table 8. Temperature

Absent	<38.0°C (100.4°F)
Mild	≥38.0°C (100.4°F) to ≤39.0°C (102.2°F)
Moderate	>39.0°C (102.2°F) to ≤40.0°C (104.0°F)
Severe	>40.0°C (104.0°F)

In addition to categorizing temperatures according to the scale in Table 8 additional analysis will be performed using the scale in Table 9.

Table 9. Temperature

37.1°C (98.8°F) to <37.6°C (<99.7°F)
≥37.6°C (≥99.7°F) to ≤39.0°C (≤102.2°F)
>39.0°C (>102.2°F)

Fever is defined as temperature of greater than or equal to 38.0°C (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 they diary was completed.

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

The caregiver will be instructed to record the presence of other systemic events for 7 days (Day 1 to Day 7) after each investigational product vaccination and record the information in the diary. For events that resolve after the last day the diary was completed, the end date will be collected in the CRF.

Table 10. 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 for 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 diary but as an adverse event on the case report form.

Table 11. 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 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 11. 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 diary but as an adverse event on the case report form.

7.3.3. 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 they diary was completed. Data on the use of other concomitant medication will not be collected.

7.4. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. All serologic testing will be conducted by the National Institutes for Food and Drug Control (NIFDC). After completion of the study, all remaining serum samples will be under the custody of NIFDC.

The subject's parent/legal guardian may request that his or her child's samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research.

- Subjects in Cohort 1 will have 8 blood draws of up to 5 mL each (Visit 1, Visit 4, Visit 5, Visit 6, Visit 8, Visit 9, Visit 10, Visit 11) over the approximately 5 year duration of the study.

- Subjects in Cohorts 2, 3 and 4 will have 2 blood draws of up to 5 mL each:

    - Cohort 2 will have 2 blood draws (Visit 1, Visit 4);

    - Cohort 3 will have 2 blood draws (Visit 1, Visit 3);

    - Cohort 4 will have 2 blood draws (Visit 1, Visit 2).

7.5. Immunogenicity Evaluation

Immunologic assays will be performed at NIFDC.

7.5.1. IgG Assessments

Serum concentrations of anticapsular IgG for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all subjects for each blood sample collected and expressed as micrograms per milliliter (μg/mL). The assay will employ 2 adsorbents: a C polysaccharide-containing cell wall extract plus serotype 22F capsular polysaccharide.

Cohort 1: Serotype-specific IgG concentrations to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all subjects from the blood samples taken before vaccination, 1 month after the infant series, before the toddler dose, 1 month after the toddler dose and at yearly intervals for 4 years after the last vaccination.

Cohorts 2, 3, 4: Serotype-specific IgG concentrations to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all subjects from the blood samples taken before vaccination and after vaccination in each of the 3 cohorts (See schedule of activities for timing of blood samples.)

Additional 280 subjects (177 subjects of Cohort 2, 73 subjects of Cohort 3, and 30 subjects of Cohort 4): Serum concentrations of anticapsular IgG for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all subjects from the blood samples taken before vaccination and after vaccination in the additional subjects.

7.5.2. OPA Assessments

Serum levels of OPA for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all selected subjects for each blood sample collected and expressed as titers.

Cohort 1: Serotype-specific OPA titers to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in a randomly selected subset of approximately 50 subjects from the blood samples taken before vaccination, 1 month after the infant series, before the toddler dose, 1 month after the toddler dose and at yearly intervals for 4 years after the last vaccination.

Cohorts 2, 3, 4: Serotype-specific OPA titers to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in a randomly selected subset of approximately 50 subjects receiving 13vPnC and approximately 25 subjects receiving Hib vaccine from the blood samples taken before vaccination and 1 month after the last vaccination in each of the 3 cohorts.

Additional 280 subjects (177 subjects of Cohort 2, 73 subjects of Cohort 3, and 30 subjects of Cohort 4): Serotype-specific OPA titers to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in a randomly selected subset.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of vaccine group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian. In addition, each study subject/parent(s)/legal guardian will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for subjects in Cohort 1, begins from the time the subject’s /parent(s)/legal guardian provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 4 and from Visit 5 to Visit 6. Between Visits 4 and 5 and between Visits 6 and 7, only SAEs and newly diagnosed chronic medical conditions will be

recorded. The subject's parent/legal guardian will be asked to report any AEs that occur within 48 hours after the blood draw at Visits 8, 9, 10, and 11.

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for subjects in Cohort 2, 3, and 4, begins from the time the subject's /parent(s)/legal guardian provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product) until 1 month after the last vaccination (13vPnC or Hib). At the 6-Month follow-up telephone contact (final telephone contact), the parent(s)/legal guardian will be contacted to inquire about SAEs, including hospitalizations and newly diagnosed chronic medical conditions since the previous visit.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as

defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);

- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize

the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;

- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);

- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with subject's usual function.
2	MODERATE	Interferes to some extent with subject's usual function.
3	SEVERE	Interferes significantly with subject's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal

elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be

collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

  An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors and Lack of Efficacy

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors and lack of efficacy[a]	All (regardless of whether associated with an AE)	Only if associated with an SAE

a. For lack of efficacy see the Lack of Efficacy section below.

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

Other examples include, but are not limited to:

- The administration of expired investigational product;

- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

8.4.4.2. Lack of Efficacy

Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety.

8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Analysis

All of the analyses will be summarized for each cohort separately.

9.2. Immunogenicity Analysis Populations

An evaluable immunogenicity population and an all-available immunogenicity population will be defined for the immunogenicity analyses separately. The evaluable immunogenicity population will be the primary population for the immunogenicity analyses.

In general, the evaluable immunogenicity population will include all subjects who are eligible, receive the investigational product to which they are randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, receive no prohibited vaccine and have no major protocol violations. The all-available immunogenicity population will include all randomized subjects who have at least 1 valid and determinate assay result for the proposed analysis.

9.2.1. Analysis of the Primary Immunogenicity Endpoint

The study primary objective is to compare the serotype specific IgG GMCs to each of the 13 pneumococcal serotypes induced by 13vPnC between each cohort in the age of 7 months to < 6 years (Cohort 2, Cohort 3, Cohort 4) and infant Cohort 1. For each cohort (Cohort 2, Cohort 3, Cohort 4), the primary objective will be achieved if the non-inferiority criterion is met, or the lower bound of the 95% CI on the geometric mean ratio (GMR) (1 month after the last vaccination of Cohort 2, Cohort 3, Cohort 4 to 1 month after the last vaccination of infant series of Cohort 1) is greater than 0.5 for all 13 serotypes. 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. The 2-sided 95% CIs on the GMRs (GMC 13vPnC in Cohort 2, 3, or 4/GMC 13vPnC in Cohort 1) will be calculated using Student's t distribution for the mean difference of the measures on the natural log (ln) scale.

9.2.2. Analysis of the Secondary Immunogenicity Endpoint

All secondary immunogenicity endpoints are descriptive and will be summarized by cohort/group, along with point estimates and 95% CIs.

The analyses as described above for primary endpoint will also be repeated for OPA geometric mean titers (GMTs) and geometric mean titer ratios (GMTRs) measured for selected subjects in each cohort.

The proportion of subjects achieving an IgG concentration ≥ 0.35 μg/mL, as well as the proportion of subjects with pneumococcal OPA titer above a defined level will be computed for each tested blood sample obtained from subjects in all cohorts, and 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, along with associated exact (Clopper-Pearson's) 2-sided 95% CIs will be provided. Within each cohort in the age of 7 months to < 6 years (Cohort 2, Cohort 3, Cohort 4), the GMRs (IgG GMC 13vPnC/GMC Hib vaccine and OPA GMT 13vPnC/GMT Hib vaccine) and associated 2-sided 95% CIs on GMRs produced by a similar approach described in above Section 9.2.1 will be provided; and proportion differences between 13vPnC and Hib, and associated exact 2-sided 95% CIs by Chan and Zhang's method 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 post baseline blood sampling time points thought 1 month after infant series for Cohort 1, and all post baseline 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.

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

9.3. Safety Analysis

The safety population will be defined for safety analysis. The safety population will include all subjects who receive at least 1 dose of an investigational product.

All safety analysis will be summarized based on the safety population in accordance with Pfizer reporting standard. All available safety and reactogenicity data will be reported. Subjects will be analyzed according to vaccine actually received. For the safety endpoints, the proportion of subjects with local reactions and systemic events reported within the 7-day period after each vaccination will be summarized by vaccine group for each cohort. AEs and SAEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by vaccine group for each cohort separately.

9.4. Analysis Timing

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.

In addition, the OPA data 1 month after the infant series in Cohort 1 and 1 month after the last dose of 13vPnC in Cohorts 2, 3, 4 will be included in the primary analysis if the data is available from NIFDC, at the time of the primary analysis. If the OPA data is not available at the time of the primary analysis it will be reported when it becomes available.

The above data will be summarized in the primary study report and will be submitted to regulatory authorities to support licensure of 13vPnC in infant 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. The additional 280 subjects will be analyzed when data becomes available.

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

9.5. Sample Size Calculation

The type I error for all comparisons between each cohort in the age of 7 months to < 6 years and Cohort 1 (infant) is 5% (or 2.5%, 1-sided test of non-inferiority). As all comparisons between children with age of 7 months to < 6 year and infants are independent of each other, the type I error is not adjusted.

Sample size estimations are based upon GMCs in all Cohorts and data from studies in China (B1841008, and B1851015). The sample size/power estimates for non-inferiority of each Cohort in the age of 7 months to < 6 years relative to the Cohort 1 are evaluated based on following assumptions:

1. 2-sided type I error of 5%,

2. 2-fold non-inferiority criterion for GMC,

3. differences in true GMCs for 7 common serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) between each Cohort in the age of 7 months to < 6 years and the Cohort 1 (infant) are the same as the data observed in study B1841008,

4. differences in true GMCs for 6 additional serotypes (1,3,5, 6A, 7F, 19A) between each cohort in the age of 7 months to < 6 years and Cohort 1 are zero and GMCs of these 6 additional serotype for Cohort 1 are the same as 1 month after infant series in Group 3 from study B1851015.

   This assumption (d) may be conservative as actually better GMCs in the children of 7 months to <6 years for these 6 additional serotypes were observed when compared GMCs between 1 month after last dose in the age of 7 months to <6 years and 1 month after infant series in the studies performed in Poland (6096A1-3000 and 6096A1-3002).

The sample size estimations for non-inferiority of 13vPnC in the Cohort 2 (age 7 months to < 12 months) relative to 13vPnC in the Cohort 1 are presented in Table 12. Non-inferiority assumptions are as stated above, the 7vPnC data for Cohort 1 were based on GMC results of 1 month after infant series in Group 1 of study B1841008, and 7vPnC data for Cohort 2 were based on GMC results of 1 month after last vaccination of Group 2 in study B1841008. With a 2:1 randomization ratio (13vPnC : Hib vaccine) in the Cohort 2, a total of 150 evaluable subjects will provide 100 evaluable subjects with 13vPnC and therefore provide more than 90% power to declare non-inferiority relative to Cohort 1 across all 13 serotypes. With about 15% of randomized subjects nonevaluable in the Cohort 2, the total number of subjects to be randomized in Cohort 2 will be 177.

Table 12. Power Estimates for Cohort 2, Based on Geometric Mean Concentration From Studies B1841008 and B1851015

Serotype	Cohort 1(13vPnC)			Cohort 2(13vPnC)			Difference (LOG)	Common SD (LOG)	Power N= 200 (100:100)
	GMC	GMC (LOG)	SD (LOG)	GMC	GMC (LOG)	SD (LOG)			
7vPnC									
4	6.38	1.853	0.652	7.16	1.969	0.760	0.115	0.708	>0.999
6B	2.88	1.058	0.994	5.79	1.756	1.041	0.698	1.018	>0.999
9V	4.18	1.430	0.826	4.64	1.535	0.776	0.104	0.801	>0.999
14	11.16	2.412	0.953	13.02	2.566	0.839	0.154	0.898	>0.999
18C	4.60	1.526	0.902	4.65	1.537	0.877	0.011	0.890	>0.999
19F	3.60	1.281	1.275	4.02	1.391	1.301	0.110	1.288	0.992
23F	2.45	0.896	1.024	3.95	1.374	1.002	0.478	1.013	>0.999
Additional									
1	7.77	2.050	0.884				0	0.884	>0.999
3	1.68	0.519	0.822				0	0.822	>0.999
5	3.61	1.284	0.842				0	0.842	>0.999
6A	4.76	1.560	0.994				0	0.994	0.998
7F	8.28	2.114	0.778				0	0.778	>0.999
19A	5.1	1.629	0.928				0	0.928	>0.999
Overall									0.990

Abbreviations: GMC = geometric mean concentration; SD = standard deviation. LOG= natural logarithm.

The sample size estimations for non-inferiority of 13vPnC in Cohort 3 (age 1 year to <2 years) relative to Cohort 1 (infant) are presented in Table 13. Non-inferiority assumptions are stated as above, the 7vPnC data for Cohort 1 were based on GMC results of 1 month after infant series in Group 1 of study B1841008, and 7vPnC data for Cohort 3 were based on GMC results of 1 month after last vaccination of Group 3 in study B1841008. With a 2:1 randomization ratio (13vPnC : Hib vaccine) in Cohort 3, a total of 150 evaluable subjects will provide 100 evaluable subjects with 13vPnC and therefore provide more than 90% power to declare non-inferiority relative to Cohort 1 across all 13 serotypes. With about 15% of randomized subjects nonevaluable in Cohort 3, the total number of subjects to be randomized in Cohort 3 will be 177.

Table 13. Power Estimates for Cohort 3, Based on Geometric Mean Concentration From Studies B1841008 and B1851015

Serotype	Cohort 1(13vPnC)			Cohort 3 (13vPnC)			Difference (LOG)	Common SD (LOG)	Power N= 200 (100:100)
	GMC	GMC (LOG)	SD (LOG)	GMC	GMC (LOG)	SD (LOG)			
7vPnC									
4	6.38	1.853	0.652	7.53	2.019	0.631	0.166	0.640	>0.999
6B	2.88	1.058	0.994	4.81	1.571	1.150	0.513	1.085	>0.999
9V	4.18	1.430	0.826	4.67	1.541	0.596	0.111	0.704	>0.999
14	11.16	2.412	0.953	11.98	2.483	0.708	0.071	0.823	>0.999
18C	4.60	1.526	0.902	5.40	1.687	0.660	0.160	0.774	>0.999
19F	3.60	1.281	1.275	4.03	1.394	1.147	0.113	1.204	0.997
23F	2.45	0.896	1.024	4.18	1.430	0.936	0.534	0.975	>0.999
Additional									
1	7.77	2.050	0.884				0	0.884	>0.999
3	1.68	0.519	0.822				0	0.822	>0.999
5	3.61	1.284	0.842				0	0.842	>0.999
6A	4.76	1.560	0.994				0	0.994	0.998
7F	8.28	2.114	0.778				0	0.778	>0.999
19A	5.1	1.629	0.928				0	0.928	>0.999
Overall									0.995

Abbreviations: GMC = geometric mean concentration; SD = standard deviation. LOG= natural logarithm.

The sample size estimations for non-inferiority of 13vPnC in Cohort 4 (age 2 to < 6 years) relative to Cohort 1 (infant) are presented in Table 14. Non-inferiority assumptions are stated as above, the 7vPnC data for Cohort 1 were based on GMC results of 1 month after infant series in Group 1 of study B1841008, and 7vPnC data for Cohort 4 were based on GMC results of 1 month after last vaccination of Group 4 in study B1841008. With a 2:1 randomization ratio (13vPnC : Hib vaccine) in Cohort 4, a total of 150 evaluable subjects will provide 100 evaluable subjects with 13vPnC and therefore provide 88.7% power to declare non-inferiority relative to Cohort 1 across all 13 serotypes. With about 15% of randomized subjects nonevaluable in Cohort 4, the total number of subjects to be randomized in the Cohort 4 will be 177.

Table 14. Power Estimates for Cohort 4, Based on Geometric Mean Concentration From Studies B1841008 and B1851015

Serotype	Cohort 1(13vPnC)			Cohort 4 (13vPnC)			Difference (LOG)	Common SD (LOG)	Power N= 200 (100:100)
	GMC	GMC (LOG)	SD (LOG)	GMC	GMC (LOG)	SD (LOG)			
7vPnC									
4	6.38	1.853	0.652	9.45	2.246	0.808	0.393	0.760	>0.999
6B	2.88	1.058	0.994	6.36	1.850	1.198	0.792	1.135	>0.999
9V	4.18	1.430	0.826	6.14	1.814	0.838	0.385	0.834	>0.999
14	11.16	2.412	0.953	9.86	2.288	1.382	-0.124	1.257	0.890
18C	4.60	1.526	0.902	7.39	2.000	0.955	0.474	0.938	>0.999
19F	3.60	1.281	1.275	4.53	1.510	1.303	0.230	1.294	0.999
23F	2.45	0.896	1.024	5.64	1.730	1.030	0.834	1.028	>0.999
Additional									
1	7.77	2.050	0.884				0	0.884	>0.999
3	1.68	0.519	0.822				0	0.822	>0.999
5	3.61	1.284	0.842				0	0.842	>0.999
6A	4.76	1.560	0.994				0	0.994	0.998
7F	8.28	2.114	0.778				0	0.778	>0.999
19A	5.1	1.629	0.928				0	0.928	>0.999
Overall									0.887

Abbreviations: GMC = geometric mean concentration; SD = standard deviation. LOG= natural logarithm.

In summary, as shown in above in Table 12, Table 13, and Table 14, 100 evaluable subjects vaccinated with 13vPnC are needed for each cohort. Assuming a nonevaluable rate of approximately 20% for Cohort 1 and 15% for Cohort 2, 3, and 4, with a 2:1 randomization ratio within Cohort 2, 3, and 4, a total of 125, 177, 177, and 177 subjects should be randomized in Cohorts 1, 2, 3, and 4, respectively, to ensure the required number of evaluable subjects to declare the non-inferiority of 13vPnC in the age of 7 months to <6 years relative to the infant group (Cohort 1) with regard to immunogenicity. For the OPA a random subset of 50 blood samples from subjects randomized to receive 13vPnC in cohorts 1 through 4 will be selected for OPA testing. For subjects who are randomized to receive Hib in Cohorts 2 to 4 a random subset of 25 blood samples from each cohorts will be selected for OPA testing.

Table 15. Planned Enrollment

	13vPnC	Control	Total
3+1 regimen (Cohort 1)	125	N/A	125
2+1 regimen (Cohort 2)	118	59	177
1+1 regimen (Cohort 3)	118	59	177
1-Dose regimen (Cohort 4)	118	59	177
Total	479	177	656

Enrollment (Approximately 20% Nonevaluable Rate for Cohort 1 and 15% Nonevaluable Rate for Cohort 2, 3, and 4)

9.6. Interim Analysis

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, and/or to support clinical development.

9.7. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject's parent(s) or legal guardian before any study-specific activity is performed. The investigator will retain the original of each subject's parent(s)- or legal guardian-signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of 13vPnC at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) promptly by Pfizer]. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	bacille Calmette-Guérin
CDC	Center for Disease Control
CDE	Center for Drug Evaluation
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRM_{197}	cross-reactive material 197
CSA	clinical study agreement
CT	clinical trial
DILI	drug-induced liver injury
DTaP	diphtheria, tetanus, and acellular pertussis
EC	ethics committee
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
GMTR	geometric mean titer ratio
Hib	*Haemophilus influenzae* type b
ICD	informed consent document
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IPD	invasive pneumococcal disease
IRB	institutional review board
IRT	interactive response technology
LFT	liver function test
LSLV	last subject last visit

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NIFDC	National Institutes for Food and Drug Control
OPA	opsonophagocytic activity
PCD	primary completion date
PI	principal investigator
PPSV23	23-valent pneumococcal polysaccharide vaccine
PS	polysaccharide
PT	prothrombin time
RCDC	reverse cumulative distribution curves
SAE	serious adverse event
SAP	statistical analysis plan
SRSD	single reference safety document
TBili	total bilirubin
ULN	upper limit of normal
UNICEF	United Nations Children's Fund
US	United States
WHO	World Health Organization

Document Approval Record

Document Name:	B1851178 Protocol Amendment 2, Clean Copy, 07 Feb 2019
Document Title:	B1851178 Protocol Amendment 2, Clean Copy, 07 Feb 2019

Signed By:	Date(GMT)	Signing Capacity
PPD	15-Mar-2019 12:58:46	Final Approval
PPD	15-Mar-2019 19:47:34	Business Line Approver