A PHASE 2, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A MULTIVALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY INFANTS

Investigational Product Number:	PF-06482077
Investigational Product Name:	20-valent pneumococcal conjugate vaccine (20vPnC)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	CCI [redacted]
Protocol Number:	B7471003
Phase:	2

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	11 Feb 2020	- Added the IND number, as this was not available during the last amendment. - Section 4.2: Exclusion criterion 5 was updated to "Prior receipt of hepatitis B vaccine at age ≥30 days" to clarify the age of administration and to enable the criterion to be answered with a "yes/no" response. - Section 5.10.2: Clarified that licensed inactivated influenza vaccine may be given to eligible study subjects during influenza season. - Section 8.2.1: Added wording to clarify that events consistent with normal growth and development are generally not to be considered adverse events.
Amendment 1	05 Jan 2018	- Added editorial changes throughout the document to improve clarity and to fix typographic errors. - Schedule of activities and relevant sections of the document: Added the collection of prior vaccinations to verify exclusion criteria. – Section 1.2: Updated the background and rationale to make the wording more applicable to pediatrics. – Section 2.1: Removed "safety" from the titles of

		"primary safety objective" and "primary safety endpoints," as we do not need to specify that the primary objective and primary endpoints are safety related. – Section 4.2: Revised exclusion criteria to <30 days to ensure subjects received the hepatitis B vaccine at less than 30 days of age. – Section 5.6.1: CCI [redacted] – Section 5.10: Clarified that Pfizer will provide the diphtheria, tetanus, and acellular pertussis (DTaP)-containing vaccine. CCI [redacted] – Section 8.4.3 and relevant sections of the document: Added pregnancy, breastfeeding, and

		occupational exposure text per protocol template. CCI [redacted]
Original protocol	29 Aug 2017	Not applicable (N/A)

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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PROTOCOL SUMMARY

Background and Rationale

Streptococcus pneumoniae are gram-positive encapsulated cocci that are a leading cause of bacteremia, bacterial meningitis, pneumonia, and acute otitis media (AOM) and continue to be a major global public health concern. Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk. Individuals with certain comorbidities and immunocompromising conditions are also at risk, especially persons with chronic heart, lung, liver, and renal disease, as well as those who are functionally asplenic. AOM carries the risk of complications such as tympanostomy tube placement, hearing loss, mastoiditis, and meningitis as well as being a significant burden on the healthcare system. *S pneumoniae* remains an important cause of serious disease in the United States and worldwide.

The polysaccharide capsule has been identified as an important virulence factor for this pathogen. While more than 95 pneumococcal serotypes, differentiated by their capsular polysaccharide composition, have been identified, serious disease is generally caused by a smaller subset of serotypes. Pneumococcal disease can be prevented with polysaccharide-based vaccines that induce antibody responses with functional (opsonophagocytic) activity and target the capsular serotypes responsible for disease. Pneumococcal vaccines containing free polysaccharides, such as the licensed 23-valent pneumococcal polysaccharide vaccine (PPSV23), are poorly immunogenic in immunocompromised populations, older adults, and children less than 2 years of age, and are not recommended in this younger age group. This led to development of pneumococcal conjugate vaccines, which contain capsular polysaccharides covalently linked to a protein carrier, and which induce protective immune responses in young children and older adults, as well as populations with high-risk conditions. Prevnar® (7-valent pneumococcal conjugate vaccine [7vPnC]), which was licensed in the United States in 2000, and Prevnar 13® (13-valent pneumococcal conjugate vaccine [13vPnC]), which was licensed in the United States in 2010, are pneumococcal conjugate vaccines containing 7 and 13 pneumococcal capsular polysaccharides, respectively, that are each covalently linked to a nontoxic variant of diphtheria toxin, cross-reactive material 197 (CRM_{197}). These vaccines targeted serotypes that caused the majority of pneumococcal disease in infants and older adults at the time of their introduction. They have demonstrated efficacy/effectiveness against vaccine-type (VT) invasive pneumococcal disease (IPD) such as bacteremia and meningitis, as well as AOM, and community-acquired pneumonia (CAP). Additionally, they have been found to reduce nasopharyngeal carriage and transmission, resulting in beneficial indirect effects.

Pfizer is developing a new 20-valent pneumococcal conjugate vaccine (20vPnC) candidate to expand protection against pneumococcal disease beyond that covered by current pneumococcal vaccines in children and adults. 20vPnC has the same composition as Prevnar 13, but contains an additional 7 pneumococcal conjugates to protect against serotypes responsible for a substantial burden of remaining pneumococcal disease. A meta-analysis of serotypes causing IPD in children <5 years of age in regions of the world that have introduced higher-valent pneumococcal conjugate vaccines (such as 13vPnC) showed that, overall, these 7 serotypes accounted for approximately 70% of disease not due

to the 13vPnC vaccine types. 20vPnC uses the same platform as Prevnar and Prevnar 13 and contains components that have undergone extensive clinical research. A Phase 1 study has been conducted with 20vPnC in healthy adults 18 to 49 years of age, and the safety and immunogenicity results support further development of 20vPnC in older adults and infants.

The purpose of this Phase 2 study is to describe the safety and immunogenicity of 20vPnC in infants administered vaccine (20vPnC or 13vPnC control) at 2, 4, 6, and 12 months of age. Safety and immunogenicity data from this study will inform further clinical development of 20vPnC in pediatric populations.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the 20vPnC investigator's brochure (IB). The SRSD for 13vPnC is the US package insert (USPI).

Study Design

This is a Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design. It is planned to be conducted at investigator sites in the United States. Approximately 460 infants aged ≥42 to ≤98 days will be randomized (1:1) to receive either 20vPnC or 13vPnC at 2, 4, and 6 months of age (infant series, Doses 1 through 3) and 12 months of age (Dose 4). Vaccine containing diphtheria, tetanus, and acellular pertussis antigens will be administered concomitantly with Doses 1 to 3. Other routine pediatric vaccines may be administered as specified in the protocol as well. Local reactions (pain, redness, and swelling) at the injection site and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) will be prompted for and collected by an electronic diary (e-diary; device or application) from Day 1 to Day 7 after each vaccination. Adverse events (AEs) will be collected from the signing of the informed consent document to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4. Serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) will be collected from the time of informed consent through 6 months after Dose 4. Blood will be collected 1 month after Dose 3, immediately prior to Dose 4, and 1 month after Dose 4 to assess immunogenicity.

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Primary Objective and Endpoints

Primary Objective

- To describe the safety profile of 20-valent pneumococcal conjugate vaccine (20vPnC) in healthy infants.

Primary Endpoints

- Proportions of subjects reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days of each dose.

- Proportions of subjects reporting prompted systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep) within 7 days of each dose.
- Proportions of subjects reporting AEs from Dose 1 to 1 month following Dose 3 and from Dose 4 to 1 month following Dose 4.
- Proportions of subjects reporting SAEs and NDCMCs from Dose 1 to 6 months following Dose 4.

Secondary Objective and Endpoints

Secondary Objective

- To describe the immunogenicity of 20vPnC in healthy infants.

Secondary Endpoints

- Pneumococcal serotype-specific immunoglobulin G (IgG) concentrations 1 month after Dose 3.
- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4.

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Statistical Methods

An analysis of safety and immunogenicity data will be conducted when data are available as described in Section 9 according to the statistical analysis plan (SAP). All analyses will be descriptive. No hypothesis tests between vaccine groups are planned; therefore, no power calculations for comparison of vaccine groups are included.

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.

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Description	**Dose 1 2-Month Visit**	**Dose 2 4-Month Visit**	**Dose 3 6-Month Visit**	**Follow-up 7-Month Visit**	**Dose 4 12-Month Visit**	**Follow-up 13-Month Visit**	**Follow-up Phone Call 18-Month Visit**
Visit Window (Days)	**Day 1**	**42 to 63 Days After Visit 1**	**42 to 63 Days After Visit 2**	**28 to 42 Days After Visit 3**	**365 to 386 Days of Age**	**28 to 42 Days After Visit 5**	**168 to 196 Days After Visit 5**
Obtain informed consent	X						
Record demography	X						
Obtain medical history data	X						
Perform physical examination	X						
Obtain prevaccination rectal temperature	X	X	X		X		
Record prior and interim vaccinations	X	X	X	X	X	X	
Review inclusion and exclusion criteria	X						
Review temporary delay criteria	X	X	X	X	X	X	
Review continued eligibility		X	X	X	X	X	
Assign a subject number and a randomization number	X						
Obtain blood sample (~5 mL)				X	X[a]	X	
Administer investigational product (20vPnC or 13vPnC)	X	X[b]	X[b]		X[b]		
Administer DTaP-containing vaccine[c]	X	X	X				
Administer other permitted concomitant vaccines[c]	X	X	X		X		
Assess and record acute reactions for at least 30 minutes after investigational product administration	X	X	X		X		

Visit Number	1	2	3	4	5	6	7
Visit Description	**Dose 1 2-Month Visit**	**Dose 2 4-Month Visit**	**Dose 3 6-Month Visit**	**Follow-up 7-Month Visit**	**Dose 4 12-Month Visit**	**Follow-up 13-Month Visit**	**Follow-up Phone Call 18-Month Visit**
Visit Window (Days)	**Day 1**	**42 to 63 Days After Visit 1**	**42 to 63 Days After Visit 2**	**28 to 42 Days After Visit 3**	**365 to 386 Days of Age**	**28 to 42 Days After Visit 5**	**168 to 196 Days After Visit 5**
Provide legally acceptable representative with an e-diary (device or application), thermometer, and measuring device and instruct how to collect prompted local reactions, systemic events, and antipyretic/pain medication use until Day 7[d]	X				X		
Review e-diary events[e,]		X	X	X		X	
Collect e-diary (if device provided)				X		X	
Record and report adverse events	X----------X				X----------X		
Record and report serious adverse events and newly diagnosed chronic medical conditions[g,h]	X----------X						

Abbreviations: DTaP = diphtheria, tetanus, and acellular pertussis; e-diary = electronic diary.

a. Blood sample will be collected prior to vaccination.
b. Remind the subject's legally acceptable representative that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
c. The subject may receive vaccines with inactivated poliovirus, hepatitis B, or *Haemophilus influenzae* type b (either separately or in combination with diphtheria, tetanus, and pertussis antigens) at 2, 4, and 6 months of age, Measles, mumps, and rubella (MMR) vaccine may be administered concomitantly at 12 months of age with Dose 4 or more than 1 month after Dose 4. Rotavirus vaccine may be administered orally at any time.
d. The subject's legally acceptable representative will record prompted local reactions and systemic events in an e-diary for the 7 days following each dose of 20vPnC or 13vPnC. The subject's legally acceptable representative will be instructed to contact the study staff if the subject experiences redness or swelling >14 caliper units, severe pain at the injection site, or a fever >104.0°F (>40.0°C) or has an emergency room visit or hospitalization.
e. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following each dose of 20vPnC or 13vPnC to evaluate subject compliance and as part of the ongoing safety review.
[redacted]
g. Record concomitant medications used to treat SAEs and NDCMCs as described in Section 5.10.3.
h. A newly diagnosed chronic medical condition is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

1. INTRODUCTION

1.1. Indication

20-valent pneumococcal conjugate vaccine (20vPnC) is being developed for:

- Active immunization to prevent disease caused by the *Streptococcus pneumoniae* serotypes in the vaccine.

1.2. Background and Rationale

1.2.1. Pneumococcal Disease

S pneumoniae are gram-positive encapsulated cocci that are a leading cause of bacteremia, bacterial meningitis, pneumonia, and acute otitis media (AOM) and continue to be a major global public health concern.[1,2,3] Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk.[4] Individuals with certain comorbidities and immunocompromising conditions are also at risk, especially persons with chronic heart, lung, liver, and renal disease, as well as those who are functionally asplenic. The global burden of pneumococcal disease has been substantially impacted by pneumococcal conjugate vaccines. *S pneumoniae* caused an estimated 14.5 million cases of serious disease and 826,000 deaths annually in children <5 years of age prior to introduction of pneumococcal conjugate vaccines.[2] A recent estimate suggested that in 2015, several years following introduction of pneumococcal conjugate vaccines into the national infant immunization programs of more than 100 countries, the global disease burden had declined, but *S pneumoniae* still accounted for 2.6 million cases of severe pneumococcal disease, 332,000 deaths in children <5 years of age, and 11% of deaths in children between the ages of 1 and 5 years.[5]

The overall invasive pneumococcal disease (IPD) burden was estimated in 2013 to have decreased approximately 90% in the population <5 years of age in the United States since the introduction of pneumococcal conjugate vaccines; however, there was a slight increase in the proportions of IPD cases associated with hospitalization (63% to 71%), and the IPD case fatality rate was also slightly but statistically significantly increased (2% to 3%) in that age group.[6] This is due to the decrease in disease due to the serotypes in Prevnar® (7-valent pneumococcal conjugate vaccine [7vPnC]) and Prevnar 13® (13-valent pneumococcal conjugate vaccine [13vPnC]). However, disease due to serotypes not covered by those vaccines remains, and causes significant morbidity and mortality. Pediatric surveillance studies conducted between 2007 and 2013 in 8 US children's hospitals, and between 1997 and 2010 in a referral center in Utah, found case fatality rates of 10% and 13% with pneumococcal meningitis, respectively. These studies also found that between 52% and 63% of children surviving pneumococcal meningitis experience neurologic sequelae.[7,8]

Surveillance studies conducted in 2010-2012 by the Centers for Disease Control and Prevention (CDC) found that *S pneumoniae* remains among the most common pathogens identified in community-acquired pneumonia (CAP) requiring hospitalization in the United States in both children and adults.[9,10] These data suggest that *S pneumoniae* remains an important cause of serious disease in the United States and worldwide.

AOM is a common childhood illness, with the 2011 visit rates of 0.82 and 0.81 visits for AOM/child-year in children <2 years of age and 2 to 6 years of age, respectively, and represents a significant medical burden.[11] While AOM is generally not considered a serious disease, it does carry the risk of more serious complications. These complications can range from the development of chronic or recurrent otitis media necessitating surgical intervention (tympanostomy tube placement), and accompanied by hearing losses with potential developmental and language delays, to invasive extension leading to mastoiditis and meningitis.

Although the introduction of pneumococcal conjugate vaccines into the United States and other national infant immunization programs has brought about substantial reductions in the various manifestations of pneumococcal disease in pediatric (and to some extent adult) populations, a substantial burden of pneumococcal disease remains.

1.2.2. Vaccines to Prevent Pneumococcal Disease

The polysaccharide capsule has been identified as an important virulence factor for this pathogen. While more than 95 pneumococcal serotypes, differentiated by their capsular polysaccharide composition, have been identified, serious disease is generally caused by a smaller subset of serotypes.[12,13] Anticapsular antibodies directed against the specific serotype bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.[14] Pneumococcal disease can be prevented with polysaccharide-based vaccines that induce antibody responses with functional (opsonophagocytic) activity and target the capsular serotypes responsible for disease.[15]

1.2.2.1. Pneumococcal Polysaccharide Vaccines

Vaccines containing free polysaccharides have been licensed since the 1970s. One such vaccine, the 23-valent pneumococcal polysaccharide vaccine (PPSV23), has been licensed in the United States since 1983.[16,17] PPSV23 contains capsular polysaccharides for 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). Pneumococcal vaccines containing free polysaccharides such as PPSV23 elicit a T-cell–independent immune response. Unconjugated polysaccharide vaccines do not induce robust responses in certain populations (eg, immunocompromised persons, children <2 years of age, and adults ≥65 years of age), nor do they generate immunologic memory, so that their protective effect wanes over 2 to 5 years.[4,17,18,19] Moreover, their ability to prevent nonbacteremic pneumonia, CAP, and AOM is limited or lacking.[15,19,20,21,22] In addition, polysaccharide vaccines do not reduce vaccine-type (VT) nasopharyngeal carriage, which is important for herd immunity.[22] PPSV23 is not recommended for children <2 years of age and only recommended in children >2 years of age who are at high risk for IPD to provide some degree of protection from disease caused by serotypes not covered by existing pneumococcal conjugate vaccines.[15]

1.2.2.2. Pneumococcal Polysaccharide Conjugate Vaccines

Pneumococcal conjugate vaccines contain polysaccharides that are covalently linked (conjugated) to an immunogenic protein. This modification results in T-cell–dependent immune responses, which have been shown to be protective in young children, older adults,

and populations with high-risk conditions.[18,23] 7vPnC was the first pneumococcal conjugate vaccine to be licensed (2000) and was indicated for prevention of pneumococcal disease in infants and young children on the basis of efficacy studies. Prevnar contained capsular polysaccharide conjugates for 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), each covalently linked to cross-reactive material 197 (CRM_{197}), a nontoxic variant of diphtheria toxin. These 7 serotypes were responsible for approximately 80% to 90% of IPD in children <5 years of age in the United States and approximately 60% to 80% of IPD in the same age group in Europe at that time (1998-2000).[24,25,26,27,28] These serotypes also accounted for a high proportion of antibiotic-resistant strains.[29] 7vPnC demonstrated efficacy against VT IPD, pneumonia, and AOM in large randomized, controlled efficacy studies in infants.[30,31] The 7vPnC components contained in a related pneumococcal conjugate vaccine also were demonstrated to be efficacious against clinically/radiographically defined pneumonia.[32,33,34,35] Following introduction of Prevnar, reduction of nasopharyngeal carriage and transmission has resulted in indirect herd effects, with a 92% reduction of 7vPnC VT IPD in older adults ≥65 years of age.[36]

13vPnC was developed to expand serotype coverage and was licensed in the United States in 2010. 13vPnC includes the same *S pneumoniae* serotypes as Prevnar and an additional 6 polysaccharide conjugates for serotypes 1, 3, 5, 6A, 7F, and 19A.[23,27,37] The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific serum immunoglobulin G (IgG) concentrations to 7vPnC, with supportive data to demonstrate the functional activity of the immune responses. 13vPnC was later licensed in adults based on demonstration of efficacy against VT CAP in adults 65 years of age and older.[38] 13vPnC has replaced 7vPnC and is licensed in the United States and many other countries, with national recommendations for use in children and older adults.[39,40,41,42] It has also been prequalified by the World Health Organization (WHO) for use in national infant immunization programs in lower- and middle-income countries.[43,44] Surveillance data from several countries following introduction of 13vPnC into the routine infant immunization program have demonstrated vaccine effectiveness against VT IPD in the vaccinated population.[45,46,47] 13vPnC is now licensed for use in children 6 weeks through 17 years of age and adults 18 to 49 years of age in the United States and elsewhere.

1.2.2.3. Rationale for 20vPnC

20vPnC is being developed to further expand protection against the global burden of vaccine-preventable pneumococcal disease in children and adults over that of 13vPnC. 20vPnC contains the serotypes present in Prevnar 13 plus 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) individually conjugated to CRM_{197}. 20vPnC uses the same platform and contains the same excipients as 7vPnC and 13vPnC. These 7 additional serotypes were selected based on their relative prevalence as a cause of IPD, their generalized geographic distribution, and other factors that would support inclusion, such as the presence of antibiotic resistance and greater disease severity (eg, meningitis, mortality).[48,49,50,51,52,53,54,55,56,57,58,59] These 7 serotypes have a long-standing association with serious pneumococcal disease. The incidence of IPD due to these 7 serotypes in children <5 years of age has remained relatively stable or slightly increased over the past several years, and these serotypes cause a significant amount of IPD in children.[60,61,62,63,64,65,66] A meta-analysis of serotypes causing IPD in

children <5 years of age in regions of the world that have introduced higher-valent pneumococcal conjugate vaccines (such as 13vPnC) showed that, overall, these 7 serotypes accounted for approximately 70% of disease not due to the 13vPnC vaccine types.[62]

The 20vPnC candidate is modeled after 7vPnC and 13vPnC, and contains polysaccharides of capsular serotypes of *S pneumoniae*, each covalently linked to CRM_{197}. CCI [redacted] A Phase 1 study has been conducted in healthy adults 18 to 49 years of age, and safety and immunogenicity results from that study support further development of 20vPnC in Phase 2 evaluations. Additional epidemiology data of the 7 serotypes, the preclinical program, and the Phase 1 study results are described in the 20vPnC investigator's brochure (IB). Study details can be found in the IB.

The purpose of this study is to assess the safety and immunogenicity of 20vPnC in infants, and to generate a safety and immunogenicity data set with 20vPnC to support and inform the design of the Phase 3 clinical development program. The targeted age of the population for this study, infants ≥42 to ≤98 days of age, has been selected as this is the historical population studied for licensure of Prevnar and Prevnar 13 in infants. The subjects will be administered either 20vPnC or 13vPnC at 2, 4, 6, and 12 months of age.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the 20vPnC IB. The SRSD for the Prevnar 13 control vaccine is the US package insert (USPI).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective and Endpoints

2.1.1. Primary Objective

- To describe the safety profile of 20vPnC in healthy infants.

2.1.2. Primary Endpoints

- Proportions of subjects reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days of each dose.
- Proportions of subjects reporting prompted systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep) within 7 days of each dose.
- Proportions of subjects reporting adverse events (AEs) from Dose 1 to 1 month following Dose 3 and from Dose 4 to 1 month following Dose 4.

- Proportions of subjects reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) from Dose 1 to 6 months following Dose 4.

2.2. Secondary Objective and Endpoints

2.2.1. Secondary Objective

- To describe the immunogenicity of 20vPnC in healthy infants.

2.2.2. Secondary Endpoints

- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 3.
- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4.

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3. STUDY DESIGN

This will be a Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design, conducted at investigator sites in the United States.

Approximately 460 infants ≥42 to ≤98 days of age at the time of consent will be enrolled and randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (as the active control vaccine). At 2, 4, 6, and 12 months of age (Doses 1, 2, 3, and 4, respectively), subjects will receive 20vPnC or 13vPnC (investigational products). The investigational products will have the same appearance in this study. Blood will be drawn for immunogenicity assessments 1 month after Dose 3 (7 months of age), prior to receipt of Dose 4 (12 months of age), and 1 month after Dose 4 (13 months of age). Subjects will be observed for 30 minutes after vaccination with 20vPnC or 13vPnC and other concomitantly administered vaccines. Prompted local reactions (pain, redness, and swelling at the injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and use of antipyretic/pain medications occurring within 7 days after vaccination will be collected each day in the electronic diary (e-diary; device or application). SAEs and NDCMCs will be

collected for the entire duration of the study. AEs (including nonserious AEs, SAEs, and NDCMCs) will be collected from the signing of the informed consent document to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4. Approximately 6 months after Dose 4, the sites will contact the subject's legally acceptable representative via telephone to inquire about SAEs and NDCMCs. CCI [redacted]

CCI [redacted]

3.1. Duration of Subject Participation

Each subject will participate in the study for approximately 16 months.

3.2. Duration of Study

The study duration is estimated to be approximately 21 months.

3.3. Number of Subjects

Approximately 460 subjects will be randomized (230 subjects per arm). Assuming a 15% dropout rate, approximately 200 subjects would be evaluable for immunogenicity. Subjects who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

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 informed consent document indicating that the subject's legally acceptable representative has been informed of all pertinent aspects of the study.

2. Subjects whose legally acceptable representative is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male or female infant born at >36 weeks of gestation and aged 2 months (≥42 to ≤98 days) at the time of consent (the day of birth is considered day of life 1).

4. Healthy infant determined by medical history, physical examination, and clinical judgment to be eligible for the study.

5. Expected to be available for the duration of the study and whose legally acceptable representative can be contacted by telephone during study participation.

4.2. Exclusion Criteria

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

1. Subjects who are direct descendants (child or grandchild) of: investigational site staff members directly involved in the conduct of the study; direct descendants of site staff members otherwise supervised by the investigator; or direct descendants of Pfizer employees directly involved in the conduct of the study.

2. Previous vaccination with licensed or investigational pneumococcal vaccine.

3. Prior receipt of diphtheria, tetanus, pertussis, or polio vaccines.

4. Previous receipt of >1 dose of hepatitis B vaccine.

5. Prior receipt of hepatitis B vaccine at age ≥30 days.

6. Contraindication to immunization with diphtheria, tetanus, pertussis, or 13-valent pneumococcal conjugate vaccines, according to each vaccine's product information.

7. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of investigational product or any diphtheria toxoid–containing vaccine.

8. History of microbiologically proven invasive disease caused by *S pneumoniae*.

9. Major known congenital malformation or serious chronic disorder.

10. 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's palsy and/or hypotonic-hyporesponsive episodes.

11. Other acute or chronic medical or psychiatric condition or 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.

12. Subjects who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last postvaccination blood draw. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, subjects should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

13. Subjects with known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, human immunodeficiency virus (HIV) infection, leukemia, lymphoma, or organ or bone marrow transplant.

14. Bleeding diathesis or condition associated with prolonged bleeding time that would in the opinion of the investigator contraindicate intramuscular injection.

15. Receipt of blood/plasma products or immunoglobulins (including hepatitis B immunoglobulin) since birth or planned receipt through the last planned blood draw in the study (~13 months).

16. Participation in studies involving investigational drug(s) or interventional studies or receipt of any other investigational vaccines, drugs, or medical devices prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

4.3. Temporary Delay Criteria

The following conditions are temporary or self-limiting and a subject may be vaccinated and/or have blood drawn at the visit once the condition(s) has/have resolved and no other exclusion criteria are met. The blood draw prior to Dose 4 and administration of investigational product should take place on the same day.

4.3.1. Criteria for Temporarily Delaying Dose Administration (Doses 1, 2, 3, and 4)

- Febrile illness (eg, rectal temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before 20vPnC or 13vPnC administration.

- Receipt of any inactivated vaccine within 14 days or any live vaccine within 28 days before 20vPnC or 13vPnC administration.

- Receipt of short-term (<14 days) systemic corticosteroids. 20vPnC or 13vPnC administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days (inhaled/nebulized, intra-articular, intrabursal, or topical [skin or eyes] corticosteroids are permitted).

4.3.2. Criteria for Temporarily Delaying Blood Draw (1 Month After Dose 3, Prior to Dose 4, and 1 Month After Dose 4)

- Receipt of antibiotic therapy within 72 hours before blood draw.

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, the subject's legally acceptable representative is provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study number, 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's legally acceptable representative directly, and if the subject's legally acceptable representative 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).

For this study, the investigational products are 20vPnC and 13vPnC.

5.1. Allocation to Investigational Product

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site

personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a randomization number and container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and container number assigned. The confirmation report must be stored in the site's files.

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

5.2. Blinding of the Site Personnel

Site personnel taking part in any subject randomization, assessments, interviews, data collection, or case report form (CRF) data entry, including the investigator and investigator staff, will be blinded to 20vPnC and 13vPnC assignments during the study.

Vaccination will be administered in a double-blind fashion, as 20vPnC and 13vPnC will be supplied in identical prefilled syringes.

5.3. Blinding of the Sponsor

Certain sponsor staff outside of the core study team will monitor unblinded safety data [redacted] for unexpected safety findings as the data are collected. Sponsor personnel directly involved in evaluating subject data will be blinded [redacted] following the principles outlined in ICH E9 guideline on Statistical Principles for Clinical Trials.[67] A data blinding plan will be created to describe the blinding requirements and unblinding events. [redacted] Laboratory personnel performing the immunologic assays will be blinded until the database has been locked and unblinded.

5.4. Breaking the Blind

The study will be subject- and investigator-blinded.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind for an individual subject. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

5.5. Subject Compliance

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

5.6. Investigational Product Supplies

20vPnC and 13vPnC will be packed and labeled as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. The formulations of 20vPnC and 13vPnC are described below.

5.6.1. Dosage Form(s) and Packaging

20vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM_{197}. CCI

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM_{197}. CCI

20vPnC and 13vPnC will be supplied to the site as packaged single-use prefilled identical syringes and labeled according to local regulatory requirements.

5.6.2. Preparation and Dispensing

See the Investigational Product Manual (IP manual) for instructions on how to prepare 20vPnC and 13vPnC for administration. 20vPnC and 13vPnC 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.

All site staff are blinded.

5.7. Administration

All subjects will receive a single dose (0.5 mL) of 20vPnC or 13vPnC intramuscularly into the anterolateral thigh muscle of the left leg at the vaccination visits. All other vaccinations should be administered into a limb other than the site of 20vPnC or 13vPnC injection. The location of the injection of each vaccine administered (investigational product and other) will be recorded.

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 all vaccines at visit 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.

Details of administration of 20vPnC and 13vPnC and other vaccines (other than 20vPnC and 13vPnC) will be recorded on the CRF.

5.8. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist or dispenser/administrator, will ensure that all investigational products including any comparator and/or marketed products 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.

Investigational products will be shipped to the study site after required regulatory and legal documents have been received by the sponsor.

CCI [redacted]

Any storage conditions stated in the SRSD (20vPnC IB and 13vPnC USPI) 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. 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 nonworking 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.

Once an excursion is identified, 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.

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.

5.9. Investigational Product Accountability

The dispenser/administrator at the investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of 20vPnC or 13vPnC supplies. All investigational products will be accounted for using a drug accountability form/record.

Used needles and syringes should be disposed of according to local practice. Empty outer investigational product containers must be retained until reviewed by the sponsor's site staff and then may be destroyed after the sponsor's site staff has performed accountability. Investigational product return/destruction must be documented on the accountability log.

5.9.1. 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.

5.10. Concomitant Vaccines/Medications

Diphtheria, tetanus, and acellular pertussis (DTaP)-containing vaccine (in combination with other antigens such as polio) will be administered concomitantly with the first 3 doses of 20vPnC or 13vPnC. CCI

All vaccines administered will be recorded in the CRFs.

5.10.1. Prohibited Vaccines/Medications During the Study

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during subject participation in the study.

- Receipt of any nonstudy pneumococcal vaccine is prohibited during subject participation in the study.

- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a ≥14-day course of systemic corticosteroids) is prohibited during subject participation in the study.

5.10.2. Permitted Vaccines/Medications During the Study

- If not in the DTaP-combination vaccine, polio, hepatitis B, and *Haemophilus influenzae* type b vaccines may be given with 20vPnC or 13vPnC at 2, 4, and 6 months of age.

- Measles, mumps, and rubella (MMR) vaccine may be administered concomitantly at 12 months of age with 20vPnC or 13vPnC Dose 4, or more than 1 month after Dose 4.

- Rotavirus vaccine may be given at any time throughout the study.

- Receipt of quadrivalent meningococcal conjugate vaccine is permitted during the study only after blood is collected at the visit occurring 1 month after Dose 4.

- Other nonprohibited licensed vaccines (as described in this section) may be given between the blood draw 1 month after Dose 3 and 14 days before Dose 4 for inactivated vaccines or 28 days before Dose 4 for live vaccines, according to local or national recommendations. Following the blood draw performed 1 month after Dose 4, all licensed vaccines are permitted.

- Licensed inactivated influenza vaccine may be given to eligible study subjects during influenza season.

- Use of a topical anesthetic is permitted.

- The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

- Inhaled/nebulized, topical (skin, eyes or ears), or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted during subject participation in the study.

- Prescription and nonprescription medications, vitamins, minerals, and herbal remedies are permitted during subject participation in the study.

5.10.3. Recording Prior and Concomitant Treatments

The name and date of administration for all vaccinations should be collected from the time of signing of the informed consent document to 1 month after Dose 4 and will be recorded in the CRF. At Visit 1, information on prior vaccinations will also be recorded in the CRF.

Concomitant medications used to treat an NDCMC or SAE should be collected from the signing of informed consent through 6 months after Dose 4 (Visit 7 telephone call) and will be recorded in the CRF.

6. STUDY PROCEDURES

The study procedures are summarized in the Schedule of Activities. The day of Dose 1 is considered to be Day 1.

6.1. Visit 1 (Dose 1: 2-Month Visit, Day 1)

Prior to vaccination:

- A personally signed and dated informed consent document indicating that the subject's legally acceptable representative has been informed of all pertinent aspects of the study before performing any study-specific procedures.
- Record the subject's demographic information (including date of birth, sex, race, and ethnicity).
- Obtain and record the subject's medical history including prior vaccinations.
- Assign a subject number via the IRT.
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Clinically significant abnormal results will be recorded in the CRF.
- Measure and record the subject's rectal temperature (°F/°C).
- Ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- Assign a randomization number and investigational product container number via the IRT. This must be the last step before proceeding. A blinded site staff member will prepare the investigational product according to the IP manual.

After randomization:

- Administrator will administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.
- Administer DTaP-containing vaccine and other permitted vaccines (to be administered into a limb other than the site of 20vPnC or 13vPnC injection and the site captured on the CRF).
- Site staff will observe the subject for at least 30 minutes after vaccination for any acute reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.

- Issue the subject's legally acceptable representative a measuring device to measure injection site reactions and a digital thermometer and provide instructions on their use.

- Issue the subject's legally acceptable representative an e-diary (device or application). Provide instructions on use and completion of the e-diary. Ask the subject's legally acceptable representative to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the subject's legally acceptable representative to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the subject has a fever >104.0°F (>40.0°C), redness and/or swelling at the injection site measuring >14 measuring device units (>7 cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Ask the subject's legally acceptable representative to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.

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

6.2. Visit 2 (Dose 2: 4-Month Visit, 42 to 63 Days After Dose 1)

- Ensure and document that the subject continues to be eligible for the study (Section 6.9 for subject withdrawal information), and none of the temporary delay criteria are met.

- Record vaccines administered since Visit 1 as described in Section 5.10.

- Review the subject's e-diary data with the subject's legally acceptable representative; collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 8, and record concomitant medications used to treat NDCMCs and SAEs.

- Measure and record the subject's rectal temperature (°F/°C).

- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.

- Administer DTaP-containing and other permitted vaccines (to be administered into a limb other than the site of 20vPnC or 13vPnC injection).

After vaccination:

- Site staff will observe the subject for at least 30 minutes after vaccination for any acute reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medication used to treat NDCMCs and SAEs.

- Confirm that the e-diary is working and review instructions if necessary. Remind the subject's legally acceptable representative to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination. Provide thermometer or measuring device if needed.

- Ask the subject's legally acceptable representative to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the subject experiences fever >104.0°F (>40.0°C), redness or swelling at the injection site measuring >14 measuring device units (>7 cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Remind the subject's legally acceptable representative to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.

- Remind the subject's legally acceptable representative that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

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

6.3. Visit 3 (Dose 3: 6-Month Visit, 42 to 63 Days After Dose 2)

- Ensure and document that the subject continues to be eligible for the study (see Section 6.9 for subject withdrawal information), and none of the temporary delay criteria are met.

- Record vaccinations administered since Visit 2 as described in Section 5.10.

- Review the subject's e-diary data with the subject's legally acceptable representative; collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 8 and record concomitant medications used to treat NDCMCs and SAEs.

- Measure and record the subject's rectal temperature (°F/°C).

- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.

- Administer DTaP-containing and other permitted vaccines (to be administered into a limb other than the site of 20vPnC or 13vPnC injection).

After vaccination:

- Site staff will observe the subject for at least 30 minutes after vaccination for any acute reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.

- Confirm that the e-diary is working appropriately and review instructions if needed. Remind the subject's legally acceptable representative to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination. Provide a thermometer and/or measuring device if needed.

- Ask the subject's legally acceptable representative to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the subject experiences fever >104.0°F (>40.0°C), redness or swelling at the injection site measuring >14 measuring device units (>7 cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Remind the subject's legally acceptable representative to contact the investigator or investigator site staff immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.

- Remind the subject's legally acceptable representative that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

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

6.4. Visit 4 (Follow-up: 7-Month Visit, 28 to 42 to Days After Dose 3)

- Ensure and document that the subject continues to be eligible for the study (see Section 6.9 for subject withdrawal information), and none of the temporary delay criteria are met.

- Record vaccines administered since Visit 3 as described in Section 5.10.

- Review the subject's e-diary data with the subject's legally acceptable representative; collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Collect the e-diary (if device provided).

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 8 and record concomitant medications used to treat NDCMCs and SAEs.

- Collect a blood sample of approximately 5 mL for immunogenicity (a topical anesthetic is permitted).

- Remind the subject's legally acceptable representative that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

- Remind the subject's legally acceptable representative to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.

- The investigator or an authorized designee completes the CRF.

6.5. Visit 5 (Dose 4: 12-Month Visit, 365 to 386 Days of Age)

- Ensure and document that the subject continues to be eligible for the study (see Section 6.9 for subject withdrawal information), and none of the temporary delay criteria are met.

- Record vaccines administered since Visit 4 as described in Section 5.10.

- Determine whether any SAEs or NDCMCs have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 8, and record concomitant medications used to treat SAEs and NDCMCs.

- Measure and record the subject's rectal temperature (°F/°C).

- Collect a blood sample of approximately 5 mL for immunogenicity prior to vaccination **(**a topical anesthetic is permitted**).**

- Administer a single 0.5-mL injection of investigational product (20vPnC or 13vPnC) into the anterolateral left thigh.

- Administer permitted vaccines (to be administered into a limb other than the site of 20vPnC or 13vPnC injection).

After vaccination:

- Site staff will observe the subject for at least 30 minutes after vaccination for any acute reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.

- Issue the subject's legally acceptable representative a diary (device or application). Review and provide instructions on use and completion of the e-diary. Ask the subject's legally acceptable representative to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of investigational product vaccination. Provide with thermometer or measuring device if needed.

- Ask the subject's legally acceptable representative to contact the investigator site staff or investigator immediately during the 7-day postvaccination period if the subject experiences fever >104.0°F (>40.0°C), redness or swelling at the injection site measuring >14 measuring device units (>7 cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Remind the subject's legally acceptable representative to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.

- Remind the subject's legally acceptable representative that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

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

6.6. Visit 6 (Follow-up: 13-Month Visit, 28 to 42 to Days After Dose 4)

- Ensure and document that the subject continues to be eligible for the study (see Section 6.9 for subject withdrawal information), and none of the temporary delay criteria are met.

- Record vaccines administered since Visit 5 as described in Section 5.10.

- Review the subject's e-diary data with the subject's legally acceptable representative; collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Collect the e-diary (if device provided).

- Determine whether any AEs (includes nonserious AEs, SAEs, or NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and

record as described in Section 8, and record concomitant medications used to treat NDCMCs and SAEs.

- Collect a blood sample of approximately 5 mL for immunogenicity assessments (a topical anesthetic is permitted).

- Remind the subject's legally acceptable representative to contact the investigator or investigator site staff immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.

- The investigator or an authorized designee completes the CRF.

6.7. Visit 7 (Follow-up: 18-Month Visit, 168 to 196 Days After Dose 4)

- Contact the subject's legally acceptable representative by telephone approximately 6 months after the last study vaccination; this contact should be attempted for all subjects who have received at least 1 study vaccination, unless the subject's legally acceptable representative has withdrawn consent.

- Determine whether any SAEs or NDCMCs have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 8, and record concomitant medications used to treat NDCMCs and SAEs.

- The investigator or an authorized designee completes the CRF.

6.8. Unscheduled Visits

If the subject's legally acceptable representative reports redness or swelling at the injection site measuring >14 measuring device units (>7 cm) or severe injection site pain or a fever >104.0°F (>40.0°C) during the 7-day postvaccination period, a telephone contact must occur as soon as possible between the investigator or medically qualified designee and subject to assess if an unscheduled investigator site visit is required. Note that for a fever >104.0°F (>40.0°C), the subject's legally acceptable representative should be instructed not to delay seeking medical care, as appropriate, while arranging for an unscheduled visit. An investigator site visit should be scheduled as soon as possible to assess the extent of the reaction unless any of the following is true:

- The subject's legally acceptable representative is unable to bring the subject to the unscheduled visit.

- The reaction is no longer present at the time of the telephone contact.

- The subject's legally acceptable representative recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).

- The principal investigator (PI) or authorized designee determined it was not needed.

This telephone contact will be recorded in the subject's source documentation and the CRF.

If the subject's legally acceptable representative is unable to bring the subject to an unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing reactions must be assessed at the next study visit.

During the investigator site visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure rectal temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain in accordance with the grades provided in Section 7.1.2 (if present).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

The subject's legally acceptable representative will also be instructed to contact investigator site staff if the subject experiences any emergency room visit or hospitalization for decreased appetite, drowsiness/increased sleep, irritability, or local reaction within 7 days of vaccination.

The subject's legally acceptable representative will also be instructed to contact the investigator site to report any significant illness, medical event, or hospitalization that occurs during the study period. The investigator site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

Additionally, study staff may contact the subject's legally acceptable representative to obtain additional information on Grade 3 events entered into the e-diary.

6.9. Subject Withdrawal

An investigator and/or sponsor can withdraw a subject from the study if deemed appropriate. In addition, if a subject fails to continue to meet the inclusion criteria, new information becomes available that would exclude the subject, or the subject develops a condition or situation that would meet exclusion criteria (eg, exclusion criteria 1, 6 to 13), the subject may be considered for withdrawal.

Reasons why a subject may discontinue or be withdrawn from the study by the investigator or sponsor include, but are not limited to, failure to meet entrance criteria (screening failure),

AE, death, protocol deviation, lost to follow-up, legally acceptable representative no longer willing to participate in the study, study terminated by the sponsor, or any other reason. Subjects who have received the investigational product will not be replaced regardless of the reason for withdrawal.

The investigator should capture the reason for withdrawal in the database for all subjects and a follow-up telephone contact for the collection of safety information should be completed for all subjects who have been withdrawn after administration of investigational product unless consent for further contact has been withdrawn.

The subject's legally acceptable representative may withdraw the study subject from the study at any time at the representative's own request, or the subject may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also Withdrawal From the Study Due to Adverse Events, in Section 8) or behavioral reasons, or the inability of the subject and or the subject's legally acceptable representative to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject's legally acceptable representative. All attempts to contact the subject's legally acceptable representative 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's legally acceptable representative regarding any unresolved AEs.

If the subject's legally acceptable representative withdraws the subject from the study, and 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.

Withdrawal of consent:

Subjects whose legally acceptable representative requests the subject to discontinue receipt of investigational product will remain in the study and must continue to be followed for protocol-specified safety procedures. The only exception to this is when the subject's legally acceptable representative specifically withdraws consent for any further contact with the subject. The subject's legally acceptable representative should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page.

Lost to follow-up:

All reasonable efforts must be made to locate the subject and/or the subject's legally acceptable representative to determine and report their ongoing status. This includes

follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject's legally acceptable representative after a minimum of 2 documented phone calls, faxes, or emails as well as lack of response by the subject's legally acceptable representative to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

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.

7.1. Safety Parameters

Safety parameters will be assessed as described in the Schedule of Activities, Section 8, and below.

A medical history, physical examination, and measurement of rectal temperature will be performed on all subjects prior to Dose 1 to determine subject eligibility and to establish a clinical baseline. Significant medical history and clinically significant observations from the physical examination and temperature measurement will be documented and recorded in the CRF.

Acute reactions within the first 30 minutes after investigational product and concomitant vaccination administration will be assessed and documented as an AE with or without an SAE in the CRF and SAE form, as appropriate.

Prompted e-diary events, including local reactions (pain, redness, and swelling) and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) that occur 7 days after each investigational product administration, are graded as described in Section 7.1.2.

7.1.1. Subject Electronic Diary

The subject's legally acceptable representative will be asked to monitor and record local reactions, specific systemic events, and antipyretics/pain medication taken for 7 days, each evening following each vaccination using an e-diary (in a provisioned device or application on a personal device), which allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions, specific systemic events, and antipyretics/pain medication reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting.

The daily e-diary data will not be captured in the CRF. However, if a subject withdraws because of prompted events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

The investigator or designee must obtain stop dates for any reactions ongoing on the last day that the e-diary was completed. The stop dates should be entered in the CRF.

Investigators (or an appropriately qualified designee) are required to review the e-diary data online at frequent intervals (daily is optimal) to evaluate subject compliance and reported events as part of the ongoing safety review.

7.1.2. Grading Scale for Prompted Events

The grading scales used in this study to assess prompted events as described below are based on concepts outlined in the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for adults and adolescent volunteers enrolled in preventive vaccine clinical trials, but have been adapted for applicability to healthy infants.[68]

7.1.2.1. Local Reactions

For the first 7 days following each vaccination from Day 1 through Day 7, the subject's legally acceptable representative will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device units (range: 1 to >14; an entry in the e-diary of 15 will denote >14), and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 1 below. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the subject's legally acceptable representative as mild, moderate, or severe according to the grading scale in Table 1 below. The subject's legally acceptable representative will be prompted to contact the investigator if the subject experiences a severe (Grade 3 or above) local reaction to assess the reaction and perform an unscheduled assessment or visit as appropriate.

Only an investigator is able to classify a subject's local reaction as Grade 4, after physical examination of the subject or documentation from another medically qualified source (eg, emergency room or hospital record). If a subject experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the subject's legally acceptable representative regarding signs and symptoms that would prompt site contact.

The procedure for notification of the sponsor is provided in the study reference manual (SRM) or equivalent.

Table 1. Grading Scales for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Redness (synonymous with erythema)	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis or exfoliative dermatitis
Swelling (synonymous with edema)	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis
Pain at injection site (tenderness)	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched, with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe pain (tenderness) at injection site

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

a. Legally acceptable representatives of the subjects experiencing local reactions >14 caliper units (>7.0 cm) are to be contacted by the study site. An unscheduled visit may be required.
b. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but as an AE on the CRF. The severity of the local reaction should be graded using the AE severity grading scale in Section 8.3.

7.1.2.2. Systemic Events (Systemic Symptoms and Fever)

7.1.2.2.1. Systemic Event Symptoms

For the first 7 days following each vaccination from Day 1 through Day 7, the subject's legally acceptable representative will be asked to assess decreased appetite, drowsiness/increased sleep, and irritability and to record the symptoms in the e-diary (in a provisioned device or application on a personal device) in the evening. The symptoms will be assessed by the subject's legally acceptable representative as mild, moderate, or severe according to the grading scale in Table 2 below. The subject's legally acceptable representative will also be instructed to contact site staff if the subject experiences any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for

severe decreased appetite, severe drowsiness/increased sleep, or severe irritability) within 7 days after vaccination. Study staff may also contact the subject's legally acceptable representative to obtain additional information on Grade 3 events entered into the e-diary.

Only an investigator is able to classify a subject's systemic event as Grade 4, after physical examination of the subject or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the subject's legally acceptable representative. If a subject experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor.

The procedure for notification of the sponsor is provided in the SRM or equivalent.

Table 2. Grading Scales for Systemic Events

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

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

a. Grade 4 assessment should be made by the investigator; Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF. The severity of the systemic event should be graded using the AE severity grading scale in Section 8.3.

7.1.2.2.2. Fever

In order to record information on fever, a digital thermometer will be given to the subject's legally acceptable representative with instructions on how to measure rectal temperature at home. Temperature will be collected in the evening daily for 7 days following vaccination (Days 1 to 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as a rectal temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 100.4°F [38.0°C]) in order to collect a stop date in the CRF. A subject's legally acceptable representative will be prompted to contact the investigator if the subject experiences a fever >104.0°F (>40.0°C) to assess the fever and perform an unscheduled assessment. Study staff may also contact the subject's legally acceptable representative to

obtain additional information if a temperature of >102°F is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis; see Table 3 below.

Table 3. Ranges for Fever

100.4°F to 101.1°F (38.0°C to 38.4°C)
101.2°F to 102.0°F (38.5°C to 38.9°C)
102.1°F to 104.0°F (39.0°C to 40.0°C)
>104.0°F (>40.0°C)

7.1.2.3. Use of Antipyretic/Pain Medication

The subject's legally acceptable representative will be asked to record the use of antipyretic/pain medication (yes/no) in the e-diary (in a provisioned device or application on a personal device) in the evening daily for 7 days after each dose of investigational product.

The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

7.2. Immunogenicity

Blood samples (approximately 5 mL/visit) for immunogenicity assessments will be collected from all subjects 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4. Sample collection, processing, storage, and shipping information can be found in the SRM or equivalent manual.

CCI [redacted]

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

CCI [redacted]

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. Serum samples should be processed and stored as indicated in the SRM or equivalent document.

Immunogenicity assays will be performed at the Pfizer Vaccine Research & Development laboratory located at 401 North Middletown Road, Pearl River, NY 10965 and/or at an external laboratory designated by Pfizer.

7.3. Biological Samples

Blood 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. [redacted] No testing of the subject's genetic material will be performed.

The subject's legally acceptable representative 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.

[redacted]

CCI

[redacted]

CCI

[redacted]

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) SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious 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
Nonserious AE[a]	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)

a. Nonserious AEs will be recorded from the time the subject's legally acceptable representative provides informed consent through 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4. Newly diagnosed chronic medical conditions (can be nonserious) and SAEs will be reported from the time the subject provides informed consent through 6 months after Dose 4.

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 or 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 nonserious 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 subject's legally acceptable representative. In addition, each study subject's legally acceptable representative will be questioned about the occurrence of AEs in a nonleading 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/NDCMC Information

The time period for actively eliciting and collecting AEs, SAEs, and NDCMCs ("active collection period") for each subject begins from the time the subject's legally acceptable representative 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). AEs will be collected through 1 month after Dose 3 and from Dose 4 through 1 month after Dose 4. NDCMCs and SAEs will be collected from signing of informed consent through 6 months after Dose 4. An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

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 Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious 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 nonserious); 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.

Events that, in the clinical judgment of the investigator, are 1) consistent with normal growth and development and 2) do not differ significantly in frequency or severity from expected, are not generally to be considered AEs. Examples may include, but are not limited to, teething, contact diaper rash, spitting up, colic, or typical fussiness/crying in infants and children.

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

An SAE 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, or SEVERE 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.

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 laboratory 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, 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, or 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 preprocedure 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	All (regardless of whether associated with an AE)	Only if associated with an SAE

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;
- 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.

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 AEs, serious and nonserious, 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.**

8.4.4.2. Lack of Efficacy

Lack of efficacy in an approved indication (approved 13vPnC indication in this age group) 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. Sample Size Determination

The study size is not based on any formal statistical hypothesis test. Approximately 230 infants per vaccine group are planned to be randomized. No hypothesis tests between vaccine groups are planned; therefore, no power calculations for comparison of vaccine groups are included.

With 230 subjects per arm, the probabilities of observing at least 1 AE, local reaction, or systemic event where the true rate is 0.5%, 1%, and ≥5% are presented in Table 4.

Table 4. Probability of Observing at Least 1 AE, Local Reaction, or Systemic Event by Assumed True Event Rates

Sample Size	Assumed True Event Rate of at Least 1 AE, Local Reaction, or Systemic Event		
	0.5%	1%	≥5%
N = 230	0.684	0.901	>0.999

9.2. Analysis Populations

The safety population will include all subjects who receive 1 dose of 20vPnC or 13vPnC. Subjects will be assigned to vaccine groups corresponding to the vaccine actually received. The safety population will be the only analysis population for the primary endpoints.

The Dose 3 evaluable immunogenicity population will include any subject:

1. Who was eligible for the study.
2. Who was randomly assigned to receive the vaccine.
3. Who was 42 to 98 days of age, inclusive, on the day of first vaccination.
4. Who received the vaccine to which he or she was randomly assigned at all 3 doses.
5. Who had an IgG concentration for at least 1 serotype after Dose 3.
6. Whose blood collection was within 28 to 42 days, inclusive, after Dose 3.
7. Who received no prohibited vaccines before the blood draw after Dose 3.
8. Who had no other major protocol deviations as determined by the clinician or medical monitor.

Additional criteria are described in the SAP. The Dose 3 evaluable immunogenicity population will be the primary analysis population for immunogenicity results from the blood collected 1 month after Dose 3.

CCI [redacted]

CCI [redacted]

The Dose 4 evaluable immunogenicity population will include any subject:

1. Who was eligible for the study.
2. Who was randomly assigned to receive the vaccine.
3. Who was 42 to 98 days of age, inclusive, on the day of first vaccination.
4. Who received the assigned vaccine, as randomized, within the defined window for Dose 4 (365-386 days of age; see Schedule of Activities).
5. Who received the vaccine to which he or she was randomly assigned at all 4 doses.
6. Who had an IgG concentration for at least 1 serotype after Dose 4.
7. Whose blood collection was within 28 to 42 days, inclusive, after Dose 4.
8. Who received no prohibited vaccines before the blood draw after Dose 4.
9. Who had no other major protocol deviations as determined by the clinician or medical monitor.

Additional criteria are described in the SAP. The Dose 4 evaluable immunogenicity population will be the primary analysis population for immunogenicity results after Dose 4.

CCI [redacted]

9.3. Immunogenicity Analysis

All serotypes will be analyzed in the same way. All endpoints will be summarized by vaccine group.

9.3.1. Immunogenicity Analysis CCI [redacted]

The endpoints will be summarized by geometric mean concentrations (GMCs) CCI [redacted]. Ninety-five percent confidence intervals (CIs) will also be calculated. GMCs and their CIs will be obtained by taking log transforms of concentrations, calculating the 95% CI with reference to the t-distribution, then exponentiating the mean and the limits. Proportions of subjects with IgG concentrations ≥ reference concentration CCI [redacted] will be compiled. The Luminex assay IgG concentration of 0.35 µg/mL will be used as the predefined IgG

reference concentration for all serotypes, with the exception of serotypes 5 (0.23 µg/mL), 6B (0.1 µg/mL), and 19A (0.12 µg/mL). The 95% CIs will be obtained using the Clopper-Pearson method.[71]

CCI

[redacted]

9.4. Safety Analysis

All safety analyses will be performed using the safety population.

Descriptive statistics for local reactions and systemic events from Day 1 to Day 7 will be presented by severity and cumulatively across severity levels. Descriptive statistics will include proportions of subjects with the indicated endpoint and the associated Clopper-Pearson 95% CIs. Vaccine groups will be compiled separately.

Descriptive statistics for local reactions and systemic events will be compiled separately for each dose. The same descriptive statistics will be compiled across all 4 doses.

AEs (including nonserious AEs, SAEs, and NDCMCs) will be compiled over 2 intervals: from Dose 1 to 1 month following Dose 3 and from Dose 4 to 1 month following Dose 4. SAEs and NDCMCs will be summarized from Dose 1 until 6 months after Dose 4. The descriptive statistics for AEs will be summarized as the number and percentage of subjects reporting at least 1 event of each preferred term with the associated Clopper-Pearson 95% CIs, arranged by system organ class.

CCI

CCI

[redacted]

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 investigational 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 [CIOMS] 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's, legally acceptable representative, if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's 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 the Participating Country

End of trial in all participating countries is defined as last subject last visit (LSLV). After this time, sites will be closed out, the IRB/EC will be informed, and no further CIOMS reports will be sent.

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 20vPnC 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) within 30 days. 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 have 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 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

The 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
20vPnC	20-valent pneumococcal conjugate vaccine
AE	adverse event
ALT	alanine aminotransferase
AOM	acute otitis media
AST	aspartate aminotransferase
CAP	community-acquired pneumonia
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
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 pertussis
EC	ethics committee
e-diary	electronic diary
CCI	[redacted]
ELISA	enzyme-linked immunosorbent assay
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio

Abbreviation	Term
IP	investigational product
IPD	invasive pneumococcal disease
IRB	institutional review board
CCI	[redacted]
IRT	interactive response technology
IU	international units
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LSLV	last subject last visit
MMR	measles, mumps, and rubella
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
CCI	[redacted]
PCD	primary completion date
PI	principal investigator
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	prothrombin time
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SRM	study reference manual
SRSD	single reference safety document
TBili	total bilirubin
ULN	upper limit of normal
US	United States
USPI	US package insert
VT	vaccine-type
WHO	World Health Organization

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