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

Study Intervention Number:	PF-06482077
Study Intervention Name:	20-valent Pneumococcal Conjugate Vaccine (20vPnC)
US IND Number:	N/A
EudraCT Number:	N/A
Protocol Number:	B7471016
Phase:	3

Short Title: 20-valent Pneumococcal Conjugate Vaccine Safety and Immunogenicity Study in Healthy Japanese Infants

CCI

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	09-June-2020	N/A

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: 20-valent Pneumococcal Conjugate Vaccine Safety and Immunogenicity Study in Healthy Japanese Infants.

Rationale

Pfizer is developing a new 20-valent pneumococcal conjugate vaccine (20vPnC) candidate to expand protection against pneumococcal disease beyond what is covered by current pneumococcal vaccines in children. 20vPnC has the same composition as 13-valent pneumococcal conjugate vaccine (13vPnC; Prevenar 13®), and contains an additional 7 polysaccharide conjugates targeting serotypes responsible for a substantial burden of remaining pneumococcal disease. 20vPnC uses the same platform and contains the same excipients as 13vPnC. A Phase 1 study (B7471005) in Japanese healthy adults conducted in the United States has shown that 20vPnC was safe and immunogenic when the vaccine was given intramuscularly in Japanese people. Phase 2 (B7471003) safety and immunogenicity data from 20vPnC (given by the intramuscular route) in infants from the United States support further development of 20vPnC in the pediatric population.

Objectives, Estimands, and Endpoints

Primary Safety Objective	Estimands	Primary Safety Endpoints
• To describe the safety profile of 20vPnC by both SC injection and IM injection	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination: • The percentage of participants reporting prompted local reactions at injection site of investigational product within 7 days after each vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after each vaccination in each group • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 3 in each group • The percentage of participants reporting AEs from Dose 4 to 1 month after Dose 4 in each group • The percentage of participants reporting SAEs	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs

	up to 1 month after Dose 4 in each group • The percentage of participants reporting an NDCMC up to 1 month after Dose 4 in each group	
Primary Immunogenicity Objectives	**Estimands**	**Primary Immunogenicity Endpoints**
<u>For 20vPnC SC group:</u>		
• To demonstrate that the percentage of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC SC group are noninferior to the percentage of the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC SC group and the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate that the percentage of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest percentage among the 13 serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations, between the 20vPnC SC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
<u>For 20vPnC IM group:</u>		
• To describe the immune response to 20 serotypes induced by 20vPnC given by IM injection at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC IM group and the 20vPnC SC group	• Pneumococcal serotype-specific IgG concentration

Secondary Immunogenicity Objectives	Estimands	Secondary Immunogenicity Endpoints
• To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC SC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of the serotype-specific IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest IgG GMC among the 13 serotypes induced by the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: GMR of the serotype-specific IgG concentration from the 20vPnC group to the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
• To further describe the immunogenicity of 20vPnC by both SC and IM injection	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC IM group to the 20vPnC SC group In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: Serotype-specific IgG GMCs at 1 month after Dose 4 in each group In evaluable participants at 1 month after Dose 3 and 1 month after Dose 4: • Serotype-specific OPA GMTs at 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4 in each group In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: percentage of participants with the predefined serotype-specific IgG concentration in each group	• Pneumococcal serotype-specific IgG concentrations • Pneumococcal serotype-specific IgG concentrations • Pneumococcal serotype-specific OPA titers • Pneumococcal serotype-specific IgG concentrations

	In evaluable participants: • GMFRs in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations

Overall Design

This Phase 3, multicenter, randomized, double-blinded, third party unblind study will be conducted at investigator sites in Japan. CCI [redacted] The purpose of this study is to describe safety and conduct the pivotal immunogenicity comparison of 20vPnC administered by SC injection to the licensed pneumococcal conjugate vaccine, 13vPnC, administered by the currently indicated SC injection in infants CCI [redacted] Data will also be generated from 20vPnC administered by IM injection, with the 20vPnC administered by SC as a control.

Approximately 666 infants between 2 through 6 months of age at the time of consent, by their parent(s)/legal guardian(s), will be enrolled into the study. Participants will be randomized equally to 1 of the following vaccine groups: (1) 20vPnC SC group, (2) 13vPnC SC group (control vaccine), or (3) 20vPnC IM group. Participants will receive the same vaccine (20vPnC or 13vPnC) by the same injection method (SC or IM injection) for all 4 doses at Visits 1, 2, 3, and 5 (refer to the SoA table for the timing of the visits). All vaccine groups will be blinded to all members of the site involved in the study except unblinded staff who will administer 20vPnC or 13vPnC.

Specific vaccines containing *Haemophilus influenza* type b (Hib), hepatitis B (Hep B), rotavirus, diphtheria, tetanus, acellular pertussis, and poliovirus antigens will also be administered concomitantly with Doses 1 to 3 (Visit 1, Visit 2, and Visit 3) in the upper arm or orally (in the case of rotavirus vaccine) consistent with the vaccination schedule recommended by the Japan Pediatric Society.[1] Specific vaccines containing Hib, diphtheria, tetanus, acellular pertussis, poliovirus, measles, rubella, and varicella antigens will be administered concomitantly with Dose 4 (Visit 5) in the upper arm(s) consistent with the vaccination schedule recommended by the Japan Pediatric Society.

Local reactions (redness, swelling, and pain at the injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), and use of antipyretic/pain medication will be prompted for and collected by the participant's parent(s)/legal guardian(s) in an e-diary, device or application, from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination).

AEs will be collected from the time the participant's parent(s)/legal guardian(s) provides informed consent through 1 month after Dose 3 (Visit 4) and from Dose 4 (Visit 5) through 1 month after Dose 4 (Visit 6). SAEs and NDCMCs will be collected from informed consent through 1 month after Dose 4 (Visit 6).

Blood will be collected 1 month after Dose 3 (Visit 4), immediately prior to Dose 4 (Visit 5), and 1 month after Dose 4 (Visit 6) to assess immunogenicity.

Number of Participants

Approximately 666 participants will be enrolled to achieve a target of 600 evaluable participants (200 in each vaccine group) at the follow-up time point 1 month after Dose 3.

Note: "Enrolled" means a participant's, parent(s)/legal guardian(s) agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomized in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Each participant will participate in the study approximately 7 to 14 months depending on the age of commencing in the study.

Participants will receive 1 dose of 20vPnC or 13vPnC at each vaccination visit (Visits 1, 2, 3, and 5 with Doses 1, 2, 3, and 4, respectively) in accordance with the study's SoA.

In the 20vPnC SC and 13vPnC SC groups, 20vPnC or 13vPnC should be administered subcutaneously by injecting 0.5 mL into the anterolateral thigh (preferably into the left anterolateral thigh) at the vaccination visits. In the 20vPnC IM group, 20vPnC should be administered intramuscularly by injecting 0.5 mL into the anterolateral thigh muscle of the leg (preferably of the left leg) at the vaccination visits.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Statistical Methods

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs, including SAEs and NDCMCs, for each vaccine group. A 3-tier approach will be used to summarize AEs.

The primary pneumococcal immunogenicity objectives for the 20vPnC SC group will be evaluated by formal hypothesis test for noninferiority of 20vPnC to 13vPnC based on serotype-specific IgG results. At 1 month after Dose 3, noninferiority for a serotype will be declared if the lower bound of the 2-sided 95% CI for the between-group difference in percentage of participants with a predefined serotype-specific IgG concentration level (20vPnC SC – 13vPnC SC) is greater than –10% (10% noninferiority margin). The primary pneumococcal immunogenicity objectives for the 20vPnC SC group of the study for pneumococcal immunogenicity assessment at 1 month after Dose 3 will be achieved, in principle, if noninferiority of the pneumococcal immune response to 20vPnC SC compared to 13vPnC SC is met for all 20 serotypes; each of the 13 matched serotypes in the 20vPnC SC group relative to each serotype in the 13vPnC SC group, and each of the 7 additional serotypes in 20vPnC group relative to the lowest value in the 13vPnC SC group.

The primary pneumococcal immunogenicity objective for 20vPnC IM group will be evaluated by descriptive assessments for difference in the percentage of participants with a predefined serotype-specific IgG concentration level (20vPnC IM – 20vPnC SC) at 1 month after Dose 3.

CCI [redacted]

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section 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 in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Number	1	2	3	4	5	6
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Dose 3 Visit**	**Dose 3 Follow-up Visit**	**Dose 4 Visit**	**Dose 4 Follow-up Visit**
Visit Windows (Days)	**Day 1 (2 through 6 Months of Age)**	**4 to 8 Weeks After Visit 1**	**4 to 8 Weeks After Visit 2 (Completed by 12 Month of Age)**	**28 to 42 Days After Visit 3**	**12 to 15 Months of Age (≥60 Days After Dose 3)**	**28 to 42 Days After Visit 5**
Obtain informed consent	X					
Assign participant number via the IRT	X					
Record demography	X					
Perform clinical assessment, including medical history	X					
Record vaccine history	X					
Record nonstudy vaccinations	X	X	X	X	X	X
Record concomitant medications[a]	X	X	X	X	X	X
Obtain prevaccination axillary temperature	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 randomization number	X					
Obtain ~5-mL blood sample				X	X[b]	X
Administer investigational product (20vPnC or 13vPnC)[c]	X	X	X		X	
Administer specific concomitant vaccines as applicable for the visit[d]	X	X	X		X	

Visit Number	1	2	3	4	5	6
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Dose 3 Visit**	**Dose 3 Follow-up Visit**	**Dose 4 Visit**	**Dose 4 Follow-up Visit**
Visit Windows (Days)	**Day 1 (2 through 6 Months of Age)**	**4 to 8 Weeks After Visit 1**	**4 to 8 Weeks After Visit 2 (Completed by 12 Month of Age)**	**28 to 42 Days After Visit 3**	**12 to 15 Months of Age (≥60 Days After Dose 3)**	**28 to 42 Days After Visit 5**
Observe and record acute reactions for 30 minutes after investigational product administration	X	X	X		X	
Provide a participant contact card	X					
Provide parent(s)/legal guardian(s) with an e-diary, thermometer, and measuring device and instruct to collect prompted local reactions and systemic events until 7 days after vaccination[e]	X	X	X		X	
Review and/or collect e-diary (if applicable)[f]		X	X	X		X
Record and report adverse events	X---------- X				X ---------- X	
Record and report SAEs and NDCMCs[g]	X ----------X					

Abbreviations: IRT = interactive response technology; NDCMC = newly diagnosed chronic medical condition.

a. Record only concomitant medications used to treat SAEs and NDCMCs.
b. Blood sample will be collected prior to vaccination.
c. Remind the participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
d. Specific concomitant vaccines containing Hib, Hep B, rotavirus, diphtheria, tetanus, acellular pertussis, poliovirus, measles, rubella, and varicella antigens will be administered with Doses 1 through 4 into the upper arm(s) or orally (in the case of rotavirus vaccine).
e. The participant's parent(s)/legal guardian(s) will record prompted local reactions and systemic events in an e-diary for the 7 days following each dose of 20vPnC or 13vPnC. Use of antipyretic/pain medications will also be prompted for and collected daily in an e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling >14 caliper units, severe pain at the 20vPnC or 13vPnC injection site, or a fever >40.0°C, or has an emergency room visit or hospitalization.
f. 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 participant compliance and as part of the ongoing safety review.
g. An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

2. INTRODUCTION

Pneumococcal Disease

Streptococcus pneumoniae are gram-positive encapsulated cocci that are a leading cause of bacteremia, bacterial meningitis, pneumonia, and AOM and continue to be a major global public health concern.[2,3,4] Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk.[5] 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.[3] It has been estimated 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.[6]

The overall 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.[7] This is due to the decrease in disease due to the serotypes in 7-valent pneumococcal conjugate vaccine (7vPnC; Prevnar®) and 13vPnC. However, disease due to serotypes not covered by those vaccines remains, and causes significant morbidity and mortality. National IPD surveillance data in England and Wales for the epidemiological year 2016-2017, approximately 10 years after the introduction of 7vPnC in the national infant immunization program and 6 years after the introduction of 13vPnC, showed the overall incidence of IPD was 9.87 per 100,000 population, with an incidence of 13.90 per 100,000 population <2 years of age.[8] The data for England and Wales are consistent with the patterns observed in data from the EU for 2017, which showed an overall IPD incidence of 6.2 cases per 100,000 population, with an incidence of 14.5 per 100,000 infants under 1 year of age.[9] 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.[10,11] More recent pediatric surveillance conducted between 2014 and 2017 in 8 US children's hospitals following 13vPnC introduction in 2010 showed that 76.1% of residual IPD was caused by non-13vPnC serotype isolates.[12] Serotypes 10A, 12F, 15B/15C, 22F, and 33F accounted for 36% of isolates causing IPD. The most common clinical presentations of IPD due to non-13vPnC serotypes included bacteremia (49.6%), meningitis (19.1%), and pneumonia (18.8%). These data demonstrate the continued need for expanded serotype coverage.

Surveillance studies conducted in 2010-2012 by the CDC found that *S pneumoniae* remains among the most common pathogens identified in CAP requiring hospitalization in the United States in both children and adults.[13,14] It was the most common bacterial cause in children <2 years of age, even in the setting of a 43% reduction in CAP hospitalizations over the previous decade between 1997-1999 and 2007-2009, due to the introduction to 7vPnC.[13,15] Surveillance reported in 2017 by the ECDC showed that among cases of IPD for which the clinical presentation was known across all age groups, bacteremic pneumonia was reported in 42% of cases. The most common clinical presentations in children <5 years of age were septicemia and bacteremic pneumonia (1-4 year olds), and meningitis (<1 year olds).[9] 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 2011 visit rates of 0.82 and 0.81 visits per AOM/child-year in children <2 years of age and 2 to 6 years of age, respectively, and represents a significant medical burden.[16] *S pneumoniae* is one of the common bacterial causes of AOM, and accounted for an estimated 850,000 outpatient and 125,000 emergency room visits in the United States in 2004 in children <5 years of age, representing a significant burden on the healthcare system.[4] 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.

In Japan, 7-valent pneumococcal conjugate vaccine (7vPnC; Prevenar®) was licensed in February 2010 to prevent IPD in children and was incorporated into the NIP in April 2013. Subsequently 7vPnC was replaced by 13vPnC, in the NIP in November 2013. Since 2008 active surveillance for IPD in children <15 years of age has been conducted in 10 prefectures.[17] The incidence rate of IPD caused by serotypes covered by 7vPnC in children <5 years of age decreased by 98% compared to before 7vPnC launch (2008 to 2010). After introduction of 13vPnC in the NIP in November 2013, the incidence rate of IPD caused by 13vPnC serotypes decreased by 97% compared to before the launch of 7vPnC. The overall IPD incidence rate was reduced by 50% compared to before the 7vPnC launch although the incidence of disease due to serotypes not in 13vPnC (NVT) increased. In 2017 96% of isolates causing IPD were NVT. In the surveillance by Ubukata et al,[18] serotype distribution of clinical isolates from IPD patients collected from April 2010 to March 2017 was investigated. Considering the isolates from children, serotypes contained in 7vPnC accounted for 73.3% of the isolates in 2010 (during the pre-7vPnC period) which decreased to 7.4% in 2013 after 7vPnC introduction. IPD caused by the 6 additional serotypes contained in 13vPnC decreased from 25.9% in 2013 to 11.1% in 2016. The proportion of IPD in 2016 due to all serotypes contained in 20vPnC was estimated at 50.7% (17.2% for the 13 serotypes in 13vPnC, and 33.5% for 7 additional serotypes [estimated by Pfizer based on the serotype distribution]).

Although the introduction of pneumococcal conjugate vaccines into the NIP in Japan and other national infant immunization programs has brought about substantial reductions in the various manifestations of pneumococcal disease in pediatric (infants and children) populations, a substantial burden of pneumococcal disease remains. Serotypes not included in existing vaccines continue to contribute significantly to morbidity and mortality.

CCI [redacted]

Vaccines to Prevent Pneumococcal Disease

Pneumococcal Polysaccharide Vaccines

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.[19,20] Anticapsular antibodies directed against the specific serotype bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.[21] Pneumococcal disease can be prevented with polysaccharide-based vaccines that induce antibody responses with functional OPA activity and target the capsular serotypes responsible for disease.[22]

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.[23,24] 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, and children <2 years of age), nor do they generate immunologic memory, so that their protective effect wanes over 2 to 5 years.[5,24,25,26] Moreover, their ability to prevent nonbacteremic pneumonia, CAP, and AOM is limited or lacking.[22,26,27,28,29] In addition, polysaccharide vaccines do not reduce VT nasopharyngeal carriage, which is important for herd immunity.[29] 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.[22]

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.[25,30] 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. 7vPnC contained capsular

polysaccharide conjugates for 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), each covalently linked to 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).[31,32,33,34,35] These serotypes also accounted for a high proportion of antibiotic-resistant strains.[36] 7vPnC demonstrated efficacy against VT IPD, pneumonia, and AOM in large randomized, controlled efficacy studies in infants.[37,38] The 7vPnC components contained in a related pneumococcal conjugate vaccine also were demonstrated to be efficacious against clinically/radiographically defined pneumonia.[39,40,41,42] Following introduction of 7vPnC, 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.[43]

13vPnC was developed to expand serotype coverage and was licensed in the United States in 2010. 13vPnC includes the same *S pneumoniae* serotypes as 7vPnC and an additional 6 polysaccharide conjugates for serotypes 1, 3, 5, 6A, 7F, and 19A.[30,34,44] The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific serum IgG antibody concentrations to 7vPnC, with supportive data to demonstrate the functional activity of the immune responses. 13vPnC has also been licensed in adults based on demonstration of efficacy against CAP due to serotypes contained in 13vPnC in adults 65 years of age and older.[45] 13vPnC has replaced 7vPnC and is licensed in the United States and many other countries including Japan, with national recommendations for use in children and older adults.[46,47,48,49,50] It has also been prequalified by the WHO for use in national infant immunization programs in lower- and middle-income countries.[51,52] Surveillance data from several countries following introduction of 13vPnC into the routine infant immunization program have demonstrated vaccine effectiveness against 13vPnC VT IPD in the vaccinated population.[53,54,55]

Development of 20vPnC

The 20vPnC candidate is modeled after 7vPnC and 13vPnC, and contains polysaccharides of capsular serotypes of *S pneumoniae*, each covalently linked to CRM_{197}. The amount of polysaccharide (2.2 µg/dose) selected for each new serotype (8, 10A, 11A, 12F, 15B, 22F, and 33F) contained in the 20vPnC candidate mirrors the approach taken for the addition of the 6 new serotypes when developing 13vPnC. The 20vPnC candidate contains the same components as 13vPnC, including the 13 polysaccharide conjugates, excipients (polysorbate 80, succinate buffer, sodium chloride), and aluminum phosphate, in addition to the 7 new polysaccharide conjugates. Additional epidemiology data of the 7 serotypes and the preclinical program are described in the 20vPnC IB. The vaccine is being developed for use in pediatric and adult populations.

2.1. Study Rationale

CCI [redacted] In Japan, 7vPnC and 13vPnC have been administered to infants by SC injection on a 4-dose vaccination schedule (3 doses for infant series and 1 dose

for toddler dose). CCI [redacted]

CCI [redacted] The targeted age of the population for this study, infants ≥2 to ≤6 months of age, has been selected as the routinely recommended vaccination schedule for pneumococcal conjugate vaccines and other vaccines in infants starts at approximately 2 months of age. The participants will be administered either 20vPnC (SC or IM injection) or 13vPnC SC by the same injection route for all 4 doses starting from 2 months of age.

2.2. Background

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 13vPnC, and 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) individually conjugated to CRM_{197}. As noted above, 20vPnC uses the same platform and contains the same excipients as 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 (11A,15B), association with outbreaks (8, 12F), and greater disease severity (eg, meningitis, mortality) (10A, 11A, 22F).[56,57,58,59,60,61,62,63,64,65,66,67] These 7 serotypes have a long-standing association with serious pneumococcal disease and are responsible for a substantial burden of remaining 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.[68,69,70,71,72,73,74] These 7 serotypes contribute to the burden of IPD in the United States and elsewhere. It is estimated that between 2015 and 2016, these 7 serotypes accounted for 34% to 39% of IPD in children in the United States.[75] In the EU, according to the ECDC annual IPD epidemiological report, in 2017, approximately 75% of cases of IPD in children <5 years of age were caused by a serotype not in 13vPnC, increased from 63% in 2013. Five of the 10 most common serotypes included serotypes 8, 10A, 11A, 12F, and 22F, with serotypes 8, 10A, 12F, and 24F being among the most common in children in this age group.[9]

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

2.2.1. Clinical Overview

Safety and immunogenicity data from a 20vPnC Phase 1 study (B7471001) conducted in healthy adults 18 through 49 years of age demonstrated that the vaccine induced immune responses to the 20 vaccine serotypes and had a safety profile consistent with other

pneumococcal conjugate vaccines. These data supported clinical development in other populations, including pediatric populations.

A Phase 1 study (B7471005) of 20vPnC in healthy Japanese adults 18 through 49 years of age was conducted in the United States. The administration of 20vPnC by IM injection was well tolerated and induced immune responses to the 20 vaccine serotypes. These data support continued development of 20vPnC in Japan.

A Phase 2 study (B7471003) of 20vPnC in healthy infants ≥42 to ≤98 days of age has been conducted. The study randomized 460 US participants to receive either blinded 20vPnC or 13vPnC by IM injection. Safety and immunogenicity data are available from this study. 20vPnC was well tolerated in the infants and the safety profile was similar to that of the 13vPnC group in the study and consistent with other pneumococcal conjugate vaccines. Immune responses (either IgG GMCs or percentages of participants meeting a predefined IgG concentration) after 3 doses of 20vPnC were similar to those in the 13vPnC group. These data support continued development of 20vPnC in a pediatric population.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of 20vPnC may be found in the IB, which is the SRSD for this study. The SRSD for the 13vPnC agent is the Japan package insert.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
20vPnC and 13vPnC		
13vPnC is a licensed vaccine and the most common AEs noted in children <5 years of age after vaccination are primarily related to local reactions (injection site pain or tenderness, redness, and swelling) and systemic events (fever, irritability, decreased appetite, and increased sleep). As with any vaccine, an allergic reaction can occur. The allergic reaction can vary from skin rash to swelling of the face or lips, wheezing, and/or shortness of breath. A severe allergic reaction (anaphylactic shock, collapse, or shock-like state [hypotonic-hyporesponsive episode]) may also occur. There may also be additional risks related to the vaccines administered in the study that are not known at this time.	The 20vPnC investigational product contains the same components and excipients as 13vPnC, and also contains the polysaccharide conjugates for the 7 additional pneumococcal serotypes. Thus, the AE profile of 20vPnC is expected to be similar to 13vPnC, but AEs may be different with the investigational 20vPnC. In a randomized, active-controlled, double-blind study with a 2-arm parallel design (B7471003), 20vPnC was administered intramuscularly to 460 infants ≥42 to ≤98 days of age naive to pneumococcal vaccine. The vaccine was well tolerated and the AE profile was consistent with events commonly seen in this age group. The most common AEs after 20vPnC administration were local reactions (pain, redness, and swelling at the injection site) and systemic events (irritability, drowsiness/increased sleep, and decreased appetite).	Safety assessments (ie, local reactions, systemic events, AEs [including observation for 30 minutes after vaccination], SAEs, and NDCMCs) described in the protocol and ongoing review of safety data by the investigator and sponsor study team will serve to monitor and mitigate these risks. CCI [redacted]
This study is the first study that 20vPnC will be administered subcutaneously and the study participants are infants.	The 20vPnC investigational product contains the same components and excipients as 13vPnC, and also contains the polysaccharide conjugates for the 7 additional pneumococcal serotypes. Thus, the AE profile of 20vPnC is expected to be similar to 13vPnC, but AEs may be different with the investigational 20vPnC. In a clinical study of 13vPnC administered by SC injection in Japan, local reactions at the 13vPnC injection site (SC injection), particularly redness	Daily enrollment will be limited initially with enhanced monitoring of the safety and tolerability of the study vaccine after Dose 1. If there are no unexpected safety concerns after Dose 1 in the first 45 participants, the daily enrollment limit will be removed. Ongoing regular monitoring and review of safety and tolerability of the blinded study data by the study team.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
20vPnC and 13vPnC		
	and swelling, occurred at somewhat higher rates compared with studies that administered 13vPnC by IM injection. However local reactions in the study were generally mild or moderate, consistent with other published studies of 13vPnC.[76] In another clinical study of 13vPnC administered by SC injection in Japan, local reactions, particularly redness and swelling, occurred at higher rates at the 13vPnC injection site were comparable with those of 7vPnC administered by SC injection.[77]	
Study Procedures		
Risks that may be associated with study procedures include risks from blood sample collection, including pain, swelling, bruising, and infection where blood is taken.	Risks and possible discomforts from the study procedures such as pain, swelling, bruising, infection around the vein where the child's blood is collected may also occur, although this is very uncommon.	The volume and frequency of blood sample collection required during the study has been minimized as far as possible.

2.3.2. Benefit Assessment

13vPnC is approved in Japan (and in many other countries worldwide) for the prevention of IPD due to the serotypes in the vaccine, and should provide a clinical benefit to those receiving the vaccine. In the B7471003 study, 20vPnC induced immune responses to the pneumococcal serotypes in the vaccine. This suggests that protection against pneumococcal disease will be similar to 13vPnC. If 20vPnC is successful in Phase 3 studies, and approved, it is anticipated to provide a public health benefit by reducing the burden of IPD due to pneumococcal serotypes contained in the vaccine.

2.3.3. Overall Benefit/Risk Conclusion

Pfizer considers that the available information from Study B7471003 with 20vPnC, the available safety profile of similar pneumococcal conjugate vaccines (ie, Prevenar and Prevenar 13), and the limited risks from study procedures support a favorable benefit-risk profile for 20vPnC and this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Primary Safety Objective	Estimands	Primary Safety Endpoints
• To describe the safety profile of 20vPnC by both SC injection and IM injection	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination: • The percentage of participants reporting prompted local reactions at injection site of investigational product within 7 days after each vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after each vaccination in each group • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 3 in each group • The percentage of participants reporting AEs from Dose 4 to 1 month after Dose 4 in each group • The percentage of participants reporting SAEs up to 1 month after Dose 4 in each group • The percentage of participants reporting NDCMCs up to 1 month after Dose 4 in each group	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs

Primary Immunogenicity Objectives	Estimands	Primary Immunogenicity Endpoints
For 20vPnC SC group:		
• To demonstrate the percentage of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC SC group are noninferior to the percentage of the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC SC group and the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate the percentage of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest percentage among the 13 serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations, between the 20vPnC SC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentration
For 20vPnC IM group:		
• To describe the immune responses to 20 serotypes induced by 20vPnC given by IM injection at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: difference in the percentage of participants with predefined serotype-specific IgG concentrations between the 20vPnC IM group and the 20vPnC SC group	• Pneumococcal serotype-specific IgG concentration

Secondary Immunogenicity Objectives	Estimands	Secondary Immunogenicity Endpoints
• To demonstrate the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC SC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC SC group to the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
• To demonstrate the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC SC group are noninferior to the lowest IgG GMC among the 13 serotypes induced by the 13vPnC SC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC SC group to the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
• To further describe the immunogenicity of 20vPnC by both SC and IM injection	In evaluable participants at 1 month after Dose 3: • For each of the serotypes in 20vPnC: GMR of serotype-specific IgG concentrations from the 20vPnC IM group to the 20vPnC SC group	• Pneumococcal serotype-specific IgG concentrations
	In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: Serotype-specific IgG GMCs at 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations
	In evaluable participants at 1 month after Dose 3 and 1 month after Dose 4: • Serotype-specific OPA GMTs at 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4 in each group	• Pneumococcal serotype-specific OPA titers
	In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: percentage of participants with the predefined serotype-specific IgG concentration in each group	• Pneumococcal serotype-specific IgG concentrations

	In evaluable participants: • GMFRs in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 in each group	• Pneumococcal serotype-specific IgG concentrations
CCI		

4. STUDY DESIGN

4.1. Overall Design

This Phase 3, multicenter, randomized, double-blind, third party unblind study will be conducted at investigator sites in Japan. CCI [redacted] The purpose of this study is to describe safety and conduct the pivotal immunogenicity comparison of 20vPnC administered by SC injection to the licensed pneumococcal conjugate vaccine, 13vPnC, administered by the currently indicated SC injection CCI [redacted] Data will also be generated on 20vPnC administered by IM injection, with the 20vPnC administered by SC as a control.

Approximately 666 infants between 2 through 6 months of age at the time of consent, by their parent(s)/legal guardian(s), will be enrolled into the study. Participants will be randomized equally to one of the following vaccine groups: (1) 20vPnC SC group, (2) 13vPnC SC group (control vaccine), or (3) 20vPnC IM group. Participants will receive the same vaccine (20vPnC or 13vPnC) by the same injection method (SC or IM injection) for all 4 doses at Visits 1, 2, 3, and 5 (refer to the SoA table for the timing of the visits). All vaccine groups will be blinded to all members of the site involved in the study except unblinded site staff who will administer 20vPnC or 13vPnC.

On Day 1 (Visit 1, Dose 1 vaccination) of the study, participants will be assessed for eligibility and information collected, including medical history and vaccine history.

At Visit 1, participants will be randomized. In the 20vPnC SC and 13vPnC SC groups, 20vPnC or 13vPnC will be administered subcutaneously into the anterolateral thigh (preferably into the left anterolateral thigh). In the 20vPnC IM group, 20vPnC will be administered intramuscularly into the anterolateral thigh muscle of the leg (preferably into the left anterolateral thigh). The inner syringe label will be open labeled. Except for the inner syringe label, 20vPnC and 13vPnC will be identical in appearance including outer carton and will be administered by a qualified and unblinded site staff member. Specific vaccines containing Hib, Hep B, and rotavirus antigens will also be administered concomitantly with Dose 1 in the upper arm(s) or orally (in the case of rotavirus vaccine) consistent with the vaccination schedule recommended by the Japan Pediatric Society".[1] Participants will be observed for 30 minutes after vaccination and any reactions occurring during that time will be recorded as AEs. The parent(s)/legal guardian(s) will be provided with an e-diary (or e-diary application), thermometer, and measuring device and instructed to collect prompted local reactions at the pneumococcal vaccine injection site (redness, swelling, and pain at the injection site), systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) occurring within 7 days after each vaccination. Use of antipyretic/pain medication will also be prompted for and collected by the participant's parent(s)/legal guardian(s) in an e-diary, device or application, from Day 1 through Day 7 after each vaccination (where Day 1 is the day of vaccination).
The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling >14 caliper units, severe pain at the injection site,

or fever >40.0°C (axillary) in the 7 days after vaccination or has an emergency room visit or hospitalization.

As this study is the first study where 20vPnC is administered subcutaneously and the study participants are infants, a daily enrollment limit of ≤5 participants will be in place from study start until the study has accumulated safety data from 45 participants through 7 days of follow up after Dose 1. These data will be carefully monitored and reviewed by the study team. If there are no safety signals in the first 45 participants after Dose 1, the daily enrollment limit will be removed (see Section 8.2.4).

Participants will return to the site for Visit 2 (4 to 8 weeks after Visit 1) and Visit 3 (4 to 8 weeks after Visit 2); they will be assessed for continued eligibility and information will be collected from the participants' parent(s)/legal guardian(s) on AEs, including nonserious AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs will be recorded.

Information on vaccines administered since the last visit will also be recorded. Participants with continued eligibility will be administered Dose 2 (Visit 2) and Dose 3 (Visit 3). Consistent with the vaccination schedule recommended by the Japan Pediatric Society",[1] specific vaccines containing Hib, Hep B, rotavirus, diphtheria, tetanus, acellular pertussis, and poliovirus antigens will also be administered concomitantly with Doses 2 and 3 (apart from HepB vaccine which is not given with Dose 3) in the upper arm(s) or orally (in the case of rotavirus vaccine). Participants will be observed for 30 minutes after vaccination. Participant's parent(s)/legal guardian(s) will be instructed as in Visit 1.

Participants will return to the site for Visit 4, approximately 1 month (28 to 42 days) after Visit 3. Information will be collected from the participants' parent(s)/legal guardian(s) on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs will be recorded. Information on vaccines administered since the last visit will also be recorded. A blood sample will be collected for immunogenicity assessment.

Participants will return to the site for Visit 5 (12 to 15 months of age with ≥60 days after Dose 3) and be assessed for continued eligibility. Information will be collected from the participants' parent(s)/legal guardian(s) on SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs will be recorded. Information on vaccines given since the last visit will also be recorded. A blood sample will be taken for immunogenicity assessment prior to vaccination. Dose 4 (of 20vPnC or 13vPnC) will be administered at this visit. Consistent with the vaccination schedule recommended by the Japan Pediatric Society,[1] specific concomitant vaccines containing Hib, diphtheria, tetanus, acellular pertussis, poliovirus, measles, rubella, and varicella antigens will be administered subcutaneously into the upper arm(s) at this visit. Participants will be observed for 30 minutes after vaccination and any reactions occurring during that time will be recorded as AEs. Participant's parent(s)/legal guardian(s) will be instructed as in Visit 1.

Participants will return for Visit 6, approximately 1 month (28 to 42 days) after Visit 5. Information will be collected from the participants' parent(s)/legal guardian(s) on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs will be recorded. Information on vaccines given since the last visit will also be recorded. A blood sample will be taken for immunogenicity assessment.

CCI [redacted]

4.1.1. Approximate Duration of Participation for Each Participant

Each participant will participate in the study approximately between 7 to 14 months depending on the age of commencing in the study.

4.1.2. Approximate Number of Participants

Approximately 666 participants will be enrolled to achieve a target of 600 evaluable participants (200 in each vaccine group) at the follow-up time point 1 month after Dose 3.

4.2. Scientific Rationale for Study Design

CCI [redacted] Infants 2 through 6 months of age will be eligible if they are naive to pneumococcal vaccination and the specified concomitant vaccines. This study population has been selected as this is the historical population studied for licensure of 13vPnC in infants. The participants will be administered either 20vPnC or 13vPnC for all 4 doses by the same injection route (SC or IM) at Visits 1, 2, 3, and 5. This is consistent with the current vaccination schedule recommended by the Japan Pediatric Society for infants in Japan.[1] 13vPnC will serve as the comparator to 20vPnC for assessment of safety and immunogenicity when 20vPnC or 13vPnC will be administered by SC injection. The safety and immunogenicity of 20vPnC administered by IM injection will also be assessed.

4.3. Justification for Dose

The 20vPnC candidate is modeled after 7vPnC and 13vPnC, and contains capsular polysaccharides 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}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. In infants, administration of all 4 doses of pneumococcal conjugate vaccine given at the defined schedule shown in the SoA induce protective immune responses.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants 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 participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Japanese male or female infants ≥2 months to ≤6 months (defined as the first day the participant is 2 months of age to the last day the participant is 6 months of age) at the time of consent.

Type of Participant and Disease Characteristics:

2. Participants whose parent(s)/legal guardian(s) is willing and able to comply with all scheduled visits, treatment plan, and other study procedures.

3. Healthy infants determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study.

4. Expected to be available for the duration of the study and whose parent(s)/legal guardian(s) can be contacted by telephone during study participation.

Informed Consent:

5. Participants whose parent(s)/legal guardian(s) is capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of investigational product, the specified concomitant vaccines containing Hib, HepB, rotavirus, diphtheria, tetanus, acellular

pertussis, poliovirus, measles, rubella, and/or varicella antigens, or any diphtheria toxoid-containing vaccine.

2. Contraindication to vaccination with pneumococcal conjugate vaccine, or the specified concomitant vaccines containing Hib, Hep B, rotavirus, diphtheria, tetanus, acellular pertussis, poliovirus, measles, rubella, and/or varicella antigens.

3. 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.

4. Major known congenital malformation or serious chronic disorder.

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

6. Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, HIV infection, leukemia, lymphoma, or organ or bone marrow transplant.

7. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular or subcutaneous injection.

8. Congenital, functional, or surgical asplenia.

9. 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 participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

10. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.

11. Prior receipt of Hib, Hep B, rotavirus, diphtheria, tetanus, acellular pertussis, and/or poliovirus vaccines.

12. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood sample collection (Visit 6). If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants 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, eyes, or ears) corticosteroids are permitted.

13. Receipt of blood/plasma products or immunoglobulins (including hepatitis B immunoglobulin and monoclonal antibodies) since birth or planned receipt through the last planned blood sample collection in the study (through Visit 6).

Prior/Concurrent Clinical Study Experience:

14. Participation in other studies involving investigational drug(s), investigational vaccines, or investigational devices within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

15. Children or grandchildren who are direct descendants of investigator site staff or Pfizer employees who are directly involved in the conduct of the study, or children or grandchildren of site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants whose parent(s)/legal guardian(s) have consented for them to participate in the clinical study but are not subsequently randomly assigned to investigational product/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs and SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

5.5. Temporary Delay Criteria

The following conditions are temporary or self-limiting and a participant may be vaccinated and/or have blood sample collection in the study once the condition(s) has/have resolved and no other exclusion criteria are met.

The blood sample collection prior to vaccination (Dose 4 at Visit 5) should take place on the same day as the vaccination.

Criteria for Temporarily Delaying Vaccine Administration

- Current febrile illness (eg, axillary temperature ≥37.5°C) or other acute illness within 48 hours before investigational product administration.

- Receipt of any inactivated or otherwise nonlive vaccine within 14 days or any live vaccine within 28 days before investigational product administration (with the exception of the influenza vaccine, which may be given at any time during the influenza season). Receipt of permitted concomitant vaccines on the same day as Dose 1, 2, 3, or 4 does not require temporary delay of investigational product administration.

- Receipt of short-term (<14 days) systemic corticosteroids. Investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

Criteria for Temporarily Delaying Immunogenicity Blood Sample Collection

- Receipt of antibiotic therapy within 72 hours before blood sample collection. Topical antibiotics are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to investigational product.

Administration and vaccination schedule of the specified concomitant vaccines containing Hib, Hep B, rotavirus, diphtheria tetanus, acellular pertussis, polio virus, measles, rubella, and varicella antigens will be described in Section 6.5.2.

6.1. Study Intervention(s) Administered

20vPnC is a sterile liquid suspension formulation containing 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 [redacted]

13vPnC is a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14,18C, 19A, 19F, and 23F individually conjugated to

CRM_{197}. CCI [redacted]

CCI [redacted]

The inner syringe label will be open labeled. Except for the inner syringe label, 20vPnC and 13vPnC are both white suspensions and are identical in appearance including outer carton, and will be supplied as prefilled syringes.

All vaccines listed in this section will be provided by Pfizer as prefilled syringes. Each syringe will be packaged in a carton with a label and a tamper-evident seal, and will be labeled as required per country requirement (refer to the investigational product manual).

6.1.1. Administration

Participants will receive 1 dose of 20vPnC or 13vPnC at each vaccination visit (Visits 1, 2, 3, and 5 with Doses 1, 2, 3, and 4, respectively) in accordance with the study's SoA. Doses 1 to 3 will be preferred to be administered at 2, 3, and 4 months of age consistent with the vaccination schedule recommended by the Japan Pediatric Society.[1] In addition, Dose 3 will be completed by 12 months of age and Dose 4 will be administered ≥60 days after Dose 3.

In the 20vPnC SC and 13vPnC SC groups, 20vPnC or 13vPnC should be administered subcutaneously by injecting 0.5 mL into the anterolateral thigh (preferably into the left anterolateral thigh) at the vaccination visits. In the 20vPnC IM group, 20vPnC should be administered intramuscularly by injecting 0.5 mL into the anterolateral thigh muscle of the leg (preferably of the left leg) at the vaccination visits.

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 study interventions should be performed by an appropriately qualified, GCP-trained, vaccine-experienced, and unblinded 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. (NOTE: A **blinded** site staff **should not** open a carton of the investigational product in order to maintain the blind).

Study intervention administration details will be recorded on the CRF.

6.1.2. Medical Devices

1. In this study, medical devices being deployed are the 20vPnC and 13vPnC prefilled syringes.

2. Instructions for medical device use are provided in the IP manual.

3. All medical device deficiencies (including malfunctions, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

CCI

CCI

[redacted]

CCI

[redacted]

6.2.1. Preparation and Dispensing

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

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Participants will be randomized equally to one of the following vaccine groups:
(1) 20vPnC SC group, (2) 13vPnC SC group (control vaccine), or (3) 20vPnC IM group.

Allocation of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee; either blinded or unblinded) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site files.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

An otherwise uninvolved third party (unblinded site staff) will be responsible for administration of the study intervention. This includes ensuring that there are no differences in time or effort taken to administer the study intervention and no blinded site staff or participant's parent(s)/legal guardian(s) are able to view the administration (refer to SRM for details).

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

6.3.2. Blinding of Site Personnel

In this observer-blinded study, the study staff administering the vaccine and confirming the administration route of study intervention will be unblinded, but all other site study personnel, including the principal investigator and the parent(s)/guardian(s) of the participant, will be blinded.

The principal investigator will assign the responsibility of the unblinded administrator who will not participate in the evaluation of any study subject. At least 1 unblinded administrator will be assigned per site. A member of the study site staff should fulfill this role.
The investigator, study coordinator, and any site staff other than the unblinded administrator must not be allowed to know the investigational product assigned (including the route of administration) to any study participant and must not be allowed to see the investigational product container contents.

6.3.3. Blinding of the Sponsor

Those study team members who are involved in ensuring that protocol requirements for study intervention handling, allocation, and administration are fulfilled at the site (eg, study manager; CRAs and unblinded medical monitor) will be unblinded for the duration of the study. All other study team members and all laboratory personnel performing the serology assays will remain blinded to vaccine assigned/received throughout the study.

6.3.4. Breaking the Blind

The study will be participant-, participant's parent(s)/legal guardian(s)-, and investigator-blinded.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and the CRF.

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated unblinded study staff at the investigator site. The date and time of each dose administered in the study site will be recorded in the source documents and recorded in the CRF. The administration route (SC or IM) of study intervention and study participant identification will be confirmed at the time of dosing by an unblinded member of the study site staff.

6.5. Concomitant Therapy

6.5.1. Prohibited Concomitant Vaccines and Treatments

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during study participation.
- Receipt of nonstudy pneumococcal vaccine is prohibited during study participation.
- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a ≥14-day course of systemic corticosteroids) is prohibited through Visit 6.

6.5.2. Permitted Concomitant Vaccines and Treatments

Specified concomitant vaccines

Consistent with the vaccination schedule recommended by the Japan Pediatric Society",[1] specified concomitant vaccines containing Hib, HepB, rotavirus, diphtheria, tetanus, acellular

pertussis, polio virus, measles, rubella, and varicella antigens will be administered concomitantly with the relevant dose of investigational product. The vaccination schedule of the specified concomitant vaccines are shown in Table 1.

Table 1. Vaccination Schedule for Investigational Product and Specified Concomitant Vaccines

Visit Number	Visit 1	Visit 2	Visit 3	Visit 5
IP Vaccination[a]	Dose 1	Dose 2	Dose 3	Dose 4
Visit Window	2 through 6 Months of Age	4 to 8 Weeks After Visit 1	4 to 8 Weeks After Visit 2 (Completed by 12 Month of Age)	12 to 15 Months of Age (≥60 Days After Dose 3)
Investigational Product (20vPnC or 13vPnC)	X	X	X	X
Specified concomitant vaccines				
Hib vaccine	X (Vax 1)	X (Vax 2)	X (Vax 3)	X (Vax 4)
Hep B vaccine[b]	X (Vax 1)	X (Vax 2)		
Rotavirus vaccine	X (Vax 1)	X (Vax 2)	X[c] (Vax 3)	
DTaP-IPV[b]		X (Vax 1)	X (Vax 2)	X (Vax 4)
MR combination vaccine[d]				X (Vax 1)
Varicella vaccine[d]				X (Vax 1)

Abbreviation: DTaP-IPV = diphtheria, tetanus, acellular pertussis, inactivated polio combination vaccine, Hep B = hepatitis B, Hib = *Haemophilus influenzae* type b, MR = measles and rubella, Vax = vaccination

a. Doses of vaccines to be administrated at visits 1 to 3 will be preferred to be administered at 2, 3, and 4 months of age consistent with the recommended vaccination schedule..
b. Dose 3 of DTaP-IPV and Hep B vaccine will be administered according to the vaccination schedule defined in the labeling. These vaccines will be administered between the blood sample collection 1 month after Dose 3 (Visit 4) and 14 days before Dose 4 (Visit 5).
c. Dose 3 for penta-valent rotavirus vaccine only.
d. Dose 2 of MR combination vaccine and varicella vaccine will be administered according to the vaccination schedule defined in the labeling.

Other Concomitant Vaccines and Treatments

- Influenza vaccine is permitted at any time during influenza season in this study.

- Other nonprohibited licensed age appropriate vaccines may be given between the blood sample collection 1 month after Dose 3 (Visit 4) and 14 days before Dose 4 (Visit 5) for inactivated vaccines or 28 days before Dose 4 (Visit 5) for live vaccines, according to vaccination schedule recommended by the Japan Pediatric Society".[1] Following the blood sample collection performed 1 month after Dose 4 (Visit 6), all licensed vaccines are permitted.

- Use of topical anesthetic is permitted.

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

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

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

6.5.3. Recording Prior and Concomitant Vaccines and Treatments

The name and date of administration for all vaccinations should be collected from the time of signing of the ICD to Visit 6 and will be recorded in the CRF. At Visit 1, information on prior vaccinations will also be recorded in the CRF. Vaccines required by the protocol, as well as those not stipulated, will be recorded throughout study participation.

Medications taken to treat SAEs or NDCMCs from the signing of informed consent to the final visit will be recorded in the CRF.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participant eligibility must be confirmed at each visit (for the vaccination visit, prior to each vaccination) in order to continue in the study.

If a participant no longer meets the eligibility criteria during the vaccination period of the study, further vaccinations should be discontinued, but the participant may remain in the study. If a participant is discontinued from vaccination and the participant's parent(s)/legal guardian(s) consents, safety follow-up will be conducted as per Section 8.3 (AEs and SAEs will be collected for 1 month after the last study vaccination).

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may be withdrawn from the study at any time at the request of his/her parent(s)/legal guardian(s) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. Reasons for discontinuation from the study include the following:

- Adverse event;
- Death;
- No longer meets eliginility criteria;
- Protocol deviation;
- Physician decision;
- Study terminated by sponsor;
- Medication error without associated adverse event;
- Withdrawal by participant's parent(s)/legal guardian(s);
- Lost to follow-up;
- Other.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant's parent(s)/legal guardian(s). All attempts to contact the participant's parent(s)/legal guardian(s) and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

At the time of discontinuing please refer to the ISF and SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant's parent(s)/legal guardian(s) should ideally notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The participant's parent(s)/legal guardian(s) should be questioned regarding their reason for withdrawal. The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

The participant should be requested to return for a final visit, if applicable, and the investigator will perform the procedures indicated for the next visit. Any AEs or SAEs that are continuing at the time of withdrawal from the study should be followed until resolution or, in case of permanent impairment, until the condition stabilizes.

If a participant is withdrawn from the study, his/her parent(s)/legal guardian(s) may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant is withdrawn from the study and his/her parent(s)/legal guardian(s) also withdraws consent (see Section 7.2.1) 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.

When a participant is withdrawn from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Vaccine SAE Reporting form.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participant's parent(s)/legal guardian(s) who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant's parent(s)/legal guardian(s) specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participant's parent(s)/legal guardian(s) 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 study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and the participant's parent(s)/legal guardian(s) is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant's parent(s)/legal guardian(s) and reschedule the missed visit as soon as possible and counsel the participant's parent(s)/legal guardian(s) on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant's parent(s)/legal guardian(s) wishes the participant to, and/or should, continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant's parent(s)/legal guardian(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant's parent(s)/legal guardian(s) continue to be unreachable, the participant will be considered to have been withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Section 10.1 (Appendix 1).

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

The total blood sampling volume for individual participants in this study is approximately 15 mL.

8.1. Immunogenicity Assessments

8.1.1. Immunogenicity Assessments

Blood samples (approximately 5 mL per sample) will be collected from all participants at Visit 4 (1 month after Dose 3), Visit 5 (prior to administration of Dose 4), and Visit 6 (1 month after Dose 4). These are the immunogenicity time points.

8.1.1.1. Pneumococcal Responses

IgG Responses to the 20 Serotypes Contained in 20vPnC

IgG antibody concentrations for serotypes present in 20vPnC (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) will be determined on all sera collected at the 3 immunogenicity time points (Visits 4, 5, and 6). The serotype-specific IgG concentrations will be measured by Pfizer's multiplex Luminex immunoassay.

OPA Responses to the 20 Serotypes Contained in 20vPnC

OPA titers for serotypes present in 20vPnC (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 selected subsets of sera for the immunogenicity time points (Visits 4, 5, and 6). These subsets will be randomly selected, by an unblinded third party, to assure that each subset has equal representation of all vaccine groups. Further details will be described in the CSAP.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.2. Safety Assessments

A clinical assessment, including medical history and measurement of axillary temperature, will be performed on all participants prior to vaccination to determine participant eligibility and to establish a clinical baseline. Significant medical history and significant findings from any physical examination (if performed) will be recorded as medical history in the CRF. Temperature measurement prior to vaccination will be documented and recorded in the CRF.

The participant will be observed for 30 minutes after each study vaccination and any reactions occurring during that time will be recorded as AEs.

Prompted e-diary events, including local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) that occur 7 days after investigational product administration (Days 1 through 7, where Day 1 is the day of vaccination), are graded as described in Section 8.2.2.1 and Section 8.2.2.2. Furthermore, AEs, SAEs, and NDCMCs will be collected as defined in Section 10.3.

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Participant Electronic Diary

The participant's parent(s)/legal guardian(s) will be asked to monitor and record local reactions, specific systemic events, and antipyretic/pain medication taken for 7 days, each evening, following each administration of investigational product (20vPnC or 13vPnC) using an e-diary (in a provisioned device or application on a personal device). This allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience. Data on local reactions, specific systemic events, and antipyretic/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 participant is withdrawn 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 local reactions or specific systemic events 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 participant compliance and reported events as part of the ongoing safety review.

8.2.2. 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 FDA 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.[78]

8.2.2.1. Local Reactions

For the first 7 days following each study vaccination (Days 1 through 7, where Day 1 is the day of vaccination), the participant's parent(s)/legal guardian(s) will be asked to assess redness, swelling, and pain at the 20vPnC or 13vPnC injection site (anterolateral thigh) and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device (caliper) 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 2. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scale in Table 2. The participant's parent(s)/legal guardian(s) will be prompted to contact the investigator if the participant 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 participant's local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the participant's parent(s)/legal guardian(s) regarding signs and symptoms that would prompt site contact.

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

Table 2. Grading Scales for Local Reactions

Local Reaction	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3[a] (Severe)	Grade 4[b]
Redness	1 to 4 caliper units (or measuring device units) = >0 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis or exfoliative dermatitis
Swelling	1 to 4 caliper units (or measuring device units) = >0 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 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

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

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

8.2.2.2. Systemic Events (Systemic Symptoms and Fever)

For the first 7 days following each study vaccination (Days 1 through 7, where Day 1 is the day of vaccination), the participant's parent(s)/legal guardian(s) 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 participant's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scale in Table 3. The participant's parent(s)/legal guardian(s) will also be instructed to contact site staff if the participant 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 participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

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

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

Table 3. Grading Scales for Systemic Event Symptoms

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

Abbreviations: CRF = case report form.

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

8.2.2.2.1. Fever

In order to record information on fever, a digital thermometer will be given to the participant's parent(s)/legal guardian(s) with instructions on how to measure axillary temperature at home. Temperature will be collected in the evening, daily, for 7 days following each study vaccination (Days 1 through 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 an axillary temperature of ≥37.5°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 <37.5°C) in order to collect a stop date in the CRF. A participant's parent(s)/legal guardian(s) will be prompted to contact the investigator if the participant experiences a fever >40.0°C within the 7 days following vaccination to assess the fever and perform an unscheduled assessment, as applicable (see Section 8.11.7). Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information if a temperature of >38.9°C 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 4.

Table 4. Ranges for Fever for the E-diary

≥37.5°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C

Note: Fever is defined as axillary temperature ≥37.5°C.

8.2.2.3. Use of Antipyretic/Pain Medication

The participant's parent(s)/legal guardian(s) 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.

8.2.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory tests are not required by this protocol.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.4. Procedures to Monitor Safety

As this study is the first study where 20vPnC is administered subcutaneously and the study participants are infants, a daily enrollment limit of 5 participants will be in place from study start until the study has accumulated safety data for 45 participants through 7 days of follow-up after Dose 1 and these blinded data have been carefully monitored and reviewed by the study team. If there is no safety signal in the first 45 participants after Dose 1, the daily enrollment limit will be removed.

If any safety signal in the first 45 participants after Dose 1 is identified by the study team, these safety data will be reviewed by senior Pfizer personnel not directly involved with the study conduct. The daily limit will continue until the senior Pfizer personnel reviews the safety data and makes recommendations.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 8. Device deficiencies are covered in Section 8.3.9.

AEs will be reported by the participant's parent(s)/legal guardian(s). 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.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue from the study (see Section 7).

Each participant's parent(s)/legal guardian(s) will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant's parent(s)/legal guardian(s) provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 4, and from Visit 5 to Visit 6. Between Visit 4 and Visit 5, only SAEs and NDCMCs will be reported.

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.

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed or withdrawn early from the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant 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.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant's parent(s)/legal guardian(s).

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant's parent(s)/legal guardian(s) is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure 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.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant

enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

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).

Abnormal pregnancy outcomes are considered SAEs. 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 including 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 study intervention.

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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Not applicable.

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study for the purposes of administering the investigational product. In order to fulfill regulatory reporting obligations worldwide, the unblinded site staff is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices. Refer to the SRM for details.

The definition of a medical device deficiency can be found in Appendix 8.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 8.

8.3.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The unblinded site staff is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the unblinded site staff.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the unblinded site staff determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP Manual. The Medication Error CRF will also be completed.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the unblinded site staff's awareness as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The unblinded site staff will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The unblinded site staff, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

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

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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 within 24 hours.

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

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

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;

- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 1 dose of investigational product within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

The study procedures are summarized in the SoA (Section 1.3). The day of Dose 1 is considered to be Day 1.

Unless specified in the sections below, the order of key procedures within a given visit may have some flexibility.

8.11.1. Visit 1 (Dose 1 Visit, Day 1)

Prior to vaccination:

- Obtain a personally signed and dated ICD indicating that the participant's parent(s)/legal guardian(s) has been informed of all pertinent aspects of the study before performing any study-specific procedures.
- Assign a participant number via the IRT.
- Obtain and record the participant's demographic information (including date of birth, sex, race, and ethnicity). The complete date of birth (ie, DD-MMM-YYYY) will be collected to critically evaluate the immune response and safety profile by age.
- Perform a clinical assessment including medical history (including significant birth history); record any findings on the medical history CRF.
- Record vaccine history.
- Measure and record the participant's axillary temperature (°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 an investigational product container number via the IRT. This must be the last step before proceeding. A site staff member will prepare the investigational product according to the IP manual (NOTE: A **blinded** site staff **should not** open a carton of the investigational product in order to maintain the blind).

After randomization:

- Unblinded site staff will administer a single 0.5-mL injection of 20vPnC or 13vPnC into the anterolateral thigh (preferably into the left anterolateral thigh).
- The site staff (either blinded or unblinded) will administer concomitant vaccines containing hepatitis B, Hib, and rotavirus antigens and other permitted vaccines into the upper arm(s) or orally (in the case of rotavirus vaccine) (Section 6.5.2). A blinded site staff member will record the site of administration on the CRF.

- Blinded site staff will observe the participant for 30 minutes after vaccination for any 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 participant's parent(s)/legal guardian(s) a measuring device to measure 20vPnC or 13vPnC injection site reactions and a digital thermometer and provide instructions on their use.

- Issue the participant's parent(s)/legal guardian(s) an e-diary (device or application).

- Provide instructions on use and completion of the e-diary. Ask the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C, redness and/or swelling at the 20vPnC or 13vPnC injection site measuring >14 measuring device units (>7 cm), or severe 20vPnC or 13vPnC injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Ask the participant's parent(s)/legal guardian(s) 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.

- Provide the participant's parent(s)/legal guardian(s) with the participant contact card containing the study and investigator information (see Section 10.1.10).

- Inform the participant's parent(s)/legal guardian(s) that the 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 the source documents and the site staff will update the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.2. Visit 2 (Dose 2 Visit, 4 to 8 Weeks After Visit 1 [Dose 1])

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Record nonstudy vaccinations administered since Visit 1, as described in Section 6.5.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); 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 10.3, and record concomitant medications used to treat NDCMCs and SAEs.

- Measure and record the participant's axillary temperature (°C).

- Unblinded site staff will administer a single 0.5-mL injection of 20vPnC or 13vPnC into the anterolateral thigh (preferably into the left anterolateral thigh). (NOTE: A **blinded** site staff **should not** open a carton of the investigational product in order to maintain the blind).

- The site staff (either blinded or unblinded) will administer concomitant vaccines containing hepatitis B. Hib, rotavirus, diphtheria, tetanus, acellular pertussis, and poliovirus antigens and other permitted vaccines into the upper arm(s) or orally (in the case of rotavirus vaccine) (Section 6.5.2). A blinded staff member will record the site of administration on the CRF.

After vaccination:

- Blinded site staff will observe the participant for 30 minutes after vaccination for any 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 and review instructions if necessary. Remind the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination. Provide a thermometer or measuring device if needed.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C, redness and/or swelling at the 20vPnC or 13vPnC injection site measuring >14 measuring device units (>7 cm), or severe 20vPnC or 13vPnC injection site pain (causes limitation of limb movement), to determine if the event requires further assessment by the investigator.

- Remind the participant's parent(s)/legal guardian(s) 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.

- Confirm whether the participant's parent(s)/legal guardian(s) still possesses the participant contact card. Provide a participant contact card if needed.

- Remind the participant's parent(s)/legal guardian(s) that the 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 designees completes the CRF and the source documents and the site staff will update the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.3. Visit 3 (Dose 3 Visit, 4 to 8 Weeks After Visit 2[Dose 2])

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Record nonstudy vaccinations administered since Visit 2, as described in Section 6.5.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); 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 10.3, and record concomitant medications used to treat NDCMCs and SAEs.

- Measure and record the participant's axillary temperature (°C).

- Unblinded site staff will administer a single 0.5-mL injection of 20vPnC or 13vPnC into the anterolateral thigh (preferably into the left anterolateral thigh). (NOTE: A **blinded** site staff **should not** open a carton of the investigational product in order to maintain the blind).

- The site staff (either blinded or unblinded) will administer concomitant vaccines containing diphtheria, tetanus, acellular pertussis, poliovirus, and Hib and rotavirus antigens and other permitted vaccines into the upper arm(s) or orally (in the case of rotavirus vaccine). A blinded staff member will record the site of administration on the CRF.

After vaccination:

- Blinded site staff will observe the participant for 30 minutes after vaccination for any 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 and review instructions if necessary. Remind the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination. Provide a thermometer or measuring device if needed.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C, redness and/or swelling at the 20vPnC or 13vPnC injection site measuring >14 measuring device units (>7 cm), or severe 20vPnC or 13vPnC injection site pain (causes limitation of limb movement), to determine if the event requires further assessment by the investigator.

- Remind the participant's parent(s)/legal guardian(s) 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.

- Confirm whether the participant's parent(s)/legal guardian(s) still possesses the participant contact card. Provide a participant contact card if needed.

- Remind the participant's parent(s)/legal guardian(s) that the 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 the source documents and updates the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.4. Visit 4 (Dose 3 Follow-up Visit, 28 to 42 Days After Visit 3 [Dose 3])

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Record nonstudy vaccinations administered since Visit 3, as described in Section 6.5.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); 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 applicable).

- 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 10.3, 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).

- The investigator or an authorized designee completes the CRF and the source documents.

8.11.5. Visit 5 (Dose 4 Visit, 12 to 15 Months of Age)

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Record nonstudy vaccinations administered since Visit 4, as described in Section 6.5.

- 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 10.3, and record concomitant medications used to treat NDCMCs and SAEs.

- Measure and record the participant's axillary temperature (°C).

- Prior to vaccination, collect a blood sample of approximately 5 mL for immunogenicity (a topical anesthetic is permitted).

- Unblinded site staff will administer a single 0.5-mL injection of 20vPnC or 13vPnC into the anterolateral thigh (preferably into the left anterolateral thigh). (NOTE: A **blinded** site staff **should not** open a carton of the investigational product in order to maintain the blind).

- The site staff (either blinded or unblinded) will administer concomitant vaccines containing Hib, diphtheria, tetanus, acellular pertussis, poliovirus, measles, rubella, and varicella antigens and other permitted vaccines into the upper arm(s). A blinded staff member will record the site of administration on the CRF.

After vaccination:

- Blinded site staff will observe the participant for 30 minutes after vaccination for any 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 participant's parent(s)/legal guardian(s) an e-diary (device or application). Provide instructions on use and completion of the e-diary. Ask the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C, redness and/or swelling at the 20vPnC or 13vPnC injection site measuring >14 measuring device units (>7 cm), or severe 20vPnC or 13vPnC injection site pain (causes limitation of limb movement), to determine if the event requires further assessment by the investigator.

- Remind the participant's parent(s)/legal guardian(s) 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.

- Confirm whether the participant's parent(s)/legal guardian(s) still possesses the participant contact card. Provide a participant contact card if needed.

- Remind the participant's parent(s)/legal guardian(s) that the 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 designees completes the CRF and the source documents and updates the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.6. Visit 6 (Dose 4 Follow-up Visit, 28 to 42 Days After Visit 5 [Dose 4])

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Record nonstudy vaccinations administered since Visit 5, as described in Section 6.5.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); 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 10.3, 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).

- The investigator or an authorized designee completes the CRF and the source documents.

8.11.7. Unscheduled Visits

If the participant's parent(s)/legal guardian(s) reports redness or swelling at the injection site measuring >14 measuring device units (>7 cm), severe injection site pain, or a fever >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 the participant's parent(s)/legal guardian(s) to assess if an unscheduled investigator site visit is required. Note that for a fever >40.0°C, the participant's parent(s)/legal guardian(s) should be instructed not to delay seeking medical care, as appropriate, while arranging for an unscheduled visit if applicable. A visit should be scheduled as soon as possible to assess the extent of the injection site reaction, unless any of the following is true:

- The participant's parent(s)/legal guardian(s) is unable to bring the participant to the unscheduled visit.

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

- The participant's parent(s)/legal guardian(s) 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 participant's source documentation and the CRF.

If the participant's parent(s)/legal guardian(s) is unable to bring the participant 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 axillary temperature (°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 8.2.2 (if present).
- Assess 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 participant's parent(s)/legal guardian(s) will also be instructed to contact investigator site staff if the participant experiences any emergency room visit or hospitalization for decreased appetite, drowsiness/increased sleep, irritability, or local reaction within 7 days of vaccination.

The participant's parent(s)/legal guardian(s) 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 participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a 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. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimands corresponding to each of the primary, secondary CCI [redacted] objectives is described in the table in Section 3. The estimands to evaluate the immunogenicity objectives for noninferiority are based on evaluable populations (Section 9.3). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study

schedules and protocol requirements as directed. The estimand addresses the objective of estimating the maximum potential difference between the 2 compared groups, since the impact of noncompliance is likely to diminish the observed difference between the 2 groups. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 x LLOQ in the analysis.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

9.1.2. Statistical Hypotheses

Noninferiority of the immune response at 1 month after Dose 3 for each serotype in 20vPnC is evaluated by the percentage of participants with predefined pneumococcal serotype-specific IgG concentrations based on results from the 20vPnC SC group and the 13vPnC SC group as below. The noninferiority for the immune response at 1 month after Dose 3 for a serotype will be declared if the null hypotheses (H_0) is rejected at the 0.05 level.

9.1.2.1. Noninferiority Comparing Percentage of Participants with Predefined Pneumococcal Serotype-Specific IgG Concentrations 1 Month after Dose 3 (Primary Endpoint)

Hypothesis testing will be used to assess noninferiority of 20vPnC SC to 13vPnC SC by the percentage of participants with predefined pneumococcal serotype-specific IgG concentrations 1 month after Dose 3. The null hypothesis (H_{0A}) for each serotype is

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

with a 10% margin for noninferiority, where

- $\pi_{20vPnC\ SC}$ is the percentage of participants achieving an IgG antibody concentration of a predetermined level in the 20vPnC SC group from the serotype 1 month after Dose 3;
- If the serotype is from the 13 matched serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), $\pi_{13vPnC\ SC}$ is the percentage of participants achieving a predefined IgG concentration level for the serotype from the 13vPnC SC group 1 month after Dose 3;
- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\pi_{13vPnC\ SC}$ is the percentage of participants achieving a predefined IgG concentration level from the serotype with the lowest percentage 1 month after Dose 3 among the 13 serotypes from the 13vPnC SC group, provided that the lowest percentage is not from serotype 3. If the lowest percentage in the 13vPnC SC group is from serotype 3, the next lowest percentage in the 13vPnC SC group will be used in the comparison. Historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the noninferiority of the 7 additional serotypes.

- The predefined levels for serotype-specific IgG concentrations are 0.35 μg/mL for all serotypes in 20vPnC except that the predefined levels are 0.23 μg/mL, 0.10 μg/mL, and 0.12 μg/mL for serotypes 5, 6B, and 19A, respectively.

The null hypothesis H_{0A} will be rejected and noninferiority of 20vPnC SC to 13vPnC SC for the percentage of participants with predefined IgG concentration level will be declared for a serotype if the lower bound of the 2-sided 95% CI for the difference (20vPnC SC group – 13vPnC SC group) in percentages, computed using the Miettinen and Nurminen method, is greater than –10% (10% noninferiority margin).

9.1.2.2. Noninferiority Comparing Pneumococcal Serotype-Specific IgG Concentrations 1 Month after Dose 3 (Secondary Endpoint)

Hypothesis testing will be used to assess noninferiority of 20vPnC SC to 13vPnC SC for pneumococcal serotype-specific IgG GMCs 1 month after Dose 3. The null hypothesis (H_{0B}) for each serotype is

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

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

- $\ln(\mu_{20vPnC\ SC})$ is the natural log of the IgG GMC in the 20vPnC SC group for that serotype 1 month after Dose 3;

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

- If the serotype is from the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in 20vPnC, $\ln(\mu_{13vPnC\ SC})$ is the natural log of the IgG GMC for the serotype with the lowest IgG GMC 1 month after Dose 3 among the 13 serotypes from the 13vPnC SC group, provided that the lowest GMC is not from serotype 3. If the lowest GMC in the 13vPnC SC group is from serotype 3, the next lowest GMC in the 13vPnC SC group will be used in the comparison. As stated in Section 9.1.2.1, historical data suggest that serotype 3 behaves somewhat differently from the other serotypes in 13vPnC; therefore, IgG results from serotype 3 will not be used in the comparison to assess the noninferiority of the 7 additional serotypes.

The null hypothesis H_{0B} will be rejected and noninferiority of 20vPnC SC to 13vPnC SC for the serotype-specific IgG GMC will be declared for a serotype if the lower bound of the 2-sided 95% CI for GMR of serotype-specific IgG GMCs (20vPnC SC group over 13vPnC SC group) is greater than 0.5 (2-fold margin).

9.1.3. Multiplicity Considerations

For the primary immunogenicity objectives comparing serotype-specific IgG concentrations from 20vPnC SC group to the13vPnC SC group, noninferiority of the immune response for each serotype is assessed by the hypothesis tests as described in Section 9.1.2.1.
The hypothesis is tested at an alpha level of 0.05 for the comparison of percentage of participants with the predefined threshold. The primary pneumococcal immunogenicity objective will be achieved if the noninferiority of the immune response induced by 20vPnC SC group compared to 13vPnC SC group at 1 month after Dose 3 is established for all 20 serotypes. Therefore, the overall type I error rate for the primary immunogenicity assessment of the pneumococcal immune response is well controlled at the 0.05 level.

9.2. Sample Size Determination

9.2.1. Sample size Considerations for 20vPnC SC Group and 13vPnC SC Group

Sample size and power for the primary immunogenicity objective are based on simulations of multivariate log-normal distributed random numbers with assumptions supported by IgG results from historical 13vPnC infant CCI

CCI

With 200 evaluable participants in each group (Table 6), the power to demonstrate noninferiority of 20vPnC to 13vPnC for all 20 serotypes comparing IgG results at 1 month after Dose 3 is approximately 92%, with NI for each serotype defined by the lower limit of the 2-sided 95% confidence interval for difference (20vPnC SC – 13vPnC SC) in percentages above -10%. To ensure 200 evaluable participants 1 month after Dose 3, 222 participants will be randomized by assuming a dropout rate of about 10%.

CCI

Table 6. Sample Size and Power to Demonstrate Noninferiority Comparing Serotype-Specific IgG Concentrations From 20vPnC SC Group to 13vPnC SC Group with the Specified Criteria

Evaluable Sample Size per Group	Power (%) to Demonstrate Noninferiority of Serotype-Specific IgG Concentrations for all 20 Serotypes[a]
150	82
180	89
200	92

Note: Power is estimated by 5,000 simulations.

a. Noninferiority for each serotype is defined by the lower bound of the 2-sided 95% CI for difference (20vPnC SC – 13vPnC SC) in percentage of participants with specified threshold above -10%, calculated with Miettinen and Nurminen method.

9.2.2. Sample Size Considerations for 20vPnC IM Group

The study size in the 20vPnC IM group is not based on any formal hypothesis test for any immunogenicity endpoint. All statistical analyses of immunogenicity results from 20vPnC IM group will be descriptive.

CCI

[redacted]

CCI

[redacted]

9.2.3. Sample Size Considerations for Safety Endpoints

From safety endpoints, the probabilities of observing at least 1 occurrence of any AE with a true incidence rate are displayed in Table 7.

Table 7. Probability of Observing at Least 1 Event by Assumed True Incidence Rates

Assumed True Incidence Rate	N=222
0.5%	67%
1.0%	89%
1.5%	97%

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 3 evaluable immunogenicity	All eligible randomized participants who are ≥2 to ≤6 months of age at the first vaccination, receive the vaccines to which they are randomly assigned at the first 3 doses, have at least 1 valid and determinate immunogenicity results from 1 month after Dose 3 visit (Visit 4), with blood sample collection within an appropriate window after Dose 3, have no other major protocol deviations as determined by the clinician. The Dose 3 evaluable immunogenicity population will be the primary population for the immunogenicity analyses.
Dose 4 evaluable immunogenicity	All eligible randomized participants who are ≥2 to ≤6 months of age at the first vaccination, receive all 4 randomized vaccines with Dose 4 received within the defined window (12 to 15 months of age [also at least 60 days after Dose 3]), have at least 1 valid and determinate immunogenicity results after Dose 4, have blood sample collection within an appropriate window after Dose 4, and have no other major protocol deviations as determined by the clinician.
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
Safety	All participants who receive at least 1 dose of the investigational product and have safety data after any vaccination.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analysis in Section 9.5. The SAP will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, CCI endpoints.

All CIs in the statistical analysis will be calculated as two-sided at 95% level.

9.4.1. Immunogenicity Analyses

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations (primary immunogenicity population) as defined in Section 9.3.

CCI

Participants will be summarized according to the vaccine group to which they are randomized. Missing serology data will not be imputed.

Endpoint	Statistical Analysis Methods
Primary immunogenicity	• **The difference of the percentage of participants with predefined pneumococcal serotype-specific IgG concentrations 1 month after Dose 3** For each of the 20 serotypes for 20vPnC SC and 13vPnC SC groups, between-group difference (20vPnC SC - 13vPnC SC) and the 2-sided 95% CI for the percentage of participants with predefined serotype-specific IgG concentrations 1 month after Dose 3 will be provided. If a serotype is from the 13 matched serotypes, the percentage of participants with the predefined IgG level for the serotype in the 20vPnC SC group will be compared with the percentage for that serotype in the 13vPnC SC group. If a serotype is from the 7 additional serotypes, the percentage of participants with the predefined IgG level in the 20vPnC SC group will be compared with the lowest percentage among the 13 serotypes from the 13vPnC SC group, provided that the lowest percentage is not from serotype 3. If the lowest percentage in the 13vPnC SC group is from serotype 3, the next lowest percentage in the 13vPnC group will be used in the comparison. The lower limit of the CI will be used in the hypothesis test for NI of 20vPnC to 13vPnC as detailed in Section 9.1.2.1.

Endpoint	Statistical Analysis Methods
	For each of the 20 serotypes for 20vPnC IM and 20vPnC SC groups, difference (20vPnC IM - 20vPnC SC) and the 2-sided 95% CI for the percentage of participants with predefined serotype-specific IgG concentrations 1 month after Dose 3 will be provided. The Miettinen and Nurminen method will be used to derive the CI for the difference in percentages between vaccine groups. The analysis will be based on the Dose 3 evaluable immunogenicity population. An additional analysis will be performed based on the Dose 3 all-available immunogenicity population if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary immunogenicity	• **GMRs of pneumococcal serotype-specific IgG concentrations 1 month after Dose 3** For each of the 20 serotypes, the GMR of 20vPnC SC to 13vPnC SC at 1 month after Dose 3 will be provided. GMRs and their 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale based on the Student's t-distribution, then exponentiating the results. The difference in means, on the natural log scale, will be 20vPnC SC -13vPnC SC. Hypothesis testing for noninferiority of 20vPnC SC to 13vPnC SC will be performed as described in Section 9.1.2.2. For each of the 20 serotypes, the GMR of 20vPnC IM to 20vPnC SC at 1 month after Dose 3 will be provided. • **GMCs of pneumococcal serotype-specific IgG concentrations 1 month after Dose 4** For each of the 20 serotypes, GMCs and 2-sided 95% CIs for pneumococcal serotype-specific IgG concentrations at 1 month after Dose 4 will be provided for each group. Geometric means and the associated 2-sided 95% CIs will be derived by calculating means and CIs on the natural log scale based on the Student's t-distribution, and then exponentiating the results.

Endpoint	Statistical Analysis Methods
	• **Pneumococcal serotype-specific OPA GMTs** For each of the 20 serotypes, GMTs and 2-sided 95% CIs for pneumococcal serotype-specific OPA titers at 1 month after Dose 3, prior to Dose 4 and 1 month after Dose 4 in each group will be provided. Geometric means and the associated 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the Student's t-distribution, then exponentiating the results. • **Percentages of participants with predefined pneumococcal serotype-specific IgG concentrations 1 month after Dose 4** For each of the 20 serotypes, the percentage (and 2-sided 95% CI) of participants with the predefined serotype-specific IgG concentration level 1 month after Dose 4 will be provided for each vaccine group. The Clopper-Pearson method will be used to calculate the CIs. • **GMFRs of pneumococcal serotype-specific IgG concentrations** For each of the 20 serotypes, GMFRs and 2-sided 95% CIs in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 will be provided for each vaccine group. GMFRs will be limited to participants with nonmissing values at both time points. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and transformed back to the original scale. Two-sided 95% CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale.
[redacted]	C C I [redacted]

Endpoint	Statistical Analysis Methods
	CCI CCI CCI CCI CCI

9.4.2. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	• Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs. Between-group differences (20vPnC SC – 13vPnC SC and 20vPnC IM – 20vPnC SC) in percentage and 2-sided 95% CIs will be provided. The Miettinen and Nurminen method will be used to derive the 95% CI for the difference in percentages between vaccine groups. • AEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 4 of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in percentage of participants reporting the events between 20vPnC SC and 13vPnC SC groups, or 20vPnC IM and 20vPnC SC groups will be calculated using the Miettinen and Nurminen's method. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. There is no Tier 1 event identified for 20vPnC at this stage. Descriptive summary statistics (counts and percentages and associated Clopper-Pearson 95% CIs) will be provided for Tier 3 events for each vaccine group. • SAEs and NDCMCs will be categorized according to MedDRA terms. Counts, percentages and the associated Clopper-Pearson 95% CIs of SAEs and NDCMCs from Dose 1 to 1 month after Dose 4 will be provided for each vaccine group.

Endpoint	Statistical Analysis Methods
	• The safety analyses are based on the safety population. Participant data will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.
Secondary	• Not applicable (N/A)
CCI [redacted]	[redacted]

9.5. Interim Analyses

No interim analysis is planned in this study. Statistical analyses will be carried out when the final data for the specified analyses are available.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. 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 study intervention, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant's parent(s)/legal guardian(s) and answer all questions regarding the study. The participant's parent(s)/legal guardian(s) should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

The participant's parent(s)/legal guardian(s) must be informed that their participation is voluntary. The participant's parent(s)/legal guardian(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian(s) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant's parent(s)/legal guardian(s) must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian(s).

The participant's parent(s)/legal guardian(s) must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian(s) is fully informed about his or her right to access and correct the participant's personal data and to withdraw consent for the processing of the participant's personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

The participant's parent(s)/legal guardian(s) must be reconsented to the most current version of the ICD(s) during the participant's participation in the study.

A copy of the ICD(s) must be provided to the participant's parent(s)/legal guardian(s).

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to the participant's parent(s)/legal guardian(s) the objectives of the additional research. The participants parent(s)/legal guardian(s) will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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 results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product,

regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor 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 participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response

submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the ISF.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/ CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory

requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. 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 ISF.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, the participant’s parent(s)/legal guardian(s) are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site

staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant'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 participant's parent(s)/legal guardian(s) directly, and if a participant's parent(s)/legal guardian(s) calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • 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.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Events that, in the clinical judgement 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 adverse events. Examples may include, but are not limited to, teething, contact diaper rash, spitting up, colic, or typical fussiness/crying in infants and children. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. **Results in death**
b. **Is life-threatening** The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. **Requires inpatient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation

and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Reporting 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 Vaccine SAE Reporting Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form /AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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 participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. 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 Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.3.5. Definition of NDCMC

A NDCMC is defined as a significant disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

CCI

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

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 participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede 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 participant’s individual baseline values and underlying conditions. Participants 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:

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. 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/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels 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.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

Not applicable.

10.8. Appendix 8: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator for study participants, users, and other persons. This definition also includes events considered related to the procedures for study participants only. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.8.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP Manual and completing the Medical Device Complaint CRF.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

- Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: Country-Specific Requirements

Not applicable.

10.10. Appendix 10: 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
ADE	adverse device effect
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
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
CRA	clinical research association
CRF	case report form
CRM_{197}	cross-reactive material 197
CRO	contract research organization
CSAP	clinical specimen analysis plan
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DTaP	diphtheria, tetanus, and acellular pertussis
DU	dispensable unit
EC	ethics committee
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
CCI	[redacted]
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation	Term
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
Hib	*Haemophilus influenzae* type b
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IM	intramuscular
IND	investigational new drug application
INR	international normalized ratio
IPAL	investigational product accountability log
IP manual	investigational product manual
IPD	invasive pneumococcal disease
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
ISO	International Organization for Standardization
IU	international units
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MR	measles and rubella vaccine
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
NIP	national immunization program
NVT	non-vaccine serotypes
OPA	opsonophagocytic activity
PI	principal investigator
PPSV23	23-valent pneumococcal polysaccharide vaccine
CCI	[redacted]
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SoA	schedule of activities

Abbreviation	Term
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
VT	vaccine-type
WHO	World Health Organization

11. REFERENCES

1 Japan Pediatric Society. Vaccination Schedule Recommended by the Japan Pediatric Society (Version of January 2020) (in Japanese). https://www.jpeds.or.jp/uploads/files/vaccine_schedule.pdf (Accessed on March 31, 2020).

2 Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS One 2013;8(4):e60273.

3 O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. Lancet 2009;374(9693):893-902.

4 Huang SS, Johnson KM, Ray GT, et al. Healthcare utilization and cost of pneumococcal disease in the United States. Vaccine 2011;29(18):3398-412.

5 Iyer AS, Ohtola JA, Westerink MAJ. Age-related immune response to pneumococcal polysaccharide vaccination: lessons for the clinic. Expert Rev Vaccines 2015;14(1):85-97.

6 Wahl B, O'Brien KL, Greenbaum A, et al. Global burden of *Streptococcus pneumoniae* in children younger than 5 years in the pneumococcal conjugate vaccines (PCV) era: 2000-2015. 10th International Symposium on Pneumococci & Pneumococcal Diseases (ISPPD-10); 26-30 Jun 2016; Glasgow, Scotland.

7 Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis 2015;15(3):301-9.

8 Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. Lancet Infect Dis 2018;18:441-51.

9 European Centre for Disease Prevention and Control. Invasive pneumococcal disease. In: ECDC. Annual epidemiological report for 2017. Stockholm: ECDC; 2018. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017-invasive-pneumococcal-disease.pdf. Accessed 13 Sep 2019.

10 Olarte L, Barson WJ, Barson RM, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis in US children. Clin Infect Dis 2015;61(5):767-75.

[11] Stockmann C, Ampofo K, Byington CL, et al. Pneumococcal meningitis in children:epidemiology, serotypes, and outcomes from 1997-2010 in Utah. Pediatrics 2013;132(3):421-8.

[12] Kaplan SL, Barson WJ, Lin PL, et al. Invasive pneumococcal disease in children's hospitals: 2014–2017. Pediatrics 2019;144(3):e20190567.

[13] Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372(9):835-45.

[14] Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015;373(5):415-27

[15] Griffin MR, Zhu Y, Moore MR, et al. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med 2013;369(2):155-63.

[16] Marom T, Tan A, Wilkinson GS, et al. Trends in otitis media–related health care use in the United States, 2001-2011. JAMA Pediatr 2014;168(1):68-75.

[17] NIID, MHLW. Status of invasive pneumococcal disease (IPD) in children after 13-valent pneumococcal conjugate vaccine (PCV13) was launched. Infectious Agents Surveillance Report (IASR) 2018;39112-3. https://www.niid.go.jp/niid/ja/allarticles/surveillance/2432-iasr/related-articles/related-articles-461/8167-461r04.html. (Accessed on August 22, 2019).

[18] Ubukata K, Takata M, Morozumi M, et al. Effects of pneumococcal conjugate vaccine on genotypic penicillin resistance and serotype changes, Japan, 2010-2017. Emerg Infect Dis. 2018; 24(11):2010–2020.

[19] Geno KA, Gilbert GL, Song JY, et al. Pneumococcal capsules and their types: past, present, and future. Clin Microbiol Rev 2015;28(3):871-99.

[20] Hausdorff WP, Hanage WP. Interim results of an ecological experiment-conjugate vaccination against the pneumococcus and serotype replacement. Hum Vaccin Immunother 2016;12(2):358-74.

[21] AlonsoDeVelasco E, Verheul AFM, Verhoef J, et al. Streptococcus pneumoniae: virulence factors, pathogenesis, and vaccines. Microbiol Rev 1995;59(4):591-603.

[22] Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1997;46(RR-8):1-24.

[23] Austrian R. A brief history of pneumococcal vaccines. Drugs Aging 1999;15(Suppl 1):1-10.

[24] Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med 1991;325(21):1453-60.

[25] Stein KE. Thymus-independent and thymus-dependent responses to polysaccharide antigens. J Infect Dis 1992;165 Suppl 1:S49-S52.

[26] Borrow R, Health PT, Siegrist CA. Use of pneumococcal polysaccharide vaccine in children: what is the evidence? Curr Opin Infect Dis 2012;25(3):292-303.

[27] Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med 2003;348(18):1747-55.

[28] Leventer-Roberts M, Feldman BS, Brufman I, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged ≥65 years: a retrospective case-control study. Clin Infect Dis 2015;60(10):1472-80.

[29] Wright PF, Sell SH, Vaughn WK, et al. Clinical studies of pneumococcal vaccines in infants. II. Efficacy and effect on nasopharyngeal carriage. Rev Infect Dis 1981;3 Suppl:S108-S112.

[30] Torres A, Bonanni P, Hryniewicz W, et al. Pneumococcal vaccination: what have we learnt so far and what can we expect in the future? Eur J Clin Microbiol Infect Dis 2015;34(1):19-31.

[31] Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: opportunities for prevention in the conjugate vaccine era. JAMA 2001;285(13):1729-35.

[32] Hausdorff WP, Bryant J, Paradiso PR, et al. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. Clin Infect Dis 2000;30(1):100-21.

[33] Hausdorff WP, Bryant J, Kloek C, et al. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. Clin Infect Dis 2000;30(1):122-40.

[34] Nuorti JP, Whitney CG. Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2010;59(RR-11):1-18.

[35] Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the Pneumococcal Global Serotype Project. PLoS Med 2010;7(10):1-13.

[36] Richter SS, Heilmann KP, Dohrn CL, et al. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States, 1999-2011. Emerg Infect Dis 2013;19(7):1074-83.

[37] Black SB, Shinefield HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J 2002;21(9):810-5.

[38] Hansen J, Black S, Shinefield H, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. Pediatr Infect Dis J 2006;25(9):779-81.

[39] Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005;365(9465):1139-46.

[40] Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001;344(6):403-9.

[41] O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet 2003;362(9381):355-61.

[42] Klugman KP, Madhi SA, Huebner RE, et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003;349(14):1341-8.

[43] Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010;201(1):32-41.

[44] Reinert RR, Paradiso P, Fritzell B. Advances in pneumococcal vaccines: the 13-valent pneumococcal conjugate vaccine received market authorization in Europe. Expert Rev Vaccines 2010;9(3):229-36.

[45] Bonten MJM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 2015;372(12):1114-25.

[46] Centers for Disease Control and Prevention. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children – Advisory

Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep 2010;59(9):258-61.

[47] Centers for Disease Control and Prevention. Licensure of 13-valent pneumococcal conjugate vaccine for adults aged 50 years and older. MMWR Morb Mortal Wkly Rep 2012;61(21):394-5.

[48] Prevenar 13 Summary of product characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001104/WC500057247.pdf. Accessed: 12 Sep 2016.

[49] European Medicines Agency. Prevenar 13 assessment report. 22 Jan 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001104/WC500186805.pdf. Accessed: 12 Sep 2016.

[50] Ministry of Health, Labour Welfare. Preventive vaccination law (2013) https://elaws.e-gov.go.jp/search/elawsSearch/elaws_search/lsg0500/detail?lawId=323AC0000000068. Accessed: 5 Jun 2020.

[51] World Health Organization. WHO prequalified vaccines. Pneumococcal (conjugate). Prevenar 13. Available from: https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=221. Effective:20 Aug 2010. Accessed: 12 Sep 2016.

[52] World Health Organization. WHO prequalified vaccines. Pneumococcal (conjugate). Prevenar 13 multidose vial. Available from: https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=317. Effective:14 Jul 2016. Accessed: 12 Sep 2016.

[53] Harboe ZB, Dalby T, Weinberger DM, et al. Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality [erratum appears in Clin Infect Dis 2014;59(12):1812]. Clin Infect Dis 2014;59(8):1066-73.

[54] Steens A, Bergsaker MA, Aaberge IS, et al. Prompt effect of replacing the 7-valent pneumococcal conjugate vaccine with the 13-valent vaccine on the epidemiology of invasive pneumococcal disease in Norway. Vaccine 2013;31(52):6232-8.

[55] Miller E, Andrews NJ, Waight PA, et al. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. Vaccine 2011;29(49):9127-31.

[56] Cohen R, Biscardi S, Levy C. The multifaceted impact of pneumococcal conjugate vaccine implementation in children in France between 2001 to 2014. Hum Vaccines Immunother 2016;12(2):277-84.

[57] Cohen R, Levy C, Bingen E, et al. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal nasopharyngeal carriage in children with acute otitis media. Pediatr Infect Dis J 2012;31(3):297-301.

[58] Flasche S, Van Hoek AJ, Sheasby E, et al. Effect of pneumococcal conjugate vaccination on serotype-specific carriage and invasive disease in England: a cross-sectional study. PLoS Med 2011;8(4):e1001017.

[59] Williams SR, Mernagh PJ, Lee MHT, et al. Changing epidemiology of invasive pneumococcal disease in Australian children after introduction of a 7-valent pneumococcal conjugate vaccine. Med J Aust 2011;194(3):116-20.

[60] Munoz-Almagro C, Ciruela P, Esteva C, et al. Serotypes and clones causing invasive pneumococcal disease before the use of new conjugate vaccines in Catalonia, Spain. J Infect 2011;63(2):151-62.

[61] Norton NB, Stanek RJ, Mufson MA. Routine pneumococcal vaccination of children provokes new patterns of serotypes causing invasive pneumococcal disease in adults and children. Am J Med Sci 2013;345(2):112-20.

[62] Adam HJ, Karlowsky JA, Nichol KA, et al. Baseline epidemiology of *Streptococcus pneumoniae* serotypes in Canada prior to the introduction of the 13-valent pneumococcal vaccine. Microb Drug Resist 2012;18(2):176-82.

[63] Harboe ZB, Thomsen RW, Riis A, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. PLoS Med 2009;6(5):e1000081.

[64] Wroe PC, Lee GM, Finkelstein JA, et al. Pneumococcal carriage and antibiotic resistance in young children before 13-valent conjugate vaccine. Pediatr Infect Dis J 2012;31(3):249-54.

[65] Cohen R, Varon E, Doit C, et al. A 13-year survey of pneumococcal nasopharyngeal carriage in children with acute otitis media following PCV7 and PCV13 implementation. Vaccine 2015;33(39):5118-26.

[66] Tomczyk S, Lynfield R, Schaffner W, et al. Prevention of antibiotic-nonsusceptible invasive pneumococcal disease with the 13-valent pneumococcal conjugate vaccine. Clin Infect Dis 2016;62(9):1119-25.

[67] Richter SS, Diekema DJ, Heilmann KP, et al. Changes in pneumococcal serotypes and antimicrobial resistance after introduction of the 13-valent conjugate vaccine in the United States. Antimicrob Agents Chemother 2014;58(11):6484-9.

[68] Demczuk WHB, Martin I, Griffith A, et al. Serotype distribution of invasive *Streptococcus pneumoniae* in Canada after the introduction of the 13-valent pneumococcal conjugate vaccine, 2010–2012. Can J Microbiol 2013;59(12):778-88.

[69] Cohen R, Cohen JF, Chalumeau M, et al. Impact of pneumococcal conjugate vaccines for children in high- and non-high-income countries. Expert Rev Vaccines 2017;16(6):625-40.

[70] Balsells E, Guillot L, Nair H, et al. Serotype distribution of *Streptococcus pneumoniae* causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis. PloS One 2017;12(5):e0177113.

[71] Golden AR, Adam HJ, Zhanel GG. Invasive *Streptococcus pneumoniae* in Canada, 2011–2014: characterization of new candidate 15-valent pneumococcal conjugate vaccine serotypes 22F and 33F. Vaccine 2016;34(23):2527-30.

[72] Metcalf BJ, Gertz RE Jr, Gladstone RA, et al. Strain features and distributions in pneumococci from children with invasive disease before and after 13-valent conjugate vaccine implementation in the USA. Clin Microbiol Infect 2016;22(1):60.e9-.e29.

[73] Waight PA, Andrews NJ, Ladhani SN, et al. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis 2015;15(5):535-43.

[74] van der Linden M, Falkenhorst G, Perniciaro S, et al. Effects of infant pneumococcal conjugate vaccination on serotype distribution in invasive pneumococcal disease among children and adults in Germany. PLoS One 2015;10(7):e0131494.

[75] Beall B, Chochua S, Gertz RE Jr, et al. A population-based descriptive atlas of invasive pneumococcal strains recovered within the US during 2015-2016 [online supplementary material]. Front Microbiol 2018;9:2670. Available from: https://www.frontiersin.org/articles/10.3389/fmicb.2018.02670/full#supplementarymaterial. Accessed: 03 Oct 2019.

[76] Togashi T, Yamaji M, Thompson A, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in healthy infants in Japan. Pediatr Infect Dis J 2013;32:984-9.

[77] Togashi T, Okada K, Yamaji M, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine given with DTaP vaccine in healthy infants in Japan. Pediatr Infect Dis J 2015;34:1096-104.

[78] US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.

Document Approval Record

Document Name:	B7471016_Clinical Protocol_09-Jun-2020
Document Title:	A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20 VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY JAPANESE INFANTS

Signed By:	Date(GMT)	Signing Capacity
PPD		Final Approval
PPD		Final Approval