A PHASE 3, RANDOMIZED, PARTIALLY DOUBLE-BLIND TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY TODDLERS 12 THROUGH 23 MONTHS OF AGE WITH 2 PRIOR INFANT DOSES OF PREVENAR 13

Study Intervention Number:	PF-06482077
Study Intervention Name:	20-valent pneumococcal conjugate vaccine (20vPnC)
US IND Number:	CCI
EudraCT Number:	CCI
ClinicalTrials.gov ID:	TBD
Protocol Number:	B7471027
Phase:	3

Brief Title: Safety and Immunogenicity of 20vPnC in Toddlers With 2 Prior Doses of Prevenar 13

Document History

Document	Version Date
Original protocol	10 December 2021

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Pfizer is developing a new 20-valent pneumococcal conjugate vaccine (20vPnC) to expand protection against pneumococcal disease beyond that covered by current pneumococcal vaccines in toddlers. 20vPnC has the same composition as 13vPnC (Prevenar 13®), but 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. Phase 2 safety and immunogenicity data in infants support further development of 20vPnC in the pediatric population.

This Phase 3, multicenter, randomized, partially double-blind study will be conducted at investigator sites in Europe. The purpose of this study is to describe the safety and immunogenicity of 1 or 2 doses of 20vPnC administered to European toddlers ≥12 to <24 months of age who have received 2 doses of 13vPnC in infancy (prior to 12 months of age and >56 days prior to vaccination in this study). A single dose of 13vPnC will serve as the control vaccine.

Approximately 360 toddlers ≥12 to <24 months of age at the time of consent, who previously received 2 infant doses of 13vPnC (prior to 12 months of age), will be enrolled and randomized in a 1:1:1 ratio to receive either 1 or 2 doses of 20vPnC or 1 dose of 13vPnC (control). The vaccine in toddlers randomized to receive 1 dose will be double-blind, as 20vPnC and 13vPnC have the same appearance and a single dose will be administered at Visit 1 of the study. For participants randomized to receive 2 doses of 20vPnC, the parents/legal guardians and site staff will know the randomization assignment for these participants, as the participant will need to return for a second vaccination visit and will receive 20vPnC at both Visit 1 and Visit 2.

Blood will be drawn from all participants for immunogenicity assessments before administration of study intervention and 1 month after the vaccination (last vaccination in the group receiving 2 doses) in each group.

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 and SAEs will be collected from the time the participant's parent(s)/legal guardian(s) provides informed consent through 1 month after the dose (last dose in the group receiving 2 doses) of 20vPnC or 13vPnC.

Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary Safety Objective	**Primary Safety Endpoints**	**Primary Safety Estimands**
• To describe the safety profile of 20vPnC	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs	In participants receiving at least 1 dose of study intervention with safety follow-up after the assigned vaccination: • The percentage of participants reporting prompted local reactions within 7 days after the last assigned vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after the last assigned vaccination in each group • The percentage of participants reporting AEs within 1 month after the last assigned vaccination in each group • The percentage of participants reporting SAEs within 1 month after the last assigned vaccination in each group
Primary Immunogenicity Objective	**Primary Immunogenicity Endpoint**	**Primary Immunogenicity Estimand**
• To describe the immune responses to the additional 7 serotypes after 1 or 2 doses of 20vPnC	• Pneumococcal serotype-specific IgG concentration	In participants complying with the key protocol criteria (evaluable participants) in each group: • Percentages of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes 1 month after the last assigned vaccination

Objectives	Endpoints	Estimands
Secondary Immunogenicity Objective	**Secondary Immunogenicity Endpoints**	**Secondary Immunogenicity Estimands**
• To further describe the immune response of 20vPnC after 1 or 2 doses	• Pneumococcal serotype-specific IgG concentration • Pneumococcal serotype-specific OPA titers	In evaluable participants in each group: • IgG GMCs for the vaccine serotypes 1 month after the last assigned vaccination • Percentages of participants with predefined IgG concentrations for the 13 matched serotypes 1 month after the last assigned vaccination • OPA GMTs for the vaccine serotypes 1 month after the last vaccination

Number of Participants

Approximately 360 (120 in each vaccination group) toddlers will be enrolled to reach a target of 315 evaluable participants (105 in each vaccination group).

The 360 toddlers who have been previously vaccinated with 2 doses of 13vPnC prior to 12 months of age will be enrolled in 3 vaccination groups:

- **2-Dose 20vPnC group**: Approximately 120 participants will receive 2 doses of 20vPnC.
- **1-Dose 20vPnC group**: Approximately 120 participants will receive 1 dose of 20vPnC.
- **13vPnC control group**: Approximately 120 participants will receive 1 dose of 13vPnC.

Duration of Participation for Each Participant

Each participant will participate in the study for approximately 1 or 3 months, if randomized to receive 1 dose or 2 doses, respectively.

CCI [redacted]

[redacted]

Statistical Methods

The primary safety objective will be evaluated by descriptive summary statistics for local reactions and systemic events after the last assigned vaccine, and AEs, including SAEs, for 1 month after the last assigned vaccine in each group.

The primary immunogenicity objective will be evaluated by descriptive summary statistics on the proportion of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) 1 month after the last assigned vaccination. Additionally, the percentages of participants with predefined serotype-specific IgG concentrations for the 13 matched serotypes, serotype-specific IgG GMCs, OPA [redacted]

CCI

the specified time points for each vaccine group to provide further characterization of the immune response.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

1.3.1. Schedule of Activities: 2-Dose 20vPnC Group

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section (Section 8) 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
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Follow-Up After Dose 2**
Visit Window (Days)	**Day 1**	**56 to 70 Days After Visit 1**	**28 to 42 Days After Visit 2**
Obtain informed consent	X		
Assign participant number via IRT	X		
Record demography	X		
Perform clinical assessment, including medical history[a]	X		
Record 13vPnC history	X		
Record nonstudy vaccinations	X	X	X
Record concomitant medications to treat SAEs only	X	X	X
Obtain prevaccination temperature (measured as appropriate for age)	X	X	
Review inclusion and exclusion criteria	X		
Review continued eligibility		X	X
Review temporary delay criteria	X	X	
Assign randomization number and study intervention container number via the IRT	X		
Obtain blood sample (~5 mL)	X[b]		X
Administer 20vPnC into the left thigh or left arm (as appropriate for the age and size of the child)	X	X	
If applicable, administer and record routine pediatric vaccinations[c]	X	X	

Visit Number	1	2	3
Visit Description	**Dose 1 Visit**	**Dose 2 Visit**	**Follow-Up After Dose 2**
Visit Window (Days)	**Day 1**	**56 to 70 Days After Visit 1**	**28 to 42 Days After Visit 2**
Observe and record acute reactions for 30 minutes after study intervention administration	X	X	
Provide parent(s)/legal guardian(s) with participant contact card	X		
Provide parent(s)/legal guardian(s) with an e-diary (or assist with application download to a personal device), thermometer, and measuring device and instruct to collect prompted local reactions, systemic events, and antipyretic/pain medication until 7 days after each 20vPnC vaccination[d]	X	X	
Review and/or collect e-diary (as applicable)[e]		X	X
Record and report AEs and SAEs	X----------X		

Abbreviation: IRT = interactive response technology.

a. If deemed necessary as part of the clinical assessment, the physical examination may include assessments of the general appearance, skin, head, lymph nodes, cardiovascular, respiratory, gastrointestinal, and neurological systems.
b. Blood sample will be collected before vaccination.
c. Administer permitted routine pediatric vaccinations (as applicable) after the study vaccination into a limb other than the site of the 20vPnC injection. Prohibited and permitted vaccines are described in Section 6.8.1 and Section 6.8.2, respectively.
d. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences severe redness or swelling >14 caliper units, severe pain at the 20vPnC injection site, a fever >40.0°C, or an emergency room visit or hospitalization.
e. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following each dose of 20vPnC to evaluate participant compliance and as part of the ongoing safety review.

1.3.2. Schedule of Activities: 1-Dose 20vPnC Group and 13vPnC (Control) Group

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section (Section 8) 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
Visit Description	**Dose 1 Visit**	**Follow-Up After Dose 1**
Visit Window (Days)	**Day 1**	**28-42 Days After Dose 1**
Obtain informed consent	X	
Assign participant number via IRT	X	
Record demography	X	
Perform clinical assessment, including medical history[a]	X	
Record 13vPnC history	X	
Record nonstudy vaccinations	X	X
Record concomitant medications to treat SAEs only	X	X
Obtain prevaccination temperature (measured as appropriate for age)	X	
Review inclusion and exclusion criteria	X	
Review continued eligibility		X
Review temporary delay criteria	X	
Assign randomization number and study intervention container number via the IRT	X	
Obtain blood sample (~5 mL)	X[b]	X
Administer 13vPnC or 20vPnC into the left thigh or left arm (as appropriate for the age and size of the child)	X	
If applicable, administer and record routine pediatric vaccinations[c]	X	
Observe and record acute reactions for 30 minutes after study intervention administration	X	
Provide parent(s)/legal guardian(s) with participant contact card	X	

Visit Number	1	2
Visit Description	**Dose 1 Visit**	**Follow-Up After Dose 1**
Visit Window (Days)	**Day 1**	**28-42 Days After Dose 1**
Provide parent(s)/legal guardian(s) with an e-diary (or assist with application download to a personal device), thermometer, and measuring device and instruct to collect prompted local reactions, systemic events, and antipyretic/pain medication until 7 days after 20vPnC or 13vPnC vaccination[d]	X	
Review and/or collect e-diary[e]		X
Record and report AEs and SAEs	X ---------- X	

Abbreviation: IRT = interactive response technology.

a. If deemed necessary as part of the clinical assessment, the physical examination may include assessments of the general appearance, skin, head, lymph nodes, cardiovascular, respiratory, gastrointestinal, and neurological systems.
b. Blood sample will be collected before vaccination.
c. Administer permitted routine pediatric vaccinations (as applicable) after the study vaccination into a limb other than the site of the 20vPnC or 13vPnC injection. Prohibited and permitted vaccines are described in Section 6.8.1 and Section 6.8.2, respectively.
d. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences severe redness or swelling >14 caliper units, severe pain at the 20vPnC or 13vPnC injection site, a fever >40.0°C, or an emergency room visit or hospitalization.
e. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following 20vPnC or 13vPnC vaccination to evaluate participant compliance and as part of the ongoing safety review.

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.[1,2,3] Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk.[4] Individuals with certain comorbidities and immunocompromising conditions are also at risk, especially persons with chronic heart, lung, liver, and renal disease, as well as those who are functionally asplenic. The global burden of pneumococcal disease has been substantially impacted by pneumococcal conjugate vaccines. Between 2010 and 2019, an estimated 175 million cases of pneumococcal disease and 625,000 deaths worldwide have been prevented by 13vPnC in children <5 years of age according to global modeling studies.[5] *S pneumoniae* caused an estimated 14.5 million cases of serious disease and 826,000 deaths annually in children <5 years of age prior to introduction of pneumococcal conjugate vaccines.[2] 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 US 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] However, disease due to serotypes not covered by those vaccines remains and causes significant morbidity and mortality. Remaining pneumococcal disease due to 20vPnC serotypes was estimated for 13 countries to be between 46% and 77% in a recent analysis, corresponding to approximately 1.23 million cases, 160 deaths, and $214 million in direct medical costs annually across the 13 included countries.[8]

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 that 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.[9] 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.[10] 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.[11,12] 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. 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%).[13] 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 US in both children and adults.[14,15] 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.[14,16]

Surveillance reported in 2017 by the ECDC showed that among cases of IPD for which the clinical presentation was known across all age groups, septicemia was reported in 35%, bacteremic pneumonia in 42%, meningitis in 19%, meningitis and septicemia in 1%, and other clinical syndromes in 3% of cases. The most common clinical presentations in children <5 years of age were septicemia and bacteremic pneumonia equally (1-4 years of age) and meningitis (<1 year of age).[10] Data from nationwide surveillance networks in France for the year 2012 showed the rate of IPD among children <2 years of age to be 17.2 per 100,000 population, with the incidence of pneumococcal meningitis among children <2 years of age to be 4.5 per 100,000 population. Of note, meningitis comprised 26.4%, 7.8%, and 19.6% of all cases of IPD in children <2 years of age, 2 through 4 years of age, and 5 through 15 years of age, respectively.[17] The relatively high rates of meningitis among these pediatric populations are of particular concern not only because of the severity of the acute disease, but also because of the neurological sequelae that are frequently associated with meningitis. These data suggest that *S pneumoniae* remains an important cause of serious disease in the US and worldwide.

S pneumoniae is one of the common bacterial causes of AOM.[18,19] 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 hearing loss with potential developmental and language delays, to invasive extension leading to mastoiditis and meningitis.[20]

Although the introduction of pneumococcal conjugate vaccines into the US and other national infant immunization programs worldwide 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 the morbidity and mortality caused by pneumococcal disease.

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.[21,22] Anticapsular antibodies directed against the specific serotype bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.[23] Pneumococcal disease can be prevented with polysaccharide-based vaccines that induce antibody responses with functional (opsonophagocytic) activity and target the capsular serotypes responsible for disease.[24]

Vaccines containing free polysaccharides have been licensed since the 1970s. One such vaccine, PPSV23, has been licensed in the US since 1983.[25,26] 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.[4,26,27,28] Moreover, their ability to prevent nonbacteremic pneumonia, CAP, and AOM is limited or lacking.[24,28,29,30,31] In addition, polysaccharide vaccines do not reduce VT nasopharyngeal carriage, which is important for herd immunity.[31] 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.[24]

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.[27,32] 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 US and approximately 60% to 80% of IPD in the same age group in Europe at that time (1998-2000).[33,34,35,36,37] These serotypes also accounted for a high proportion of antibiotic-resistant strains.[38] 7vPnC demonstrated efficacy against VT IPD, pneumonia, and AOM in large randomized, controlled efficacy studies in infants.[39,40]

The 7vPnC components contained in a related pneumococcal conjugate vaccine also were demonstrated to be efficacious against clinically/radiographically defined pneumonia.[41,42,43,44] 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.[45]

13vPnC was developed to expand serotype coverage and was licensed in the US in 2010. In the EU, 13vPnC was initially indicated for use in infants from 6 weeks to 5 years of age, but the indication was later expanded to include children and adolescents up to 17 years of age. 13vPnC includes the same *S pneumoniae* serotypes as 7vPnC and an additional 6 polysaccharide conjugates for serotypes 1, 3, 5, 6A, 7F, and 19A.[32,36,46] The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific serum IgG antibody concentrations to the serotypes in 7vPnC, with supportive data to demonstrate the functional activity of the immune responses. 13vPnC was later licensed in adults based on demonstration of efficacy against CAP due to serotypes contained in 13vPnC in adults 65 years of age and older.[47] 13vPnC has replaced 7vPnC and is licensed in the US and many other countries, with national recommendations for use in children and older adults.[48,49,50,51] It has also been prequalified by the WHO for use in national infant immunization programs in lower- and middle-income countries.[52,53] 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.[54,55,56]

Development of 20vPnC

20vPnC 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 20vPnC mirrors the approach taken for the addition of the 6 new serotypes when developing 13vPnC. 20vPnC 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 the pediatric population and is licensed for adults in the US.

2.1. Study Rationale

The purpose of the study is to assess safety and immunogenicity data with 1 or 2 doses of 20vPnC in toddlers ≥12 to <24 months of age who have received 2 doses of 13vPnC in infancy (prior to 12 months of age), CCI [redacted]

2.2. Background

20vPnC is being developed to further expand protection against the global burden of vaccine-preventable pneumococcal disease in children over that of 13vPnC. 20vPnC was licensed for adults in the US in June 2021, and as of October 2021 is under review by the CHMP in Europe. 20vPnC contains the serotypes present in 13vPnC and 7 additional 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 7vPnC and 13vPnC. These 7 additional serotypes were selected based on their relative prevalence as a cause of IPD, their generalized geographic distribution, and other factors that would support inclusion, such as the presence of antibiotic resistance (11A, 15B), association with outbreaks (8, 12F), and greater disease severity, eg, meningitis, mortality (10A, 11A, 22F).[57,58,59,60,61,62,63,64,65,66,67,68] 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.[69,70,71,72,73,74,75] These 7 serotypes contribute significantly to the burden of IPD in the US and elsewhere. It is estimated that between 2015 and 2016, these 7 serotypes accounted for 34% to 39% of IPD in children in the US.[76] In the EU, according to the ECDC annual IPD epidemiological report, in 2017, approximately 75% of cases in children <5 years of age were caused by a serotype not in 13vPnC, increasing 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.[10]

2.2.1. Clinical Overview

Safety and immunogenicity data from Phase 1, Phase 2, and Phase 3 studies in more than 5000 adults receiving 20vPnC have shown that 20vPnC has a safety and immunogenicity profile similar to 13vPnC.

Additionally, a Phase 2 study (B7471003) of 20vPnC in healthy infants was performed. In the study, 460 US infants ≥42 to ≤98 days of age were randomized to receive either blinded 20vPnC or 13vPnC at 2, 4, 6, and 12 months of age.

20vPnC was well tolerated in the study, with a safety profile 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 and 4 doses of 20vPnC were similar to those in the 13vPnC group. These data supported Phase 3 studies in infants, toddlers, children, and adolescents. The ongoing Phase 3 pediatric studies are described in the 20vPnC IB.

2.3. Benefit/Risk Assessment

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). 20vPnC contains the same components and excipients as 13vPnC, along with 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 20vPnC.

In a randomized, active-controlled, double-blind study with a 2-arm parallel design (B7471003), 20vPnC was administered to 460 infants ≥42 to ≤98 days of age naïve to pneumococcal vaccine. The vaccine was well tolerated and the AE profile was consistent with events commonly seen in this age group and similar to those seen in the 13vPnC group. The most common AEs after 20vPnC administration were local reactions (pain, redness, and swelling at the injection site) and systemic events (fever, irritability, drowsiness/increased sleep, and decreased appetite).

As with any vaccine, an allergic reaction can occur. The allergic reaction can vary from a 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.

Safety assessments 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.

13vPnC is approved for the prevention of pneumococcal disease due to the serotypes in the vaccine. 20vPnC was licensed for adults in the US in June 2021 for the prevention of pneumococcal pneumonia and IPD, and as of October 2021 is under review by the CHMP in Europe. Both vaccines may provide a clinical benefit to those receiving it.

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 in the pediatric population, it is anticipated to provide a public health benefit by reducing the burden of pneumococcal disease (invasive and noninvasive) due to vaccine serotypes.

Pfizer considers that the available information from Study B7471003 with 20vPnC, the available safety profile of similar pneumococcal conjugate vaccines (ie, 7vPnC and 13vPnC), and the limited risks from study procedures support a favorable benefit-risk profile for 20vPnC and this study.

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 control is the EU SmPC.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): 20vPnC and 13vPnC		
Local reactions to the vaccine (injection site pain or tenderness, redness, and swelling) and systemic events (fever, irritability, decreased appetite, and increased sleep) may occur.	13vPnC is a licensed vaccine and used in infants and children for immunization globally. 20vPnC contains the same components and excipients as 13vPnC, but also contains the polysaccharide conjugates for the 7 additional pneumococcal serotypes. Thus, the AE profile of 20vPnC is expected to be similar to that of 13vPnC.	The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call, and visit if required, to be conducted per protocol. All study participants will be observed for at least 30 minutes after vaccination.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure appropriate COVID-19 prevention strategies.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel will perform blood draws. The volume and frequency of blood sample collection required during the study has been minimized as much as possible.

2.3.2. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with 20vPnC, and 13vPnC (licensed for infants and children globally), are justified by the anticipated benefits that may be afforded to healthy toddler participants.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary Safety Objective	**Primary Safety Endpoints**	**Primary Safety Estimands**
• To describe the safety profile of 20vPnC	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs	In participants receiving at least 1 dose of study intervention with safety follow-up after the assigned vaccination: • The percentage of participants reporting prompted local reactions within 7 days after the last assigned vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after the last assigned vaccination in each group The percentage of participants reporting AEs within 1 month after the last assigned vaccination in each group • The percentage of participants reporting SAEs within 1 month after the last assigned vaccination in each group
Primary Immunogenicity Objective	**Primary Immunogenicity Endpoint**	**Primary Immunogenicity Estimand**
• To describe the immune responses to the additional 7 serotypes after 1 or 2 doses of 20vPnC	Pneumococcal serotype-specific IgG concentration	In participants complying with the key protocol criteria (evaluable participants) in each group: • Percentages of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes 1 month after the last assigned vaccination

Objectives	Endpoints	Estimands
Secondary Immunogenicity Objective	**Secondary Immunogenicity Endpoints**	**Secondary Immunogenicity Estimands**
• To further describe the immune response of 20vPnC after 1 or 2 doses	• Pneumococcal serotype-specific IgG concentration • Pneumococcal serotype-specific OPA titers	In evaluable participants in each group: • IgG GMCs for the vaccine serotypes 1 month after the last assigned vaccination • Percentages of participants with predefined IgG concentrations for the 13 matched serotypes 1 month after the last assigned vaccination • OPA GMTs for the vaccine serotypes 1 month after the last assigned vaccination
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This Phase 3, multicenter, randomized, partially double-blind study will be conducted at investigator sites in Europe. The purpose of this study is to provide safety and immunogenicity data with 20vPnC in European toddlers ≥12 to <24 months of age who have received 2 doses of 13vPnC in infancy (prior to 12 months of age) and who will receive 1 or 2 doses of 20vPnC during the study. 13vPnC will serve as the control.

Approximately 360 toddlers ≥12 to <24 months of age at the time of consent, who previously received 2 infant doses of 13vPnC (prior to 12 months of age), will be enrolled and randomized in a 1:1:1 ratio to receive either 1 or 2 doses of 20vPnC, or 1 dose of 13vPnC (control). The vaccine in toddlers randomized to receive 1 dose will be double-blind, as 20vPnC and 13vPnC have the same appearance and a single dose will be administered at Visit 1 of the study. For participants randomized to 2 doses of 20vPnC, the parents/legal guardians and site staff will know that these participants will need to return for a second vaccination visit and that they will receive 20vPnC at both Visit 1 and Visit 2. The last assigned vaccinations will be the single vaccination at Visit 1 in the groups randomized to receive 1 dose of 20vPnC or 13vPnC (control) and the second vaccination given at Visit 2 in the group randomized to receive 2 doses.

On Day 1 (Visit 1) of the study, participants will be assessed for eligibility and information will be collected, including medical history and 13vPnC history.

Participants will receive 20vPnC or 13vPnC. Participants will be observed for 30 minutes after vaccination, and any reactions occurring during that time will be recorded as AEs. The participant's 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 (redness, swelling, and pain at the injection site) and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) occurring within 7 days after each vaccination. The use of antipyretic/pain medications will also be prompted for and collected daily in the 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 fever >40.0°C or has an emergency room visit or hospitalization.

Blood will be drawn from all participants for immunogenicity assessments before administration of study intervention and 1 month after the vaccination (last vaccination in the group receiving 2 doses) in each vaccine group.

Participants in the 2-dose 20vPnC group will return 56 to 70 days after Visit 1 for Visit 2. Participants will be assessed for continued eligibility and information will be collected from the participant's parent(s)/legal guardian(s) on AEs, including nonserious AEs and SAEs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs will be recorded, as will information on nonstudy vaccinations given since the last visit. No blood will be drawn before Dose 2. Dose 2 of 20vPnC (0.5 mL) will be administered and participants observed for 30 minutes after vaccination. The remainder of the visit and instructions to the parents/legal guardians will be done as in Visit 1.

Participants in the 1-dose 20vPnC group and 13vPnC (control) group will return 28 to 42 days after Visit 1 (Visit 2) and participants in the 2-dose 20vPnC group will return 28 to 42 days after Visit 2 (Visit 3) for their follow-up visits. Information will be collected from the participant's parent(s)/legal guardian on AEs, SAEs, and e-diary follow-up (as needed), as described above for Visit 2 for the 2-dose 20vPnC group. Participants will have blood

drawn for immunogenicity assessment. Other licensed nonstudy vaccines may be administered after the blood draw at this visit.

In the case of extreme circumstances, such as natural disasters or a pandemic, visits for follow-up or procedures may need to be conducted through other means (eg, telephone calls).

4.1.1. Approximate Duration of Participation for Each Participant

Each participant will participate in the study for approximately 1 to 3 months, depending on randomization.

4.1.2. Approximate Number of Participants

Approximately 360 (120 in each vaccination group) participants will be enrolled to reach a target of 315 evaluable participants (105 in each vaccination group).

The 360 participants who have been previously vaccinated with 2 doses of 13vPnC prior to 12 months of age will be enrolled in 3 vaccination groups:

- **2-Dose 20vPnC group:** Approximately 120 participants will receive 2 doses of 20vPnC.
- **1-Dose 20vPnC group:** Approximately 120 participants will receive 1 dose of 20vPnC.
- **13vPnC (control) group:** Approximately 120 participants will receive 1 dose of 13vPnC.

4.2. Scientific Rationale for Study Design

This Phase 3, multicenter, randomized, partially double-blind study will be conducted at investigator sites in Europe. CCI The purpose of this study is to describe the safety and immunogenicity of 1 or 2 vaccinations administered to toddlers ≥12 to <24 months of age who received 2 doses of 13vPnC in infancy (prior to 12 months of age and >56 days prior to vaccination in this study). A single dose of 13vPnC will serve as the control vaccine.

4.3. Justification for Dose

20vPnC 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. This study uses a schedule of 1 dose or 2 doses of pneumococcal conjugate vaccine administered in toddlers ≥12 to <24 months of age. These schedules have been used with 13vPnC (in unvaccinated children [2-dose schedule] in this age group, and children who have begun their series with 2 prior infant doses of 7vPnC [1-dose schedule]), and are included in the 13vPnC SmPC.

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. Male or female toddlers ≥12 to <24 months of age at the time of consent.

Informed Consent:

2. 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.

Type of Participant and Disease Characteristics:

3. Participant has received exactly 2 infant doses of 13vPnC prior to 12 months of age confirmed by written documentation. The last dose of 13vPnC must have been administered >56 days before enrollment into the study.

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

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

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

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 13vPnC, 20vPnC, or any diphtheria toxoid–containing vaccine.

2. Significant neurological disorder or history of seizure (excluding febrile seizure) or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders.

3. Major known congenital malformation or serious chronic disorder.

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

5. 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.

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

7. Congenital, functional, or surgical asplenia.

8. Other medical condition or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

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

10. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw. 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 study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

11. Receipt of blood/plasma products or immunoglobulins (including hepatitis B immunoglobulin) or planned receipt through the last planned blood draw in the study.

Prior/Concurrent Clinical Study Experience:

12. 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. An exception to this is an investigational vaccine authorized by the national regulatory agency for use in infants or toddlers to prevent pandemic disease. Participation in purely observational studies is acceptable.

Other Exclusions:

13. Children or grandchildren who are direct descendants of investigator site staff members or Pfizer employees who are directly involved in the conduct of the study.

Diagnostic Assessments:

Not applicable.

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 study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the 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 recorded from signing the informed consent until the time of determination of screen failures.

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

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

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

The blood draws prior to vaccination should take place on the same day as the vaccination.

5.5.1. Criteria for Temporarily Delaying Vaccine Administration

- Current febrile illness (eg, rectal temperature ≥38.0°C or other acute illness within 48 hours before study intervention administration.

- Receipt of any inactivated or otherwise nonlive vaccine within 14 days or any live vaccine within 28 days before study intervention administration, with the exceptions of: 1) influenza vaccine, which may be given at any time during the influenza season if the participant is of the appropriate age to receive it; and 2) permitted concomitant vaccines on the same day as study intervention (Section 6.8.1 and Section 6.8.2).

- Receipt of short-term (<14 days) systemic corticosteroids. Study intervention 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.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

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}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contains 5 mM succinate buffer, 150 mM sodium chloride, 0.02% polysorbate 80, and 125 µg aluminum as aluminum phosphate, per 0.5-mL dose.

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}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contains 295 µg succinate buffer, 0.85% sodium chloride, 100 µg polysorbate 80, and 125 µg aluminum as aluminum phosphate, per 0.5-mL dose.

CCI [redacted]

20vPnC and 13vPnC are both white suspensions and have a matching appearance, 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 IP manual).

6.1.1. Administration

Participants will receive either 1 or 2 doses of 20vPnC or 1 dose of 13vPnC in accordance with the study's SoA.

20vPnC and 13vPnC should be administered intramuscularly by injecting 0.5 mL into the anterolateral thigh muscle of the left leg or left arm (as appropriate for the age and size of the toddler) by a designated site staff member. All nonstudy vaccinations should be administered into a limb other than the site of the 20vPnC or 13vPnC injection. The location of the injection of each vaccine administered (study intervention and other vaccinations) will be recorded on the CRF.

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, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.1.2. Medical Devices

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

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

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the study personnel throughout the study. Please refer to Section 8.3.9 for details.

6.2. Preparation, Handling, Storage, and Accountability

1. CCI [redacted]

2. 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.

CCI

CCI

CCI [redacted]

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

CCI [redacted]

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention 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

Allocation of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's 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's files.

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. Breaking the Blind

Toddlers randomized to receive 1 dose of 20vPnC or 13vPnC (control) at Visit 1 will be participants in the double-blind portion of the study, as the vaccines have the same appearance. For toddlers randomized to 2 doses of 20vPnC, the parent(s)/legal guardian(s) and site staff will know that these toddlers will receive 20vPnC at both Visit 1 and Visit 2.

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

6.3.3. Blinding of the Sponsor

Sponsor personnel directly involved in evaluating participant data will be blinded to vaccine assignment of both 1-dose groups (1-dose 20vPnC and 1-dose 13vPnC groups) until the final analysis of the study, following the principles outlined in the ICH E9 guideline on Statistical Principles for Clinical Trials.[77] A data blinding plan will be created to describe the blinding requirements and unblinding events. Laboratory personnel performing the immunologic assays will be blinded to vaccine assignment of all 3 groups until all assays have been completed and assay results finalized.

6.4. Study Intervention Compliance

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

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention After the End of the Study

No intervention will be provided to study participants at the end of their study participation.

6.7. Treatment of Overdose

For this study, more than 1 dose of study intervention 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 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 Pfizer 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.

6.8. Concomitant Therapy

6.8.1. Prohibited Concomitant Vaccines and Treatments

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during study participation. See the one exception to this in Section 6.8.2 below.
- Receipt of nonstudy pneumococcal vaccine is prohibited during study participation.
- Topical anesthetic at the site of vaccination is prohibited.
- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a ≥14-day course of systemic corticosteroids) is prohibited through Visit 3 for participants in the 2-dose 20vPnC group and through Visit 2 for participants in the 1-dose 20vPnC group and 13vPnC (control) group.

6.8.2. Permitted Concomitant Vaccines and Treatments

- Licensed inactivated influenza vaccine may be given at any time during the study per national recommendations. If administered concomitantly, these vaccines must be injected into a limb other than the site of the 20vPnC or 13vPnC injection.
- Investigational vaccines authorized by the national regulatory agency for use in infants or toddlers to prevent pandemic disease.
- Receipt of meningococcal conjugate vaccines is permitted only after the last blood sample is collected in each vaccination group.
- Receipt of other licensed nonstudy vaccines (except pneumococcal and meningococcal vaccines described above) is permitted. However, if feasible, it is recommended that licensed nonstudy vaccines be administered at least 14 days (for nonlive vaccines) or at least 28 days (for live vaccines) before or after 20vPnC or 13vPnC administration. Measles, mumps, and rubella and varicella vaccines can be administered concomitantly into a limb other than the site of the 20vPnC or 13vPnC injection.
- The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of study intervention administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.
- Topical anesthetic at the site of blood draw is permitted.

- 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.

6.8.3. Recording Prior and Concomitant Vaccines and Treatments

The name and date of administration of the 2 infant doses of 13vPnC given prior to 12 months of age will be collected and recorded in the CRF. The name(s) and date(s) of administration are to be obtained from sources, such as medical records or vaccination cards.

The name and date of administration for all nonstudy vaccinations received should be collected from the time of signing of the ICD to the last study visit and will be recorded in the CRF.

Medications taken to treat SAEs from the signing of the ICD to the final visit will be recorded on the CRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: AEs, participant's parent(s)'/legal guardian(s)' request, investigator request, and protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria).

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, and the participant's parent(s)/legal guardian(s) consents, the participant will remain in the study and AEs and SAEs will be collected for 1 month after the last (most recent) study vaccination. See the SoAs (Section 1.3.1 and Section 1.3.2) for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, postvaccination study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her parent(s)'/legal guardian(s)' request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant's parent(s)/legal guardian withdraws the participant from the study, the parent(s)/legal guardian(s) may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant's parent(s)/legal guardian withdraws the participant from the study and 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.

7.2.1. Withdrawal of Consent

A participant whose parent(s)/legal guardian(s) 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's parent(s)/legal guardian(s) to provide this information. A 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 postvaccination 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 attend 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, counsel the participant's parent(s)/legal guardian(s) on the importance of maintaining the assigned visit schedule, and ascertain whether the participant's parent(s)/legal guardian(s) wishes 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 withdrawn from the study.

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 SoAs (Section 1.3.1 and Section 1.3.2). Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the SoAs, 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 10 mL.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Immunogenicity Assessments

Blood samples (approximately 5 mL per sample) will be collected from all participants prior to vaccination at Visit 1 for all groups, at Visit 2 for the 1-dose 20vPnC group and 13vPnC (control) group, and at Visit 3 for the 2-dose 20vPnC group. These are the immunogenicity time points.

Pneumococcal Responses

IgG responses to the 20 pneumococcal serotypes contained in 20vPnC

IgG concentrations for the 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 prior to vaccination at Visit 1 for all groups, at Visit 2 for the 1-dose 20vPnC group and 13vPnC (control) group, and at Visit 3 for the 2-dose 20vPnC group. The serotype-specific IgG concentrations will be measured by Pfizer's Luminex-based assay platform.

OPA responses to the 20 pneumococcal 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 randomly selected subsets of sera collected prior to vaccination at Visit 1 for all groups, at Visit 2 for the 1-dose 20vPnC group and 13vPnC (control) group, and at Visit 3 for the 2-dose 20vPnC group.

CCI

[redacted]

8.1.2. Biological Samples

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. CCI [redacted]

The participant's parent(s)/legal guardian(s) may request the participant's samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (see Section 1.3.1 and Section 1.3.2). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history and measurement of 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 on the CRF. Temperature measurement prior to vaccination will be documented and recorded on 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 local reactions (redness, swelling, and pain at the injection site), systemic events (fever, drowsiness/increased sleep, decreased appetite, and irritability), and use of pain/fever medication will be prompted for and collected by the participant's parent(s)/legal guardian(s) daily for 7 days after each study vaccination (where Day 1 is the day of vaccination) in an e-diary. These prompted e-diary events are graded as described in Section 8.2.3. AEs and SAEs will be collected as defined in Section 8.3.

AEs and SAEs will be recorded and reported from the time the participant's parent(s)/legal guardian(s) provides informed consent through 1 month after the last vaccination.

Causality and severity of AEs and SAEs will be assessed for all participants.

8.2.1. Physical Examinations

A targeted physical examination will not be conducted routinely, but only based on the clinical assessment at enrollment, or if needed to further assess the participant during the study. Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 2) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. 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 vaccination 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 withdraws because of prompted events reported in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

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

Designated site staff will review the 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 reported events as part of the ongoing safety review.

8.2.3. 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.

8.2.3.1. Local Reactions

For the first 7 days following each study vaccination (Day 1 through Day 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 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 1. 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 1. 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 SRM or equivalent.

Table 1. 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

Table 1. Grading Scales for Local Reactions

Local Reaction	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3[a] Severe	GRADE 4[b]
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.

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 in Section 8.3.

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.

8.2.3.2. Systemic Event Symptoms and Fever

8.2.3.2.1. Systemic Event Symptoms

For the first 7 days following each vaccination (Day 1 through Day 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 2. 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 SRM or equivalent.

Table 2. Grading Scales for Systemic Event Symptoms

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

Abbreviation: CRF = case report form.

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

8.2.3.2.2. 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 temperature at home. Temperature will be collected in the evening, daily, for 7 days following 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 ≥38.0°C. The highest temperature for each day will be recorded in the e-diary. In the event of a fever on the last day of diary collection, temperature will be collected daily until fever has resolved (1 day of temperature less than 38.0°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 8.9.3). 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 3.

Table 3. Ranges for Fever

≥38.0°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C

Note: Fever is defined as temperature ≥38.0°C.

8.2.3.2.3. 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 study intervention. The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of study intervention administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.

8.2.4. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 2.

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 4. Device deficiencies are covered in Section 8.3.9.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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 the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant's parent/legal guardian/legally authorized representative 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 study intervention), through the final visit. At the final visit the participant's parent(s)/legal guardian(s) will be asked to report any AEs and SAEs, including hospitalizations, that have occurred since the last visit.

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.

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 permanently 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 information on 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 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 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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.

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 2.

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 or 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 2.

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 toward 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, IRB/EC, 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 SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study is 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 EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, 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 ingestion, 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.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with

authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the Vaccine SAE Reporting Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be 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

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. **Lack of efficacy or failure of expected pharmacological action in an approved indication constitutes an SAE and should be reported to Pfizer Safety**.

8.3.9. Medical Device Deficiencies

Medical devices being provided for use in this study as the study interventions are supplied in prefilled syringes. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.4.3.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.3.1 through 8.3.4 and Appendix 2 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency 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 Section 10.4.4.

8.3.9.2. Follow-Up of Medical Device Deficiencies

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

The investigator 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 investigator.

8.3.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The investigator notifies the sponsor by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint form.

3. If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.3.1.1). All relevant details related to the role of the device in the event must be included in the Vaccine SAE Reporting Form as outlined in Section 8.3.1.1 and Section 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 investigator 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 investigator 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 study intervention 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.

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.

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.**

8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Genetics

8.5.1. Specified Genetics

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

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments as described in Section 8.1.

8.8. Health Economics

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

8.9. Study Procedures

The study procedures are summarized in the SoAs (see Section 1.3.1 and Section 1.3.2. The day of Vaccination 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.

8.9.1. 2-Dose 20vPnC Group

8.9.1.1. 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 as permitted per local regulations to critically evaluate the immune response and safety profile by age.

- Perform a clinical assessment including medical history; record any findings on the medical history CRF. If deemed necessary as part of the clinical assessment, the physical examination may include assessments of the general appearance, skin, head, lymph nodes, cardiovascular, respiratory, gastrointestinal, and neurological systems.

- Record receipt of 2 infant doses of 13vPnC (prior to 12 months of age), including dates given.

- Measure and record the participant's temperature as appropriate for the age of the toddler, according to routine local practice (°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 study intervention container number via the IRT. This must be the last step before proceeding. A site staff member will prepare the study intervention according to the IP manual.

After randomization:

- Collect a blood sample of approximately 5 mL for immunogenicity.

- Administer a single 0.5-mL injection of 20vPnC into the left anterolateral thigh or left arm (as appropriate for the age and size of the child).

- If applicable, administer routine pediatric vaccinations into a limb other than the site of the 20vPnC injection and capture all details of the concomitant vaccine given on the same day as study intervention administration, including the name, date of administration, and site of administration, on the CRF.

- 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.

- Issue the participant's parent(s)/legal guardian(s) a measuring device (caliper) to measure 20vPnC 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 through 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 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 parent(s)/legal guardian(s) with the participant contact card containing the study and investigator information (see Section 10.1.11).

- 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 20vPnC administration (before or after vaccination). If symptoms develop, the use of antipyretic/pain medication is allowed.

- 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.

8.9.1.2. Visit 2 (Dose 2 Visit: 56 to 70 Days After 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 5.5.1).

- Record nonstudy vaccinations administered since Visit 1, as described in Section 6.8.

- 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 and SAEs) 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 10.2, and record concomitant medications used to treat SAEs.

- Measure and record the participant's temperature as appropriate for the age of the toddler, according to routine local practice (°C).

- Administer a single 0.5-mL injection of 20vPnC into the left anterolateral thigh or left arm (as appropriate for the age and size of the child).

- If applicable, administer routine pediatric vaccinations into a limb other than the site of the 20vPnC injection and capture all details of the concomitant vaccine given on the same day as study intervention administration, including the name, date of administration, and site of administration, on the CRF.

After vaccination:

- 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.

- 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 through 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 injection site measuring >14 measuring device units (>7 cm), or severe 20vPnC 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 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 20vPnC administration. If symptoms develop, the use of antipyretic/pain medication is allowed.

- 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.

8.9.1.3. Visit 3 (Follow-Up Visit: 28 to 42 Days After Dose 2)

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal).

- Record nonstudy vaccinations administered since Visit 2, as described in Section 6.8.

- 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 any sponsor-provisioned e-diary.

- Determine whether any AEs and SAEs 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 10.2, and record concomitant medications used to treat 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.

8.9.2. 1-Dose 20vPnC Group and 13vPnC (Control) Group

8.9.2.1. 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 as permitted per local regulations to critically evaluate the immune response and safety profile by age.

- Perform a clinical assessment including medical history; record any findings on the medical history CRF. If deemed necessary as part of the clinical assessment, the physical examination may include assessments of the general appearance, skin, head, lymph nodes, cardiovascular, respiratory, gastrointestinal, and neurological systems.

- Record receipt of 2 infant doses of 13vPnC (prior to 12 months of age), including dates given.

- Measure and record the participant's temperature as appropriate for the age of the toddler, according to routine local practice (°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 study intervention container number via the IRT. This must be the last step before proceeding. A site staff member will prepare the study intervention according to the IP manual.

After randomization:

- Collect a blood sample of approximately 5 mL for immunogenicity.

- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh or left arm (as appropriate for the age and size of the child).

- If applicable, administer routine pediatric vaccinations into a limb other than the site of the 20vPnC injection and capture all details of the concomitant vaccine given on the same day as study intervention administration, including the name, date of administration, and site of administration, on the CRF.

- 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.

- Issue the participant's parent(s)/legal guardian(s) a measuring device (caliper) to measure 20vPnC or 13vPnC (control) injection site reactions and a digital thermometer to measure temperature, 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 through 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 parent(s)/legal guardian(s) with the participant contact card containing the study and investigator information (see Section 10.1.11).

- 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 20vPnC or 13vPnC administration. If symptoms develop, the use of antipyretic/pain medication is allowed.

- Record AEs and SAEs during the visit as described in Section 8.3 and record concomitant medications as described in Section 6.8.3.

- The investigator or an authorized designee completes the CRF and updates the study intervention 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.

8.9.2.2. Visit 2 (Follow-Up Visit: 28 to 42 Days After Dose 1)

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal).

- Record nonstudy vaccinations administered since Visit 1, as described in Section 6.8.

- 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 any sponsor-provisioned e-diary.

- Determine whether any AEs and SAEs 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 10.2, and record concomitant medications used to treat 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.

8.9.3. 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 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 unscheduled 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 temperature (°C) as appropriate for the age of the toddler, according to local practice.
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.2.3.1.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

The 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 analysis of the data collected in this study is outlined 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. Statistical Hypotheses

9.1.1. Estimands

The primary objectives of the study are to describe the safety profile and immune response to 1 or 2 doses of 20vPnC in healthy toddlers (≥12 to <24 months of age) who received 2 infant doses of Prevenar 13. Estimands to address the study objectives are provided in Section 3.

For estimands to evaluate the immunogenicity objectives, these estimands estimate the immune response in the hypothetical setting where participants follow the study schedule and protocol requirements. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis.

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

Immunogenicity and safety results will be provided by descriptive summary statistics for each vaccine group. There is no formal hypothesis test for any safety or immunogenicity result.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means all participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable immunogenicity	All eligible randomized participants who receive the vaccine to which they are randomly assigned at each dose, have at least 1 valid immunogenicity result collected within an appropriate window at 1 month after the last assigned vaccination, and have no other major protocol deviations as determined by the clinician monitor. Participants will be grouped according to the vaccine as randomized in the analysis based on the evaluable immunogenicity population.
CCI [redacted]	[redacted]
Safety	All participants who receive at least 1 dose of the study intervention and have safety data reported after any dose. Participants will be grouped according to the vaccine as administered in the analysis based on the safety population.

9.3. Statistical Analyses

The SAP will be developed and finalized before database lock and 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, and CCI [redacted] endpoints.

9.3.1. General Considerations

For all the immunogenicity endpoints, the analysis will be primarily based on the evaluable [redacted]

9.3.2. Analysis for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 2-sided 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).

Three-Tier Approach for AE Summary

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. There is no Tier 1 event identified for 20vPnC at this stage.

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 participants in at least 1 vaccine group reporting the event.

3. Tier 3 events are those that are neither Tier 1 nor Tier 2 events.

For both Tier 1 (if any identified later) and Tier 2 events, the 95% CIs for the difference in percentage of participants reporting the events between each of the 20vPnC groups and the 13vPnC group will be calculated using the Miettinen and Nurminen method.

In addition, for Tier 1 events (if any identified later), the asymptotic p-values will also be presented for the difference in percentage of participants reporting the events between each of the 20vPnC groups and the 13vPnC group, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.

Descriptive summary statistics will be provided for Tier 3 events for each vaccine group.

9.3.3. Analysis for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

9.3.3.1. Geometric Mean

The geometric mean for each vaccine group will be calculated as the mean of the logarithmically transformed assay results and then exponentiating the mean. The 2-sided 95% CI will be obtained by exponentiating the limits of the CI for the mean of the logarithmically transformed assay results based on Student's t distribution.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

9.3.4. Primary Endpoint(s)/Estimand(s) Analysis

Objective	Estimands	Statistical Analysis Methods
Safety	• Proportions of participants with local reactions (redness, swelling, and pain at the injection site) within 7 days after the last assigned vaccination from each group • Proportions of participants with systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep) within 7 days after the last assigned vaccination from each group	• Descriptive summary statistics for participants with each local reaction/systemic event within 7 days after each dose by maximum severity and cumulatively across severity levels •
	• AEs from vaccination to 1 month after the last assigned vaccination in each group	• Three-tier approach •
	• SAEs from vaccination to 1 month after the last assigned vaccination in each group	• Descriptive summary statistics

Objective	Estimands	Statistical Analysis Methods
Immunogenicity	• Percentage of participants with IgG concentrations to the 7 additional serotypes with a predefined level[a] 1 month after the last assigned vaccination in each group	• Descriptive summary statistics •

a. The predefined level is 0.35 µg/mL for all 7 additional serotypes.

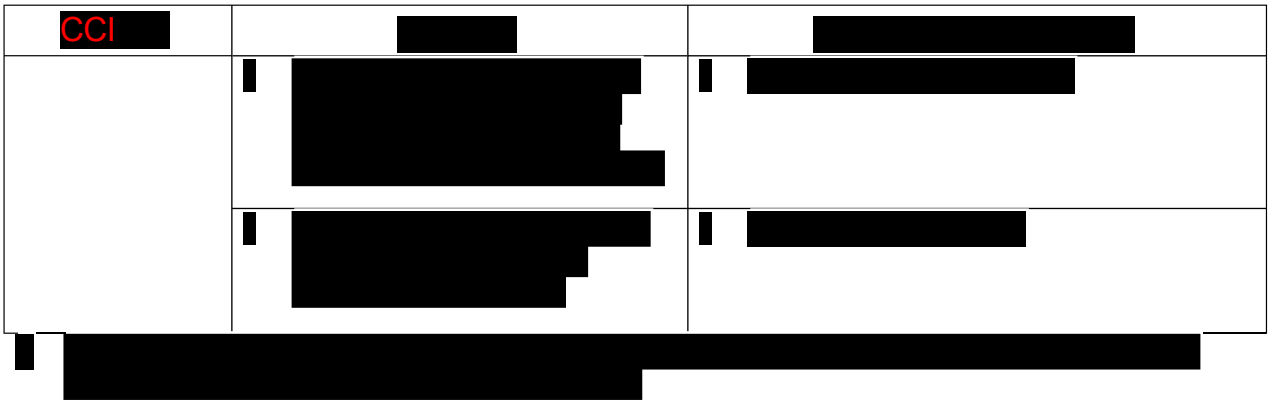
9.3.5. Secondary Endpoint(s)/Estimand(s) Analysis

Objective	Estimands	Statistical Analysis Methods
Immunogenicity	• GMC of IgG concentrations to each of the 20 vaccine serotypes 1 month after the last assigned vaccination in each group	• GMC and 2-sided 95% CI
	• Percentage of participants with IgG concentrations to the 13vPnC serotypes with a predefined level[a] 1 month after the last assigned vaccination in each group.	• Descriptive summary statistics •
	• GMT of OPA titers to each of the 20 vaccine serotypes 1 month after the last assigned vaccination in each group	• GMT and 2-sided 95% CI

a. The predefined level is 0.35 µg/mL for all 13vPnC serotypes except serotypes 5, 6B, and 19A, which have predefined levels of 0.23, 0.10, and 0.12, respectively.

CCI

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]



9.4. Interim Analyses

No formal interim analysis will be conducted for this study.

9.5. Sample Size Determination

A total of approximately 360 participants will be randomized for approximately 315 evaluable participants, with an estimate of 105 evaluable participants per vaccine group.

The sample size of the study is determined primarily based on considerations of accumulating adequate data to evaluate the safety and immunogenicity of 1 or 2 doses of 20vPnC in healthy toddlers with 2 prior infant doses of 13vPnC.

Table 4 displays the lower 2-sided 95% confidence limit of the percentage of participants with predefined IgG concentrations for the primary immunogenicity endpoint. Assumed true proportions ranging from 80% to 100% are displayed in order to help quantify the expected precision assuming 105 evaluable participants in each vaccine group.

Table 4. Precision of Percentage of Participants With Predefined IgG Concentrations

Assumed True Proportion (%)	Lower 95% Confidence Limit of Proportion (%), 105 Evaluable Participants per Group
80	71
85	78
90	83
95	89
100	97

Abbreviation: IgG = immunoglobulin G.
Note: Lower confidence limits of 2-sided 95% CI are calculated using the Clopper and Pearson method, assuming the observed number of participants with predefined IgG concentrations is 105 × true proportion.

The primary safety objective includes the endpoints for AEs reported within 1 month after the last assigned vaccination in each group. With 120 participants in each vaccine group, the probability of observing at least 1 AE in each is greater than 90%, assuming a true rate of at least 2% (Table 5).

Table 5. Probability of Observing an Event Given a Specified Incidence Rate and Assuming 120 Participants per Group

Sample Size	True Rate of AEs	Probability of Observing at Least 1 AE
120	1.0%	70.1%
120	2.0%	91.1%
120	5.0%	99.8%

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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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 the ICH GCP guidelines 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, including the risks and benefits, to the participant's parent(s)/legal guardian(s) and answer all questions regarding the study. The participant's legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants' parent(s)/legal guardian(s) must be informed that their participation is voluntary. Participants' 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, privacy and data protection 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 on which 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 their participation in the study.

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

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 will 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 participants 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 ID. 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. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will

communicate such decisions, which may include summaries of aggregate analyses of safety data to regulatory authorities, investigators, as appropriate.

10.1.6. 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), the 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 data from these trials available 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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the clinical study report.

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, including definition of study critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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 retain 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.

10.1.8. 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 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 and its origin can be found in the clinical monitoring plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. 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 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 the ICH 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.

10.1.10. 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 18 months 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.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator

or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.2.1. 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 Meeting 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 condition 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 or 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
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

10.2.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a 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 participant 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.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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.

10.2.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious 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.	All AEs or SAEs associated with exposure during pregnancy or breastfeeding. **Note**: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE).* All instances of EDB are reported (whether or not there is an associated SAE).**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.

** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- 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 or 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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 or 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 submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4. 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) 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. Appendix 3: 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 “adaptors” 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 Hy's law cases, 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, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, 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.

10.4. Appendix 4: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

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

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).

10.4.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 2 (Section 10.2.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs 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.

10.4.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 2 (Section 10.2.3).
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition
• A USADE is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.4.3. 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 information supplied by the manufacturer.

10.4.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording
• When a 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 device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and will also capture the required information on the Medical Device Complaint form. • 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 Medical Device Complaint form. • 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. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for

recording and reporting an AE or SAE are provided in Appendix 2 (Section 10.4.1).

- 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 Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 device deficiency, the investigator must document in the medical notes that he/she has reviewed the 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 Medical 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 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 regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 2.

10.4.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 2 (Section 10.2.4).

10.4.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) 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.

10.5. Appendix 5: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures is expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

10.5.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit.

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new or changes in concomitant medications to treat SAEs since the last contact.

Study participants' parent(s)/legal guardian(s) must be reminded to promptly notify site staff about any change in their health status.

10.5.2. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

10.6. Appendix 6: 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 (US)
CDC	Centers for Disease Control and Prevention (US)
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRM_{197}	cross-reactive material 197
CRO	contract research organization
CSR	clinical study report
DILI	drug-induced liver injury
DMC	data monitoring committee
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
EDB	exposure during breastfeeding
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 (US)

Abbreviation	Term
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
CCI [redacted]	[redacted]
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPD	invasive pneumococcal disease
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISO	International Organization for Standardization
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
OPA	opsonophagocytic activity
PI	principal investigator
CCI [redacted]	[redacted]
PPE	personal protective equipment
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	prothrombin time
QTL	quality tolerance limit
CCI [redacted]	[redacted]
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SmPC	summary of product characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document

Abbreviation	Term
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 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.

2 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.

3 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.

4 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.

5 Chapman R, Sutton K, Dillon-Murphy D, et al. Ten year public health impact of 13-valent pneumococcal conjugate vaccination in infants: a modelling analysis. Vaccine. 2020;38(45):7138-45.

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 Wasserman MD, Perdrizet J, Grant L, et al. Clinical and economic burden of pneumococcal disease due to serotypes contained in current and investigational pneumococcal conjugate vaccines in children under five years of age. Infect Dis Ther. 2021;10(4):2701-20.

9 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(4):441-51.

[10] 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/portal/files/documents/AER_for_2017-invasive-pneumococcal-disease.pdf. Accessed: 26 Aug 2019.

[11] 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.

[12] 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.

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

[14] 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.

[15] 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.

[16] 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.

[17] Lepoutre A, Varon E, Georges S, et al. Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001–2012. Vaccine. 2015;33(2):359-66.

[18] Levy C, Varon E, Ouldali N, et al. Bacterial causes of otitis media with spontaneous perforation of the tympanic membrane in the era of 13 valent pneumococcal conjugate vaccine. PLoS One. 2019;14(2):e0211712.

[19] Chen YJ, Hsieh YC, Huang YC, et al. Clinical manifestations and microbiology of acute otitis media with spontaneous otorrhea in children. J Microbiol Immunol Infect. 2013;46(5):382-8.

[20] Dagan R, Pelton S, Bakaletz L, et al. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. Lancet Infect Dis. 2016;16(4):480-92.

[21] 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.

[22] 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.

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

[24] 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.

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

[26] 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.

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

[28] 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.

[29] 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.

[30] 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.

[31] 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.

[32] 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.

[33] 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.

[34] 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):100-121.

[35] 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.

[36] 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.

[37] 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.

[38] 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.

[39] 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.

[40] 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.

[41] 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.

[42] 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.

[43] 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.

[44] 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.

[45] 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.

[46] 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.

[47] 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.

[48] 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.

[49] 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.

[50] 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: 06 Oct 2021.

[51] 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.

[52] 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.

[53] 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.

54 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.

55 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.

56 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.

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

58 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.

59 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.

60 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.

61 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.

62 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.

63 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.

64 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.

65 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.

66 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.

67 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.

68 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.

69 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.

70 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.

71 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.

72 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.

73 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.

74 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.

75 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.

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

[77] International Committee on Harmonisation. Statistical principles for clinical trials. ICH Harmonised Tripartite Guideline E9, 01 Sep 1998.

Document Approval Record

Document Name:	B7471027 Clinical Protocol, 10Dec2021
Document Title:	A PHASE 3, RANDOMIZED, PARTIAL DOUBLE-BLIND TRIAL TO EV ALUATE THE SAFETY AND IMMUNOGENICITY OF 20-VALENT PN EUMOCOCCAL CONJUGATE VACCINE IN HEALTHY TODDLERS 1 2 to 23 MONTHS OF AGE WITH TWO PRIOR INFANT DOSES OF P REVENAR 13

Signed By:	Date(GMT)	Signing Capacity
PPD	13-Dec-2021 23 58 41	Final Approval
PPD	15-Dec-2021 00 03 19	Final Approval