A PHASE 3, SINGLE-ARM TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY CHILDREN 15 MONTHS THROUGH 17 YEARS OF AGE

Investigational Product Number:	PF-06482077
Investigational Product Name:	20-valent pneumococcal conjugate vaccine (20vPnC)
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Short Title: Safety and Immunogenicity Study of 20vPnC in Healthy Children 15 Months Through 17 Years of Age

CCI [redacted]

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 1	18 Oct 2021	• To be consistent with the European PIP modification approved in August 2021 added 2 secondary immunogenicity endpoints. C [redacted] C l • Clarified that the primary immunogencity endpoints and the additional secondary endpoints are addressing consistencies with the approved European PIP modification.
Original protocol	13 Aug 2020	Not applicable (N/A)

This amendment incorporates all revision to date, including amendments made at the request of country health authorities and IRBs/ECs, and any protocol administrative clarification letter.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Pfizer is developing a new 20-valent pneumococcal conjugate vaccine (20vPnC) candidate to expand protection against pneumococcal disease beyond that covered by current pneumococcal vaccines in children. 20vPnC has the same composition as 13-valent pneumococcal conjugate vaccine (13vPnC; Prevnar 13®/Prevenar 13®), but contains an additional 7 pneumococcal conjugates targeting serotypes responsible for a substantial burden of remaining pneumococcal disease. 20vPnC uses the same platform and contains the same excipients as 7-valent pneumococcal conjugate vaccine (7vPnC; Prevnar®) and 13vPnC. Phase 2 safety and immunogenicity data in infants support further development of 20vPnC in the pediatric population.

This Phase 3, multicenter, single-arm study will be conducted at investigator sites in the United States. CCI [redacted] CCI [redacted] The purpose of this study is to generate safety and immunogenicity data in children in the setting of a well-established national infant immunization program of pneumococcal conjugate vaccine (7vPnC and subsequently 13vPnC). This will inform potential use of 20vPnC in children ≥15 months of age where direct protection against the additional 7 serotypes may offer benefit.

Approximately 800 children from ≥15 months to <18 years of age at the time of consent, provided by a parent/legal guardian, and assent (when age-appropriate and per local requirements), will be enrolled into 4 cohorts based on age (Cohort 1: ≥15 to <24 months, Cohort 2: ≥2 to <5 years, Cohort 3: ≥5 to <10 years, and Cohort 4: ≥10 to <18 years), 200 participants in each cohort. Documentation of at least 3 prior doses of 13vPnC will be required in children <5 years of age (Cohorts 1 and 2). Participants will receive a single dose of 20vPnC.

On Day 1 of the study (Visit 1), participants will be assessed for eligibility and information will be collected, including medical history and 13vPnC vaccination history. Blood will be collected prior to vaccination for immunogenicity assessments. Participants will receive a single dose of 20vPnC, which will be prepared and administered by a qualified site staff member or designee. Permitted routine pediatric vaccines may be given at the same time as study vaccination according to local or national recommendations, if not feasible to separate from the 20vPnC. Participants will be observed for 30 minutes after vaccination and any reactions occurring during that time will be recorded as adverse events (AEs). The participant's parent(s)/legal guardian(s) will be provided with an electronic diary (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 age-applicable systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability in Cohort 1; and fever, fatigue, headache, muscle pain, and joint pain in Cohorts 2-4) for 7 days following vaccination (Days 1 to 7, where Day 1 is the day of vaccination). Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days following vaccination. 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 injection site, or fever >40.0°C (>104.0°F), or has an emergency room visit or hospitalization.

Participants will return for Visit 2, approximately 1 month (28 to 42 days) after Visit 1. Information will be collected from the participant's parent(s)/legal guardian(s) on AEs, including nonserious AEs, serious AEs (SAEs), and newly diagnosed chronic medical conditions (NDCMCs), and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs occurring after the previous visit will be recorded. Information on vaccines given since the previous visit will also be recorded. Blood will be collected for immunogenicity assessments.

Participants will have Visit 3, approximately 6 months (168 to 196 days) after Visit 1. The sites will contact the participant's parent(s)/legal guardian(s) via telephone to inquire about SAEs and NDCMCs and concomitant medications used to treat SAEs or NDCMCs since the previous visit.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety:	**Primary Safety:**	**Primary Safety:**

To describe the safety profile of 20vPnC	In participants from each cohort receiving 20vPnC and having safety data reported after vaccination:
	• The percentage of participants reporting prompted local reactions within 7 days after vaccination
	• The percentage of participants reporting prompted systemic events within 7 days after vaccination
	• The percentage of participants reporting AEs up to 1 month after vaccination
	• The percentage of participants reporting SAEs up to 6 months after vaccination
	• The percentage of participants reporting NDCMCs up to 6 months after vaccination
		• Prompted local reactions (redness, swelling, and pain at the injection site)
		• Prompted systemic events:
		  • **Cohort 1:** Fever, decreased appetite, drowsiness/ increased sleep, and irritability
		  • **Cohorts 2 through 4:** Fever, fatigue, headache, muscle pain, and joint pain
		• AEs
		• SAEs
		• NDCMCs

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Primary Immunogenicity:**	**Primary Immunogenicity:**
Cohort 1 and Cohort 2: To demonstrate that the serotype-specific IgG concentrations for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding IgG concentrations before 20vPnC	In participants in compliance with the key protocol criteria (evaluable participants): • Geometric mean fold rises (GMFRs) of serotype-specific IgG concentrations for the 7 additional serotypes from before to 1 month after vaccination	• Pneumococcal serotype-specific IgG concentrations
Cohort 3 and Cohort 4: To demonstrate that the serotype-specific opsonophagocytic activity (OPA) titers for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding OPA titers before 20vPnC	In participants in compliance with the key protocol criteria (evaluable participants): • GMFRs of serotype-specific OPA titers for the 7 additional serotypes from before to 1 month after vaccination	• Pneumococcal serotype-specific OPA titers
Secondary Immunogenicity:	**Secondary Immunogenicity:**	**Secondary Immunogenicity:**
To further describe the immune responses to 20vPnC in Cohorts 1, 2, 3, and 4	In evaluable participants: • Percentage of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes at 1 month after vaccination in Cohort 1 only • Percentage of participants with ≥4-fold rise in serotype-specific OPA titers for the 7 additional serotypes from before to 1 month after vaccination in Cohorts 2, 3, and 4 only • Serotype-specific IgG geometric mean concentrations (GMCs) for the 20vPnC serotypes before and 1 month after vaccination • GMFRs of serotype-specific IgG concentrations for the 13vPnC serotypes from before to 1 month after vaccination (in Cohorts 1 and 2) • GMFRs of serotype-specific IgG concentrations for the 20vPnC serotypes from before to 1 month after vaccination (in Cohorts 3 and 4)	• Pneumococcal serotype-specific IgG concentrations • Pneumococcal serotype-specific OPA titers

Objectives	Estimands	Endpoints
	• Serotype-specific OPA geometric mean titers (GMTs) for the 20vPnC serotypes before and 1 month after vaccination • GMFRs of serotype-specific OPA titers for the 20vPnC serotypes from before to 1 month after vaccination (in Cohorts 1 and 2) • GMFRs of serotype-specific OPA titers for the 13vPnC serotypes from before to 1 month after vaccination (in Cohorts 3 and 4)	

Number of Participants

Approximately 800 participants (200/cohort) will be enrolled to achieve a target of 720 (180/cohort) evaluable participants at the follow-up time point 1 month after receipt of 20vPnC.

The 800 participants will be enrolled into 4 cohorts based on age and, for the 2 youngest cohorts, documented history of 13vPnC vaccination:

- **Cohort 1**: Approximately 200 children ≥15 months to <24 months (<2 years) of age who have been previously vaccinated with at least 3 doses of 13vPnC.
- **Cohort 2**: Approximately 200 children ≥2 years to <5 years of age who have been previously vaccinated with at least 3 doses of 13vPnC.
- **Cohort 3**: Approximately 200 children ≥5 years to <10 years of age regardless of documentation of previous vaccination with 7vPnC or 13vPnC.
- **Cohort 4**: Approximately 200 children ≥10 years to <18 years of age regardless of documentation of previous vaccination with 7vPnC or 13vPnC.

Duration of Participation for Each Participant

Each participant will participate in the study for approximately 6 months.

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Statistical Methods

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs, including SAEs and NDCMCs, for each age cohort.

The primary immunogenicity objectives will be evaluated by formal hypothesis tests for superiority of IgG concentrations for the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) 1 month after 20vPnC to before 20vPnC in Cohorts 1 and 2, and superiority of OPA titers for the 7 additional serotypes 1 month after 20vPnC to before 20vPnC in Cohorts 3 and 4. Superiority for a serotype in each cohort will be declared if the lower bound of the 2-sided 95% confidence interval (CI) for the IgG (or OPA) GMFR from before 20vPnC to 1 month after 20vPnC for that serotype is greater than 1.

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Number	1	2	3
Visit ID	Vaccination	Follow-up Visit	Follow-up Phone Call[a]
Study Interval Visit	Day 1	1-Month Visit	6-Month Phone Call
Visit Window (Days)		28-42 Days After Visit 1	168-196 Days After Visit 1
Obtain informed consent/assent	X		
Assign participant number via IRT	X		
Record demography	X		
Perform clinical assessment, including medical history	X		
Obtain prevaccination temperature (measured as appropriate for age)	X		
Record nonstudy vaccinations[b]	X	X	
Record concomitant medications[c]	X	X	X
Urine pregnancy test (if applicable)	X		
Contraception check (if applicable)[d]	X	X	
Review inclusion and exclusion criteria	X		
Review temporary delay criteria	X	X	
Review continued eligibility		X	
Obtain blood sample[e]	X[f]	X	
Assign an investigational product container number via the IRT	X		
Administer investigational product into left leg (option for Cohort 1 only) or left arm	X[g]		
Administer and record routine pediatric vaccinations, as applicable[h]	X		
Observe and record reactions for 30 minutes after investigational product administration	X		

Visit Number	1	2	3
Visit ID	**Vaccination**	**Follow-up Visit**	**Follow-up Phone Call[a]**
Study Interval Visit	**Day 1**	**1-Month Visit**	**6-Month Phone Call**
Visit Window (Days)		**28-42 Days After Visit 1**	**168-196 Days After Visit 1**
Provide parent(s)/legal guardian(s) with an e-diary (device or application, as appropriate), thermometer, and measuring device and instruct to collect prompted local reactions and systemic events and use of antipyretic/pain medications[i]	X		
Provide a participant contact card	X	X	
Review and/or collect e-diary (if applicable)[j]		X	
Record and report adverse events	X----------X		
Record and report SAEs and NDCMCs[k]	X----------X		

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

a. This telephone contact should occur approximately 6 months after study vaccination; this contact should be attempted for all participants who have received study vaccination, unless the parents/legal guardians have withdrawn consent.
b. For Cohorts 1 and 2, information on the prior vaccination with 13vPnC will also be recorded. For Cohorts 3 and 4, information on prior vaccination with 7vPnC or 13vPnC will be recorded, if available. See Section 6.5.3 for details.
c. Record only concomitant medications used to treat SAEs and NDCMCs.
d. The investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly until 28 days after the dose of investigational product and document the conversation and the participant's affirmation in the source notes.
e. For Cohorts 1 and 2: ~5 mL; for Cohorts 3 and 4: ~10 mL.
f. Blood sample will be collected prior to vaccination.
g. Remind the participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
h. Administer permitted routine pediatric vaccinations (as applicable) after the investigational product into a limb other than the site of the 20vPnC injection. Prohibited and permitted vaccines are described in Sections 6.5.1 and 6.5.2, respectively.
i. The participant's parent(s)/legal guardian(s) will record prompted local reactions and systemic events and antipyretic/pain medication in an e-diary for the 7 days following vaccination. 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 injection site (left leg [option for Cohort 1 only] or left arm), a fever >40.0°C (>104.0°F), or an emergency room visit or hospitalization.
j. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.
k. An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

2. INTRODUCTION

Pneumococcal Disease

Streptococcus pneumoniae are gram-positive encapsulated cocci that are a leading cause of bacteremia, bacterial meningitis, pneumonia, and acute otitis media (AOM) and continue to be a major global public health concern.[1,2,3] Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk.[4] Individuals with certain comorbidities and immunocompromising conditions are also at risk, especially persons with chronic heart, lung, liver, and renal disease, as well as those who are functionally asplenic. The global burden of pneumococcal disease has been substantially impacted by pneumococcal conjugate vaccines. *S pneumoniae* caused an estimated 14.5 million cases of serious disease and 826,000 deaths annually in children <5 years of age prior to introduction of pneumococcal conjugate vaccines.[2] 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.[5]

The overall invasive pneumococcal disease (IPD) burden was estimated in 2013 to have decreased approximately 90% in the population <5 years of age in the United States since the introduction of pneumococcal conjugate vaccines; however, there was a slight increase in the proportions of IPD cases associated with hospitalization (63% to 71%), and the IPD case fatality rate was also slightly but statistically significantly increased (2% to 3%) in that age group.[6] This is due to the decrease in disease due to the serotypes in 7vPnC and 13vPnC. However, disease due to serotypes not covered by those vaccines remains, and causes significant morbidity and mortality.

National IPD surveillance data in England and Wales for the epidemiological year 2016-2017, approximately 10 years after the introduction of 7vPnC in the national infant immunization program and 6 years after the introduction of 13vPnC, showed 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.[7] The data for England and Wales are consistent with the patterns observed in data from the European Union (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.[8] 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.[9,10] 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.[11] Serotypes 10A, 12F, 15B/15C, 22F, and 33F accounted for 36% of isolates causing IPD. The most common clinical presentations of IPD due to non-13vPnC

serotypes included bacteremia (49.6%), meningitis (19.1%), and pneumonia (18.8%). These data demonstrate the continued need for expanded serotype coverage.

Surveillance studies conducted in 2010-2012 by the Centers for Disease Control and Prevention (CDC) found that *S pneumoniae* remains among the most common pathogens identified in community-acquired pneumonia (CAP) requiring hospitalization in the United States in both children and adults.[12,13] 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.[12,14] Surveillance reported in 2017 by the European Centre for Disease Prevention and Control (ECDC) showed that among cases of IPD for which the clinical presentation was known across all age groups, bacteremic pneumonia was reported in 42% of cases. The most common clinical presentations in children <5 years of age were septicemia and bacteremic pneumonia (1-4 year olds) and meningitis (<1 year old).[8] These data suggest that *S pneumoniae* remains an important cause of serious disease in the United States and worldwide.

AOM is a common childhood illness, with the 2011 visit rates of 0.82 and 0.81 visits per AOM/child-year in children <2 years of age and 2 to 6 years of age, respectively, and represents a significant medical burden.[15] *S pneumoniae* is one of the common bacterial causes of AOM, and accounted for an estimated 850,000 outpatient and 125,000 emergency room visits in the United States in 2004 in children <5 years of age, representing a significant burden on the healthcare system.[3] While AOM is generally not considered a serious disease, it does carry the risk of more serious complications. These complications can range from the development of chronic or recurrent otitis media necessitating surgical intervention (tympanostomy tube placement), and accompanied by hearing losses with potential developmental and language delays, to invasive extension leading to mastoiditis and meningitis.

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

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.[16,17] Anticapsular antibodies directed against the specific serotype bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.[18] 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.[19]

Vaccines containing free polysaccharides have been licensed since the 1970s. One such vaccine, the 23-valent pneumococcal polysaccharide vaccine (PPSV23), has been licensed in the United States since 1983.[20,21] 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.[4,21,22,23] Moreover, their ability to prevent nonbacteremic pneumonia, CAP, and AOM is limited or lacking.[19,23,24,25,26] In addition, polysaccharide vaccines do not reduce vaccine-type (VT) nasopharyngeal carriage, which is important for herd immunity.[26] 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.[19]

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.[22,27] 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 cross-reactive material 197 (CRM_{197}), a nontoxic variant of diphtheria toxin. These 7 serotypes were responsible for approximately 80% to 90% of IPD in children <5 years of age in the United States and approximately 60% to 80% of IPD in the same age group in Europe at that time (1998-2000).[28,29,30,31,32] These serotypes also accounted for a high proportion of antibiotic-resistant strains.[33] 7vPnC demonstrated efficacy against VT IPD, pneumonia, and AOM in large randomized, controlled efficacy studies in infants.[34,35] The 7vPnC components contained in a related pneumococcal conjugate vaccine also were demonstrated to be efficacious against clinically/radiographically defined pneumonia.[36,37,38,39] 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.[40]

13vPnC was developed to expand serotype coverage and was licensed in the United States in 2010. 13vPnC includes the same *S pneumoniae* serotypes as 7vPnC and an additional 6 polysaccharide conjugates for serotypes 1, 3, 5, 6A, 7F, and 19A.[27,31,41] The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific serum IgG antibody concentrations to 7vPnC, with supportive data to demonstrate the

functional activity of the immune responses. 13vPnC has also been licensed in adults based on demonstration of efficacy against CAP due to serotypes contained in 13vPnC in adults 65 years of age and older.[42] 13vPnC has replaced 7vPnC and is licensed in the United States and many other countries, with national recommendations for use in children and older adults.[43,44,45,46] It has also been prequalified by the World Health Organization (WHO) for use in national infant immunization programs in lower- and middle-income countries.[47,48] 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.[49,50,51]

Development of 20vPnC

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

2.1. Study Rationale

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CCI [redacted] The purpose of this study is to provide safety and immunogenicity data with 20vPnC in children ≥15 months to <18 years old in the setting of well-established national infant immunization program with a pneumococcal conjugate vaccine (7vPnC and 13vPnC in the United States). This will inform potential use of 20vPnC in children ≥15 months of age in a setting where direct protection against the additional 7 serotypes may offer benefit, such as immunization campaigns intended to rapidly increase the level of serotype coverage in the pediatric population, or in specific individuals with risk factors. It is notable that after introduction of 13vPnC in the United States in 2010, there was a short-term recommendation for a single supplemental dose of 13vPnC to be given to children 14 through 59 months of age who had received the 7vPnC series, to provide protection against the 6 serotypes unique to 13vPnC.[52]

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CCI [redacted] Descriptive immunogenicity data for all 20 vaccine serotypes will also be generated.

2.2. Background

20vPnC is being developed to further expand protection against the global burden of vaccine-preventable pneumococcal disease in children and adults over that of 13vPnC. 20vPnC contains the serotypes present in 13vPnC plus 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) individually conjugated to CRM_{197}. As noted above, 20vPnC uses the same platform and contains the same excipients as 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).[53,54,55,56,57,58,59,60,61,62,63,64]

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.[65,66,67,68,69,70,71] These 7 serotypes contribute to the burden of IPD in the United States and elsewhere. It is estimated that between 2015 and 2016, these 7 serotypes accounted for 35% of IPD in children 5 through 17 years of age and 39% of IPD in children <5 years of age in the United States.[72] In the EU, according to the ECDC annual IPD epidemiological report for 2017, approximately 75% of cases of IPD in children <5 years of age were caused by a serotype not in 13vPnC, increased from 63% in 2013. Five of the 10 most common serotypes included serotypes 8, 10A, 11A, 12F, and 22F, with serotypes 8, 10A, 12F, and 24F being among the most common in children in this age group, and serotypes 8, 12F, and 10A were among the 5 most frequent serotypes causing disease in 5- to 14-year-olds in the ECDC report.[8]

A meta-analysis of serotypes causing IPD in children <5 years of age in regions of the world that have introduced higher-valent pneumococcal conjugate vaccines (such as 13vPnC) showed that, overall, these 7 serotypes accounted for approximately 70% of disease not due to the 13vPnC types.[67]

2.2.1. Clinical Overview

Safety and immunogenicity data from a 20vPnC Phase 1 study (B7471001) conducted in healthy adults 18 through 49 years of age demonstrated that the vaccine induces immune responses (IgG and OPA responses) to the 20 vaccine serotypes and has a safety profile consistent with other pneumococcal conjugate vaccines. These data support clinical development in other populations, including pediatrics.

Additional Phase 2 and Phase 3 trials have been conducted in adults 18 years of age and above, with safety and immunogenicity data on over 4000 participants who received 20vPnC, showing it to induce an immune response to all of the 20 vaccine serotypes and to have a safety profile similar to 13vPnC.

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

2.3. Benefit/Risk Assessment

The 20vPnC investigational product contains the same components and excipients as the licensed 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. This has been the case in the clinical program to date, but additional AEs may be observed with the investigational 20vPnC as more clinical experience is gained. The most common AEs noted in the pediatric population 15 months through 17 years of age after vaccination with 13vPnC are primarily related to local reactions (injection site pain or tenderness, redness, and swelling) and systemic events (fever, irritability, decreased appetite, and increased sleep). This includes data from children with prior 7vPnC immunization.[73,74]

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. The most common AEs after 20vPnC administration were local reactions (pain, redness, and swelling at the injection site) and systemic events (irritability, drowsiness/increased sleep, and decreased appetite).

As with any vaccine, an allergic reaction can occur. The allergic reaction can vary from skin rash to swelling of the face or lips, wheezing, and/or shortness of breath. A severe allergic reaction (anaphylactic shock, collapse, or shock-like state [hypotonic-hyporesponsive episode]) may also occur. There may also be additional risks related to the vaccines administered in the study that are not known at this time.

Risks that may be associated with study procedures include risks from blood draws, including pain, swelling, bruising, and infection where blood is taken.

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. CC [redacted] 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 that of 13vPnC. If 20vPnC is successful in Phase 3 studies, and approved, it is anticipated to provide a public health benefit by reducing the burden of pneumococcal disease due to the additional 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 20vPnC IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary Safety	**Primary Safety**	**Primary Safety**

To describe the safety profile of 20vPnC	In participants from each cohort receiving 20vPnC and having safety data reported after vaccination:
	• The percentage of participants reporting prompted local reactions within 7 days after vaccination
	• The percentage of participants reporting prompted systemic events within 7 days after vaccination
	• The percentage of participants reporting AEs up to 1 month after vaccination
	• The percentage of participants reporting SAEs up to 6 months after vaccination
	• The percentage of participants reporting NDCMCs up to 6 months after vaccination
		• Prompted local reactions (redness, swelling, and pain at the injection site)
		• Prompted systemic events:
		  • **Cohort 1**: Fever, decreased appetite, drowsiness/increased sleep, and irritability
		  • **Cohorts 2 through 4**: Fever, fatigue, headache, muscle pain, and joint pain
		• AEs
		• SAEs
		• NDCMCs

Primary Immunogenicity	**Primary Immunogenicity**	**Primary Immunogenicity**
Cohort 1 and Cohort 2: To demonstrate that the serotype-specific IgG concentrations for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding IgG concentrations before 20vPnC	In participants in compliance with the key protocol criteria (evaluable participants): • GMFRs of serotype-specific IgG concentrations for the 7 additional serotypes from before to 1 month after vaccination	• Pneumococcal serotype-specific IgG concentrations

Objectives	Estimands	Endpoints
Cohort 3 and Cohort 4: To demonstrate that the serotype-specific OPA titers for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding OPA titers before 20vPnC	In participants in compliance with the key protocol criteria (evaluable participants): • GMFRs of serotype-specific OPA titers for the 7 additional serotypes from before to 1 month after vaccination	• Pneumococcal serotype-specific OPA titers
Secondary Immunogenicity	**Secondary Immunogenicity**	**Secondary Immunogenicity**
To further describe the immune responses to 20vPnC in Cohorts 1, 2, 3, and 4	In evaluable participants: • Percentage of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes at 1 month after vaccination in Cohort 1 only • Percentage of participants with ≥4-fold rise in serotype-specific OPA titers for the 7 additional serotypes from before to 1 month after vaccination in Cohorts 2, 3, and 4 only • Serotype-specific IgG GMCs for the 20vPnC serotypes before and 1 month after vaccination • GMFRs of serotype-specific IgG concentrations for the 13vPnC serotypes from before to 1 month after vaccination (in Cohorts 1 and 2) • GMFRs of serotype-specific IgG concentrations for the 20vPnC serotypes from before to 1 month after vaccination (in Cohorts 3 and 4) • Serotype-specific OPA GMTs for the 20vPnC serotypes before and 1 month after vaccination • GMFRs of serotype-specific OPA titers for the 20vPnC serotypes from before to 1 month after vaccination (in Cohorts 1 and 2) • GMFRs of serotype-specific OPA titers for the 13vPnC serotypes from before to 1 month after vaccination (in Cohorts 3 and 4)	• Pneumococcal serotype-specific IgG concentrations • Pneumococcal serotype-specific OPA titers

Objectives	Estimands	Endpoints
CCI [redacted]	[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This Phase 3, multicenter, single-arm study will be conducted at investigator sites in the United States. CCI [redacted] CCI [redacted] The purpose of this study is to provide safety and immunogenicity data in children in the setting of a well-established national infant immunization program of pneumococcal conjugate vaccine (7vPnC and

subsequently 13vPnC). These data will inform potential use of 20vPnC in children ≥15 months of age where direct protection against the additional 7 serotypes may offer benefit.

Approximately 800 children from ≥15 months to <18 years of age at the time of consent, provided by a parent/legal guardian, and assent (when age-appropriate and per local requirements), will be enrolled into 4 cohorts based on age (Cohort 1: ≥15 to <24 months, Cohort 2: ≥2 to <5 years, Cohort 3: ≥5 to <10 years, and Cohort 4: ≥10 to <18 years), 200 participants in each cohort. Documentation of at least 3 prior doses of 13vPnC will be required in children <5 years of age (Cohorts 1 and 2). Participants will receive a single dose of 20vPnC.

On Day 1 of the study (Visit 1), participants will be assessed for eligibility and information will be collected including medical history and 13vPnC vaccination history (see Section 6.5.3). Blood will be collected prior to vaccination for immunogenicity assessments. Participants will receive a single dose of 20vPnC, which will be prepared and administered by a qualified site staff member or qualified designee. Permitted routine pediatric vaccines (see Section 6.5.2) may be given at the same time as study vaccination according to local or national recommendations, if not feasible to separate from the 20vPnC. 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 age-applicable systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability in Cohort 1; and fever, fatigue, headache, muscle pain, and joint pain in Cohorts 2-4) for 7 days following vaccination. 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 severe redness or swelling >14 caliper units, severe pain at the injection site, or fever >40.0°C (>104.0°F), or has an emergency room visit or hospitalization.

Participants will return for Visit 2, approximately 1 month (28 to 42 days) after Visit 1 (study Day 29 to 43). Information will be collected from the participant's parent(s)/legal guardian(s) on AEs, including nonserious AEs, SAEs, and NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs occurring after the previous visit will be recorded. Information on vaccines given since the previous visit will also be recorded. Blood will be collected for immunogenicity assessments.

Participants will have Visit 3, approximately 6 months (168 to 196 days) after Visit 1. The sites will contact the participant's parent(s)/legal guardian(s) via telephone to inquire about SAEs and NDCMCs and concomitant medications used to treat SAEs or NDCMCs since the previous 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 6 months.

4.1.2. Approximate Number of Participants

Approximately 800 participants (200/cohort) will be enrolled to achieve a target of 720 (180/cohort) evaluable participants at the follow-up time point 1 month after receipt of 20vPnC.

The 800 participants will be enrolled into 4 cohorts based on age and, for the 2 youngest cohorts, documented history of 13vPnC vaccination:

- **Cohort 1:** Approximately 200 children ≥15 months to <24 months (<2 years) of age who have been previously vaccinated with at least 3 doses of 13vPnC.
- **Cohort 2:** Approximately 200 children ≥2 years to <5 years of age who have been previously vaccinated with at least 3 doses of 13vPnC.
- **Cohort 3:** Approximately 200 children ≥5 years to <10 years of age regardless of documentation of previous vaccination with 7vPnC or 13vPnC.
- **Cohort 4:** Approximately 200 children ≥10 years to <18 years of age regardless of documentation of previous vaccination with 7vPnC or 13vPnC.

4.2. Scientific Rationale for Study Design

CCI [redacted]

CCI [redacted] The purpose of this single-arm study is to provide safety and immunogenicity data in children in the setting of well-established national infant immunization programs with 7vPnC and subsequently with 13vPnC. Similar studies were conducted with 13vPnC in a population of children in the setting of 7vPnC use showing 13vPnC was well tolerated and elicited an immune response to all 13vPnC serotypes.[73,74] Children ≥15 months of age to <5 years of age (Cohorts 1 and 2) will be eligible if they have been previously vaccinated with at least 3 prior doses of 13vPnC, and the most recent dose was received >2 months before enrollment. Children ≥5 to <18 years of age will be eligible regardless of previous vaccination status with 7vPnC or 13vPnC. Participants will be administered 1 dose of 20vPnC at Visit 1. This is consistent with the short-term catch-up recommendations by the Advisory Committee on Immunization Practices (ACIP) following 13vPnC introduction. The recommendation was for a single dose of 13vPnC in children 12 through 59 months of age who received 3 doses of 13vPnC before age 12 months, administered at least 8 weeks after the most recent dose of 13vPnC, and it is consistent with the dosing series (1 dose) indicated for 13vPnC in unvaccinated children >2 years of age.[31]

4.3. Justification for Dose

The 20vPnC candidate is modeled after 7vPnC and 13vPnC, and contains capsular polysaccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM_{197}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The design and dosing of 20vPnC in this trial are similar to previous 13vPnC trials in a population of children in the setting of 7vPnC use showing 13vPnC was well tolerated and elicited an immune response to all 13vPnC serotypes.[73,74] In children 2 years of age and older, 1 dose of pneumococcal conjugate vaccine induces protective immune responses. The population and dosing are also consistent with the ACIP recommendations after 13vPnC introduction noted above, for a single supplemental dose of 13vPnC for all children 14 through 59 months of age who had received 4 doses of 7vPnC or another age-appropriate, complete 7vPnC schedule to induce immune responses to the additional serotypes.[31] Additionally, children 12 through 23 months of age who had received 3 doses of 7vPnC before age 12 months were recommended to receive 1 dose of 13vPnC, given at least 8 weeks after the last dose of 7vPnC, and a single dose of 13vPnC was to be given to all healthy children 24 through 59 months of age with any incomplete schedule of 7vPnC or 13vPnC.

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:

5.1.1. Cohort 1 and Cohort 2

Age and Sex:

1. Male or female children ≥15 months to <5 years of age at the time of consent.

Type of Participant and Disease Characteristics:

2. Participants' parent(s)/legal guardian(s) and participants, as age-appropriate, who are willing and able to comply with all scheduled visits and study procedures.

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

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

5. Written documentation of receipt of at least 3 doses of 13vPnC. The last dose of 13vPnC must have been administered >2 months before enrollment into the study.

Informed Consent:

6. 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 informed consent document (ICD) and in this protocol.

5.1.2. Cohort 3 and Cohort 4

Age and Sex:

1. Male or female children ≥5 years to <18 years of age at the time of consent.

Type of Participant and Disease Characteristics:

2. Participants' parent(s)/legal guardian(s) and participants, as age-appropriate, who are willing and able to comply with all scheduled visits and study procedures.

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

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

5. Negative urine pregnancy test for female participants who are menstruating.

6. Female participant of childbearing potential or male participant able to father children who is willing to use a highly effective method of contraception as outlined in this protocol for at least 28 days after the last dose of investigational product if at risk of pregnancy with her/his partner; or female participant not of childbearing potential or male participant not able to father children.

Informed Consent:

7. 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. Depending on the age of the participant and according to local requirements, participants will also be asked to provide assent as appropriate (verbal or written).

5.2. Exclusion Criteria

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

5.2.1. Cohort 1 and Cohort 2

Medical Conditions:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product, 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, human immunodeficiency virus (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 acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

9. Previous vaccination with any investigational pneumococcal vaccine or with PPSV23, 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 investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) 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 (through Visit 2).

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. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

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.

5.2.2. Cohort 3 and Cohort 4

Medical Conditions:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the investigational product, 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 acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

9. Pregnant or breastfeeding female participants.

Prior/Concomitant Therapy:

10. Previous vaccination with any investigational pneumococcal vaccine or with PPSV23, or planned receipt through study participation.

11. 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 investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

12. Receipt of blood/plasma products or immunoglobulins (including hepatitis B immunoglobulin) or planned receipt through the last planned blood draw in the study (through Visit 2).

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

Not applicable.

Other Exclusions:

14. 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.

5.3. Lifestyle Considerations

5.3.1. Contraception (If Applicable)

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (Section 10.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

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 assigned to investigational product. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AE or SAE recorded from signing the informed consent until the time of determination of screen failure.

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

5.5. Temporary Delay Criteria

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

The blood draw 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 (body temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before investigational product administration.

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

5.5.2. Criteria for Temporarily Delaying Immunogenicity Blood Draw

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

20vPnC is a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM_{197}. CCI [redacted]

Investigational product will be supplied by Pfizer as prefilled syringes. Each syringe will be packaged in a carton with a label and a tamper-evident seal, and will be labeled as required per country requirement (refer to the investigational product manual [IP manual]).

6.1.1. Administration

All participants will receive a single dose of 20vPnC at Visit 1.

The 0.5-mL dose of 20vPnC will be administered intramuscularly into the left leg (option for Cohort 1 only) or left arm by a designated site staff member. All other vaccinations (if given) should be administered into a limb other than the site of 20vPnC injection. The location of the injection of each vaccine administered (investigational product and other) will be recorded.

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

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

Investigational product administration details will be recorded on the case report form (CRF).

6.1.2. Medical Devices

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

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

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

6.2. Preparation/Handling/Storage/Accountability

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

6.2.1. Preparation and Dispensing

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Since all participants will receive 20vPnC at Visit 1, this will be an open-label vaccination and will be prepared and administered by a site staff member or designee.

6.3.1. Allocation to Study Intervention

Laboratory personnel performing the immunologic assays will be blinded to the visit information until all assays have been completed and assay results finalized.

Each participant will receive a single dose of 20vPnC; however, the investigational product will be assigned using an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The site personnel will then be provided with a dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant 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.

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

6.5.1. Prohibited Concomitant Vaccines and Treatments

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during study participation.
- Receipt of nonstudy pneumococcal vaccine is prohibited during study participation.
- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a ≥14-day course of systemic corticosteroids) is prohibited through Visit 2.

6.5.2. Permitted Concomitant Vaccines and Treatments

- Influenza vaccine is permitted at any time during influenza season in this study. However, if feasible, it is recommended that influenza vaccine be administered at least 14 days before or after 20vPnC administration.
- Receipt of quadrivalent meningococcal conjugate vaccine is permitted only after the blood sample is collected at Visit 2.

- Receipt of other licensed nonstudy vaccines (except pneumococcal vaccine as 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 administration.

- Use of topical anesthetic is permitted.

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

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

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

6.5.3. Recording Prior and Concomitant Vaccines and Treatments

The name, location, and date of administration for any nonstudy vaccinations received from the time of signing of the ICD to Visit 2 will be collected and recorded in the CRF.

For Cohorts 1 and 2, confirmation in the source documents of 3 or more prior doses of 13vPnC with the date of administration of the most recent (third or fourth) dose of 13vPnC is to be recorded on the CRF. For Cohorts 3 and 4, the date of administration of the most recent dose of 7vPnC or 13vPnC will be recorded on the CRF, if available.

Only medications taken to treat SAEs or NDCMCs from the time of signing of the ICD to the final visit (approximately 6 months after vaccination at Visit 1) will be collect and recorded in the CRF.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

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

A final telephone contact 6 months after vaccination (Section 8.10.3) for the collection of safety information should be completed for all participants who withdraw or who have been withdrawn after administration of investigational product, unless consent for further contact has been withdrawn, or the participant is lost to follow-up. Participant withdrawal should be explained in the source documents and should include whether the withdrawal is from study procedures and/or postvaccination study follow-up.

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

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

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

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

7.3. Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit or fails to respond to the 6-month safety follow-up telephone call:

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

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, home visits).

8.1. Efficacy Assessments

8.1.1. Immunogenicity Assessments

Blood samples (Cohorts 1 and 2: approximately 5 mL per sample; Cohorts 3 and 4: approximately 10 mL per sample) will be collected from all participants prior to vaccination at Visit 1 and at Visit 2 (1 month after vaccination). These are the immunogenicity time points.

The total blood sampling volume for individual participants in this study is approximately 10 mL in children ≥15 months to <5 years of age (Cohorts 1 and 2), and 20 mL in children and adolescents ≥5 to <18 years of age (Cohorts 3 and 4).

Pneumococcal Responses

IgG Responses to the 20 Pneumococcal Serotypes Contained in 20vPnC

IgG antibody concentrations for serotypes present in 20vPnC (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) will be determined on all sera collected at the 2 immunogenicity time points (Visits 1 and 2). The serotype-specific IgG concentrations will be measured by Pfizer's multiplex Luminex immunoassay.

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 for the immunogenicity time points (Visits 1 and 2). These subsets will be randomly selected, by an unblinded third party, to ensure that each subset has equal representation of both vaccine groups. Further details will be described in the clinical specimen assessment plan (CSAP). The serotype-specific OPA titers will be measured by Pfizer's OPA assay.

CCI [redacted]

[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] No testing of the participant's genetic material will be performed.

The participant's parent(s)/legal guardian(s) may request that the participant's samples, if still identifiable, be destroyed at any time (depending on the age of the participant and according to local requirements, participants may also request that their samples be destroyed); 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

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

The participant will be observed for 30 minutes after study vaccination and any reactions during the visit will be assessed and recorded.

Prompted e-diary events, including local reactions (redness, swelling, and pain at the injection site) and systemic events (Cohort 1: fever, decreased appetite, drowsiness/increased sleep, and irritability; Cohorts 2-4: fever, fatigue, headache, muscle pain, and joint pain) that occur within 7 days following investigational product administration (Days 1 to 7, where Day 1 is the day of vaccination) are graded as described in Section 8.2.2. Furthermore, AEs, SAEs, and NDCMCs will be collected as defined in Section 10.3.

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

8.2.1. Participant Electronic Diary

The participant's parent(s)/legal guardian(s) will be asked to monitor and record local reactions, specific systemic events, fever, and antipyretic/pain medication taken for 7 days, each evening following the study 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 an accurate representation of the participant's experience. Data on local reactions, specific systemic events, fever, and use of antipyretic/pain medication reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting.

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

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

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

8.2.2. Grading Scale for Prompted Events

The grading scales used in this study to assess prompted events as described below are based on concepts outlined in the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for adults and adolescent volunteers enrolled in preventive vaccine clinical trials,[75] but have been adapted for applicability to healthy infants.

8.2.2.1. Local Reactions

For the first 7 days following the study vaccination (Days 1 through 7, where Day 1 is the day of vaccination), the participant's parent(s)/legal guardian(s) will be asked to assess redness, swelling, and pain at the injection site (left leg [option for Cohort 1 only] or left arm) 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 scales in Table 1 below. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scales in Table 1 below. The participant's parent(s)/legal guardian(s) will be prompted to contact the investigator if the participant experiences a severe (Grade 3 or above) local reaction to assess the reaction and perform an unscheduled assessment or visit as appropriate.

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

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

Table 1. Grading Scales for Local Reactions in Study Participants

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) = >7.0 cm	Necrosis or exfoliative dermatitis[b]
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) = >7.0 cm	Necrosis[b]
Pain at injection site (tenderness)	Cohort 1: Hurts if gently touched (eg, whimpers, winces, protests, or withdraws) Cohorts 2-4: Does not interfere with activity	Cohort 1: Hurts if gently touched with crying Cohorts 2-4: Interferes with activity	Cohort 1: Causes limitation of limb movement Cohorts 2-4: Prevents daily activity[c]	Emergency room visit or hospitalization for severe pain (tenderness) at injection site

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

a. Parent(s)/legal guardian(s) 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 in the CRF. The severity of the local reaction should be graded using the AE grading scale in Section 10.3.4.
c. Prevents daily activity, eg, results in missed days of work or school or is otherwise incapacitating.

8.2.2.2. Systemic Events – Symptoms and Fever

8.2.2.2.1. Symptoms

For the first 7 days following the study vaccination (Days 1 through 7, where Day 1 is the day of vaccination), the participant's parent(s)/legal guardian(s) will be asked to assess decreased appetite, drowsiness/increased sleep, and irritability in Cohort 1, and fatigue, headache, muscle pain, and joint pain in Cohorts 2 through 4, 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 scales in Table 2 and Table 3 below. 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) for 7 days following 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 study reference manual (SRM) or equivalent.

Table 2. Grading Scales for Systemic Events - Participants Who Are ≥15 Months to <2 Years of Age (Cohort 1)

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

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

a. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the e-diary but will be collected as an AE in the CRF. The severity of the systemic event should be graded using the AE severity grading scale provided in Section 10.3.4.

Table 3. Grading Scales for Systemic Events - Participants Who Are ≥2 to <18 Years of Age (Cohorts 2-4)

Systemic Event	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe[a]	GRADE 4[b]
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

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

a. Prevents daily routine activity, eg, results in missed days of work or school or is otherwise incapacitating; includes use of narcotics for analgesia.
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 in the CRF. The severity of the systemic event should be graded using the AE severity grading scale provided in Section 10.3.4.

8.2.2.2.2. 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 the study vaccination (Days 1 through 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as a temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature less than 38.0°C [100.4°F]) 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 (>104.0°F) to assess the fever and perform an unscheduled assessment, as applicable (see Section 8.10.4). Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information if a temperature of >38.9°C (>102.0°F) is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis; see Table 4 below.

Table 4. 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.

8.2.2.3. 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 following vaccination, where Day 1 is the day of vaccination.

8.2.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory tests are not required by this protocol.

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

8.2.4. Pregnancy Testing (If Applicable)

Urine pregnancy tests will have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in women of childbearing potential (WOCBP) at the times listed in the SoA, immediately before the administration of the vaccine. A negative pregnancy test result will be required prior to the participant's receiving the investigational product. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of investigational product and from the study.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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 it meets the criteria for classification as an SAE or caused the participant to discontinue from the study (see Section 7).

Each parent/legal guardian will be questioned about the occurrence of AEs in a nonleading manner. In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant's parent(s)/legal guardian(s) provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 2. At Month 6 (final telephone contact), the participant's parent(s)/legal guardian(s) will be contacted by telephone to collect information about SAEs, including hospitalizations and NDCMCs, since Visit 2.

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

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

If the participant is withdrawn from the study and their parent(s)/legal guardian(s) also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by 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 a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until study end.

- 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 participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

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

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

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

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

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

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study for the purposes of administering the investigational product. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of deficiencies that occur during the study with such devices.

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

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Section 10.3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

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

8.3.9.2. Follow-up of Medical Device Deficiencies

All medical device deficiencies involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This 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 Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness 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.

Information will be provided to the sponsor as described in the IP manual.

8.3.9.4. Regulatory Reporting Requirements for Medical 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 investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product 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 investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

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

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

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

Other examples include, but are not limited to:

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

8.4. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

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

8.10. Study Procedures

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

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

8.10.1. Visit 1 (Vaccination 1, 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.
- Measure and record the participant's temperature as appropriate for the age of the child, according to routine local practice (°F/°C).
- Confirm receipt of 3 or more prior doses of 13vPnC and record the date of prior administration of the most recent (third or fourth) dose of 13vPnC for Cohorts 1 and 2 only. Record the date of administration of the most recent dose of 7vPnC or 13vPnC for Cohorts 3 and 4, if available.

- Perform urine pregnancy test for female participants of childbearing potential (see Section 8.2.4).

- For participants of childbearing potential, instruct the participant to use appropriate contraceptives until 28 days after administration of investigational product and document the conversation and the participant's affirmation in the participant's source document.

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

- Assign an investigational product container number via the IRT. This must be the last step before proceeding. A site staff member will prepare the investigational product according to the IP manual.

After investigational product container number assignment:

- Collect a blood sample of approximately 5 mL for Cohorts 1 and 2, and approximately 10 mL for Cohorts 3 and 4, for immunogenicity assessments prior to vaccination.

- Administer a single 0.5-mL injection of 20vPnC into the left leg (option for Cohort 1 only) or left arm.

- Permitted routine pediatric vaccines may be given at the same time as study vaccination according to local or national recommendations (to be administered into a limb other than the site of 20vPnC). However, if feasible, it is recommended that licensed nonstudy vaccines be administered at least 14 days or 28 days (see Section 6.5.2) before or after 20vPnC administration. The location of the injection of each vaccine administered at Visit 1 (20vPnC and other, if applicable) will be recorded 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 and NDCMCs.

- Issue the participant's parent(s)/legal guardian(s) a measuring device (caliper) to measure injection site reactions in the participant's limb that received the 20vPnC 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 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C (>104.0°F), redness and/or swelling at the injection site (left leg [option for Cohort 1 only] or left arm) measuring >14 measuring device units (>7 cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Ask the participant or 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 10.1.10).

- Inform the participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of 20vPnC administration (before or after vaccination).

- Record AEs, SAEs, and NDCMCs during the visit as described in Section 8.3 and record concomitant medications as described in Section 6.5.3.

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

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

8.10.2. Visit 2 (Follow-up: 28 to 42 Days After Visit 1, ie, Study Day 29 to 43)

- Record nonstudy vaccinations administered since Visit 1, as described in Section 6.5.3.

- Perform a contraception check (see Section 10.4), if applicable (Cohort 3 and Cohort 4 only).

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and that the temporary delay criteria for the immunogenicity blood draw are not met.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Collect the e-diary (if applicable).

- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3 and record concomitant medications used to treat NDCMCs and SAEs.

- Collect a blood sample of approximately 5 mL for Cohorts 1 and 2, and approximately 10 mL for Cohorts 3 and 4, for immunogenicity (a topical anesthetic is permitted).

- Remind the participant or 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.

- Confirm whether the parent(s)/legal guardian(s) still possesses the participation contact card.

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

8.10.3. Visit 3 (6-Month Safety Collection [Telephone Contact] – 168 to 196 Days After Visit 1)

- Contact the participant's parent(s)/legal guardian(s) by telephone approximately 6 months after the study vaccination; this contact should be attempted for all participants who have received study vaccination, unless the participant's parent(s)/legal guardian(s) has withdrawn consent.

- Determine whether any SAEs and NDCMCs have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3 and record concomitant medications used to treat NDCMCs and SAEs.

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

8.10.4. Unscheduled Visits

If the participant's parent(s)/legal guardian(s) reports redness or swelling at the injection site (left leg [option for Cohort 1 only] or left arm) measuring >14 measuring device units (>7 cm) or severe injection site pain or a fever >40.0°C (>104.0°F) during the 7-day postvaccination period, a telephone contact must occur as soon as possible between the investigator or medically qualified designee and 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 (>104.0°F), 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 needed. An investigator site visit should be scheduled as soon as possible to assess the extent of the injection site reaction, unless any of the following is true:

- The participant's parent(s)/legal guardian(s) is unable to bring the participant to the unscheduled visit.
- The reaction is no longer present at the time of the telephone contact.
- The participant's parent(s)/legal guardian(s) recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The principal investigator (PI) or authorized designee determined it was not needed.

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

If the participant's parent(s)/legal guardian(s) is unable to bring the participant to an unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing reactions must be assessed at the next study visit.

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

- Measure temperature as appropriate for the age of the child, according to routine local practice (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain in accordance with the grades provided in Section 8.2.2 (if present).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

The 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, and/or irritability in Cohort 1, or fatigue, headache, muscle pain, and/or joint pain in Cohorts 2 through 4, or for a local reaction (all groups) in the 7 days following vaccination.

The participant's parent(s)/legal guardian(s) will also be instructed to contact the investigator site to report any significant illness, medical event, or hospitalization that occurs during the study period. The investigator site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

Additionally, study staff may contact the participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimands corresponding to each primary, secondary[CCI] objective are described in the table in Section 3.

The estimands for evaluating the immunogenicity objectives are based on the evaluable population (see Section 9.3 for definition) and estimate the vaccine effect in the hypothetical setting where participants follow the study schedule and protocol requirements. The estimand addresses the objective of estimating the true difference in the immune response between the 2 time points within each cohort, since noncompliance may obscure the true difference in immune response between the 2 time points in each cohort. Missing serology results will not be imputed. 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. A missing AE start date will be imputed according to Pfizer standard rules following a conservative principle to characterize the AE in the safety analysis, with details further described in the study SAP. No other missing information will be imputed in the safety analysis.

9.1.2. Statistical Hypotheses

9.1.2.1. Cohort 1 and Cohort 2

For the primary immunogenicity objective, hypothesis testing will be used to assess superiority of the IgG concentrations for the 7 additional pneumococcal serotypes 1 month after 20vPnC to the IgG concentrations before 20vPnC within each cohort. The null hypothesis (H_0) for a serotype is

$$H_0: \mu_{\text{fold-rise}} \leq 1.0$$

where

- $\mu_{\text{fold-rise}}$ is the geometric mean of the fold rise in IgG concentration from before to 1 month after vaccination;

The null hypothesis (H_0) will be rejected for a serotype if the lower bound of the 2-sided 95% CI for the IgG GMFR is greater than 1.0.

9.1.2.2. Cohort 3 and Cohort 4

For the primary immunogenicity objective, hypothesis testing will be used to assess superiority of the OPA titers for the 7 additional pneumococcal serotypes 1 month after 20vPnC to the OPA titers before 20vPnC within each cohort in a randomly selected subset of participants. The null hypothesis (H_0) for a serotype is

$$H_0: \mu_{\text{fold-rise}} \leq 1.0$$

where

- $\mu_{\text{fold-rise}}$ is the geometric mean of the fold change in OPA titer from before to 1 month after vaccination;

The null hypothesis (H_0) will be rejected for a serotype if the lower bound of the 2-sided 95% CI for the OPA GMFR is greater than 1.0.

9.1.3. Multiplicity Considerations

The primary immunogenicity objectives for superiority are evaluated separately for each cohort. Within each cohort, superiority of the immune response 1 month after 20vPnC to before vaccination (serotype-specific IgG concentrations for Cohorts 1 and 2; serotype-specific OPA titers for Cohorts 3 and 4) is assessed by the hypothesis tests as described in Section 9.1.2.1 or Section 9.1.2.2, each hypothesis test at an alpha level of 0.05 for each serotype. The primary immunogenicity objectives will be achieved if the superiority of the immune response 1 month after 20vPnC to before 20vPnC is established for all 7 additional serotypes in a given cohort. Therefore, the overall type I error rate for immunogenicity evaluation is well controlled at the 0.05 level for each cohort.

9.2. Sample Size Determination

The study size is based on considerations of 1) the evaluations of safety, tolerability, and immunogenicity of a single dose of 20vPnC in the population in each cohort, 2) operational constraints of available serum volumes from individual study participants, and 3) contribution to the overall safety database for the 20vPnC pediatric clinical development program.

Safety Endpoints

The primary safety objective includes the endpoint of reported AEs within 1 month after vaccination. The number of participants receiving 20vPnC is 200 in each of Cohorts 1 through 4. There is a greater than 90% chance of observing at least 1 AE in each of the groups, assuming the true rate is at least 2% (Table 5).

Table 5. Probability of Detecting at Least 1 AE in Each of Cohorts 1 Through 4

Sample Size	True Rate of AEs	Probability (%) of Observing at Least 1 AE
200 per Cohort	0.1%	18
200 per Cohort	0.5%	63
200 per Cohort	1%	87
200 per Cohort	2%	98

Immunogenicity Endpoints

Table 6 provides information on the probability of demonstrating superiority of IgG concentrations (Cohorts 1 and 2) and OPA titers (Cohorts 3 and 4) 1 month after 20vPnC compared with before 20vPnC based on data from the B7471003 Phase 2 20vPnC study in infants and the B7471007 Phase 3 20vPnC study in adults, respectively.

For IgG concentrations with 180 evaluable participants in each cohort (Cohort 1 or Cohort 2), there is a >99% probability that superiority will be declared for all 7 additional serotypes, if the true GMFRs from before 20vPnC to 1 month after 20vPnC are at least 50% of the observed GMFRs from before to 1 month after Dose 4 in the B7471003 study. For OPA titers with 90 evaluable participants in each cohort (Cohort 3 or Cohort 4), the probability that superiority will be declared for the 7 additional serotypes ranges from 64% (11A) to ≥99% (all other serotypes except 33F) if the true GMFRs from before 20vPnC to 1 month after 20vPnC are 75% of the observed GMFRs from before 20vPnC to 1 month after 20vPnC from participants 18 through 29 years of age in the B7471007 study. If the assumed evaluable participants are increased to 180 and GMFR assumptions are unchanged, the probability to demonstrate superiority for 11A increases to 91%.

Table 6. Probability (%) to Demonstrate Superiority of Immune Response of 1 Month After 20vPnC to Before 20vPnC

Serotype	IgG[a] (Cohorts 1 and 2)	OPA[b] (Cohorts 3 and 4)		
		Assumption 1	Assumption 2	Assumption 3
8	>99	>99	>99	>99
10A	>99	>99	>99	>99
11A	>99	64	95	91
12F	>99	>99	>99	>99
15B	>99	>99	>99	>99
22F	>99	>99	>99	>99
33F	>99	98	>99	>99
Overall	>99	63	95	91

Abbreviations: GMFR = geometric mean fold rise; IgG = immunoglobulin G; OPA = opsonophagocytic activity.
Note: The probability calculation assumes the variabilities for IgG concentration and OPA titers are the same as observed in infant study B7471003 and adult study B7471007 (18 through 29 years of age), respectively, using the t-distribution. Additional assumptions in the calculation:

a. The true IgG GMFR from before to 1 month after 20vPnC for each serotype to be 50% of the observed IgG GMFR from before to 1 month after Dose 4 of 20vPnC in Study 7471003, 180 evaluable participants in each cohort.
b. For Assumption 1, 2, or 3, respectively, the true OPA GMFR from before to 1 month after 20vPnC for each serotype to be 75%, 100%, or 75% of the observed OPA GMFR from before to 1 month after 20vPnC from participants 18 through 29 years of age in Study B7471007, and 90, 90, or 180 evaluable participants in each cohort.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Evaluable immunogenicity	All eligible participants who receive 1 dose of 20vPnC, have at least 1 valid immunogenicity result collected within the appropriate window 1 month after vaccination, and have no other major protocol deviations as determined by the clinician.
CCI [redacted]	[redacted]
Safety	All participants who receive 1 dose of the investigational product and have safety data reported after vaccination.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analysis in Section 9.5 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[CCI] endpoints.

Immunogenicity and safety results will be analyzed separately for each cohort.

9.4.1. Immunogenicity Analyses

The statistical analysis of pneumococcal immunogenicity results will be primarily based on the evaluable immunogenicity population as defined in Section 9.3. [CCI]

[CCI]

[CCI]

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

Endpoint	Statistical Analysis Methods
Primary	• **Pneumococcal serotype-specific IgG GMFRs from before to 1 month after 20vPnC** For each of the 20 serotypes in each cohort, GMFRs and the associated 95% CIs for serotype-specific IgG concentrations from before to 1 month after vaccination will be provided. The GMFR will be calculated by exponentiating the mean of the difference of logarithmically transformed assay results (1 month after vaccination – before vaccination for each participant). Two-sided CIs will be obtained by calculating the CIs using Student's t-distribution for the mean difference of measures on the logarithmically transformed assay results and exponentiating the limits. In Cohort 1 and Cohort 2, for each of the 7 additional serotypes, the lower limit of the 2-sided 95% CI of the IgG GMFR for a serotype will be used in the hypothesis test for superiority of IgG concentrations 1 month after 20vPnC to before 20vPnC for that serotype, as detailed in Section 9.1.2.1.

Endpoint	Statistical Analysis Methods
	• **Pneumococcal serotype-specific OPA GMFRs from before to 1 month after 20vPnC** For each of the 20 serotypes in each cohort, GMFRs of OPA titers from before vaccination to 1 month after vaccination will be analyzed the same way as the IgG GMFRs. In Cohort 3 and Cohort 4, for each of the 7 additional serotypes, the lower limit of the 2-sided 95% CI of the OPA GMFR for a serotype will be used in the hypothesis test for superiority of OPA titers 1 month after 20vPnC to before 20vPnC for that serotype, as detailed in Section 9.1.2.2.
Secondary	• **Percentages of participants with predefined pneumococcal serotype-specific IgG concentrations for the 7 additional serotypes at 1 month after 20vPnC** Percentages (and 2-sided 95% CIs) of participants with serotype-specific IgG concentrations ≥ the predefined level will be provided for each of the 7 additional serotypes in Cohort 1. The Clopper-Pearson method will be used to calculate the CIs. • **Percentages of participants with ≥4-fold rise in predefined pneumococcal serotype-specific OPA titers for the 7 additional serotypes from before to 1 month after 20vPnC** Percentages (and 2-sided 95% CIs) of participants with ≥4-fold rise in serotype-specific OPA titers from before to 1 month after 20vPnC will be provided for each of the 7 additional serotypes in Cohorts 2, 3, and 4. The Clopper-Pearson method will be used to calculate the CIs. • **Pneumococcal serotype-specific IgG GMCs before and 1 month after 20vPnC** GMCs and 2-sided 95% CIs for serotype-specific IgG concentrations before and 1 month after vaccination will be provided for each serotype in each age cohort. Geometric means and the associated 2-sided CIs will be obtained by calculating means and CIs on the natural log scale based on the t-distribution and then exponentiating the results.

Endpoint	Statistical Analysis Methods
	• **Pneumococcal serotype-specific OPA GMTs** OPA GMTs before and 1 month after 20vPnC for each serotype in each cohort will be analyzed the same way as IgG GMCs.
CCI	[redacted]

Endpoint	Statistical Analysis Methods
	[redacted]

9.4.2. Safety Analyses

The safety analyses are based on the safety population. Participants will be summarized by vaccine group as administered. Missing AE start dates will be imputed according to Pfizer standard rules following a conservative principle to characterize the AE in the safety analysis, with details further described in the study SAP. No other missing information will be imputed in the safety analysis.

Endpoint	Statistical Analysis Methods
Primary	• Descriptive statistics will be provided for each reactogenicity endpoint for each age cohort. Local reactions and systemic events from Day 1 after vaccination through Day 7 will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs. • AEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terms. Descriptive summary statistics (counts and percentages and the associated 2-sided Clopper-Pearson 95% CIs) for AEs from vaccination to 1 month after vaccination will be provided for each age cohort. • SAEs and NDCMCs will be categorized according to MedDRA terms. Descriptive summary statistics (counts, percentages, and the associated 2-sided Clopper-Pearson 95% CIs) for SAEs and NDCMCs from

Endpoint	Statistical Analysis Methods
	vaccination to 6 months after vaccination will be provided for each age cohort.
Secondary	Not applicable.
CCI [redacted]	

9.5. Interim Analyses

There is no interim analysis planned for the study.

9.5.1. Analysis Timing

Safety data through the visit occurring 1 month after the dose from all participants may be analyzed by the study team when available. All results will be analyzed and reported after the completion of the study.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant's parent(s)/legal guardian(s) and answer all questions regarding the study.

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

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

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

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

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

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

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

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

If a participant reaches the age at which he or she is legally able to provide consent (eg, 18 years old) during the study, his or her consent must be obtained. Since the participant is no longer a minor, the consent of the parent(s)/legal guardian(s) is no longer valid. Once the participant provides consent, the participant then becomes responsible to directly participate in study procedures and assessments. This is expected for a minority of participants in the study, and therefore any references in the protocol to parent(s)/legal guardian(s) may, in certain cases, be directly applicable to the participant.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (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 standard operating procedures (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 (clinical study report [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 European Medicines Agency (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 contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

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

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

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

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

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

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

investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

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

10.1.7. Source Documents

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

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

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

10.1.8. Study and Site Closure

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 contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

- Discontinuation of further study intervention development.

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

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 18 months after end of the study (or study termination), whichever comes first.

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

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

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

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

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

10.1.10. Sponsor’s Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, the participant’s parent(s)/legal guardian(s) are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to

provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant's parent(s)/legal guardian(s) directly, and if the participant's parent(s)/legal guardian(s) calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Events that, in the clinical judgment of the investigator, are 1) consistent with normal growth and development and 2) do not differ significantly in frequency or severity from expected, are not generally to be considered adverse events. Examples may include, but are not limited to, teething, contact diaper rash, spitting up, colic, or typical fussiness/crying in infants and children. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an NDCMC

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

10.3.3. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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

AE and SAE Recording/Reporting

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

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 investigational product under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

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

Assessment of Causality

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

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" 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 professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

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

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Report 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.


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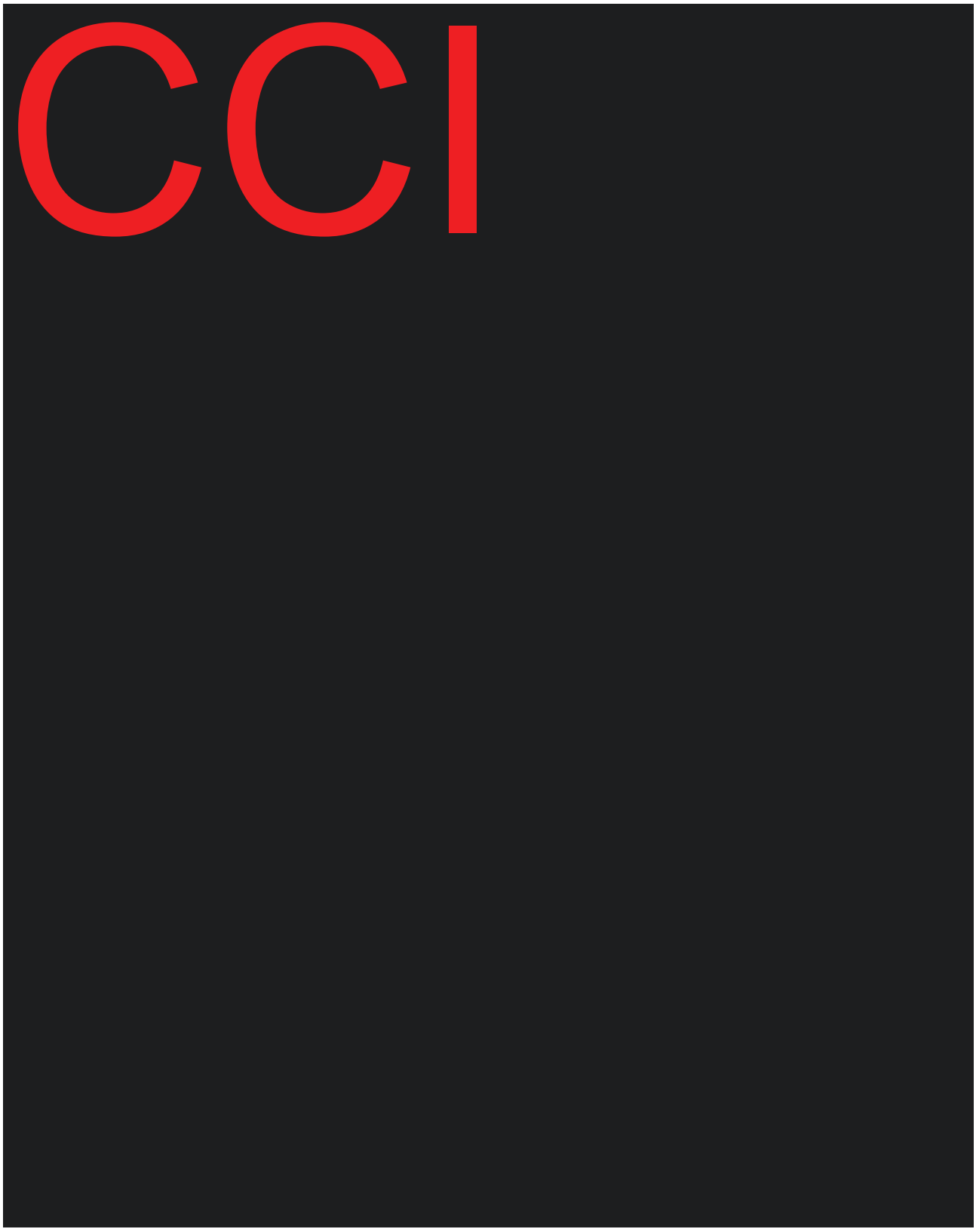
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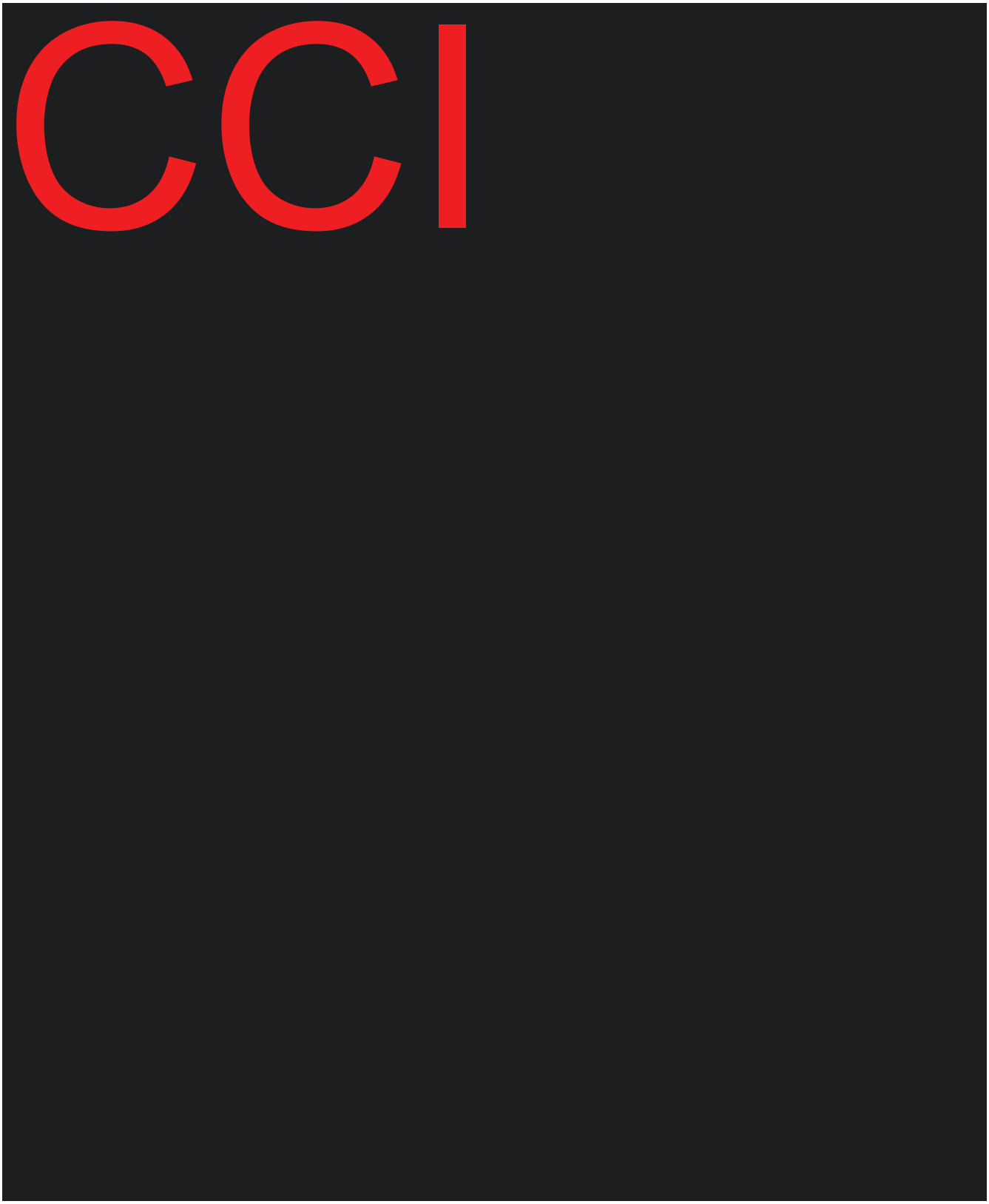
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10.5. Appendix 5: Genetics

Not applicable.

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

Potential Cases of Drug-Induced Liver Injury

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

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a 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 aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

Not applicable.

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

Definitions of a Medical Device Incident

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

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

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

10.8.1. Definition of AE and ADE

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

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

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

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

10.8.3. Definition of Device Deficiency

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

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

AE, SAE, and Device Deficiency Recording

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

Assessment of Intensity

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

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

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

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

10.8.5. Reporting of SAEs

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

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

10.8.6. Reporting of SADEs

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

10.9. Appendix 9: Country-Specific Requirements

Not applicable.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
20vPnC	20-valent pneumococcal conjugate vaccine
ACIP	Advisory Committee on Immunization Practices
ADE	adverse device effect
AE	adverse event
ALT	alanine aminotransferase
AOM	acute otitis media
AST	aspartate aminotransferase
CAP	community-acquired pneumonia
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRM_{197}	cross-reactive material 197
CRO	contract research organization
CSAP	clinical specimen assessment plan
CSR	clinical study report
DILI	drug-induced liver injury
DU	dispensable unit
EC	ethics committee
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
CCI	[redacted]
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation	Term
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPD	invasive pneumococcal disease
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
ISO	International Organization for Standardization
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
OPA	opsonophagocytic activity
PCD	primary completion date
PI	principal investigator
PIP	pediatric investigation plan
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	prothrombin time
CCI	[redacted]
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
TBili	total bilirubin
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
VT	vaccine-type
WHO	World Health Organization
WOCBP	woman of childbearing potential

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